What Makes a Psychopath?
Neuro-Developmental Pathways to Immoral and Antisocial Behavior
What Makes A Psychopath?
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The art pieces on page number 9, 10, 68 are copyright to David Ho © An amazing artist with a natural talent to symbolically visualize the dark side of man through surrealistic digital art. Were it not that I had coincidentally stumbled upon his awe-inspiring and thought provoking work, this book would likely have been without introductory art pieces to each chapter. For more information and examples or for those who like to purchase his work, see his website; www.davidho.com

Another artist who inspired me with a sole picture is Alexander Tsiaras © His art piece titled “The Human Body Revealed” on page 114 is a perfect visual expression of what I feel when I think about serotonin; balance, serenity, intimacy, peace, and attachment.

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# TABLE OF CONTENTS

Introduction into the Psychopathic Mind  
*Scope of the Problem & Overview of this Thesis*  
11

Chapter 1 - Unmasking the Elusive Psychopath  
*The Checkered History of the Psychopathy Construct*  
23

Chapter 2 - Towards A New Continuum of  
Primary and Secondary Psychopathy  
*A Matter of Deficiency versus Disturbance*  
69

Chapter 3 - Serotonergic Risks towards Emotional Pathology  
*Everything is About Balance*  
115

Chapter 4 - Dopaminergic Risks towards an Antisocial Lifestyle  
*When Wanting Overrules Having*  
179

Chapter 5 - The Role of Testosterone  
*A Real Man is Shaped by his Environment*  
253

Chapter 6 - Future Directions and Critical Comments  
*The Eternal Dance between Biology and Psychology*  
313

Appendix  
References  
335  
English Summary  
435  
Nederlandse Samenvatting  
453  
Acknowledgments  
475  
Curriculum Vitae  
479
The Psychopath

“It is impossible for him to take even a slight interest in the tragedy or joy or the striving of humanity as presented in serious literature or art. He is also indifferent to all these matters in life itself. Beauty and ugliness, except in a very superficial sense, goodness, evil, love, horror, and humor have no actual meaning, no power to move him.

He is, furthermore, lacking in the ability to see that others are moved. It is as though he were colorblind, despite his sharp intelligence, to this aspect of human existence. It cannot be explained to him because there is nothing in his orbit of awareness that can bridge the gap with comparison. He can repeat the words and say glibly that he understands, and there is no way for him to realize that he does not understand.”

Hervey Cleckley in The Mask of Sanity
Introduction into the Psychopathic Mind

Scope of the Problem & Overview of this Thesis

“As there are persons who cannot distinguish certain colours, having what is called colour blindness, so there are some who are congenitally deprived of moral sense” (Henry Maudsley).

Since our ancient nomadic history as tribesman up until our current era as citizens in modern society, there have been humans who are devoid of the natural instincts towards empathy, attachment, and reciprocity that the rest of us take for granted. Individuals who are unmoved by the love that warms our hearts and soothes our insecurities, detached from the human sorrow that stirs our compassions and incites our care, and unencumbered by the intuitive brakes that prevent us from doing harm to our fellow beings. In the absence of an internalized moral compass or emotional guidance system, these individuals are selfishly guided by their hedonistic drives and operate mainly through their cunning intellect. Their modus operandi is characterized by the assertive, and oftentimes, aggressive seeking of reward, excitement, power, wealth, and control, no matter the consequences to others and regardless of the risk for punishment. Because their emotional landscape is characterized by a profound and all-encompassing vacancy or ‘hollowness’, where little is ever moved or conflicted, they are able to perenniably sustain their insouciant, buoyant and often charming attitude, regardless of the circumstances or the shamefulness of their acts.

Apart from the clear-cut examples such as the fearless and callously violent criminals, the majority of these conscienceless individuals are
outwardly well-adjusted and refrain from direct aggression or violence. Our scientific knowledge about such people has dramatically increased in the last couple of decades, and we denote these individuals as psychopaths (categorical) or as being psychopathic (dimensional). In the case of mental health, I personally prefer dimensional constructs over categorical ones because of my belief that the arbitrary boundaries of what is and what is not pathological are nearly always set by man himself and bound by cultural beliefs and dynamically shifting values (e.g., homosexuality was considered a psychiatric disorder in the 50’s). Nonetheless, for the sake of convenience, and the fact that we do not have conclusive evidence whether psychopathy is a category or a dimensional construct, both terms (i.e., psychopath and psychopathic) will be used interchangeably throughout this thesis. Furthermore, the precise meaning of the term psychopathy and its differentiation into separate subtypes (i.e., primary and secondary psychopathy) is still a source of heated scientific debate.

I. The Scope of the Problem

Psychopathic personality traits, such as callousness, selfishness, and unemotionality, have presumably been present since the ascent of man (Cleckley, 1941; Kiehl and Hoffman, 2011; Lykken, 1995; Mealey, 1995). Psychopathic individuals have even been identified in pre-industrialized cultures and indigenous tribes that still rely on hunting and gathering and direct social cooperation to survive (Lykken, 1995; Murphy, 1976). For example, one primitive tribe indigenous to southwestern Nigeria, the Yorubas, use the term arankan to describe individuals “who always go on their own way regardless of others, who are uncooperative, full of malice, and bullheaded” (pp. 1026, Murphy, 1976). Another pre-industrialized culture, the Yupic-speaking Inuit Eskimos in northwest Alaska use the name kunlangeta for the “mind who knows what to do but does not do it” and the “man who, for example, repeatedly lies and cheats and steals things and does not go hunting and, when the other men are out of the village takes sexual advantage of many women – someone who does not pay attention to reprimands and who is always being brought to the elders for punishment” (pp. 1026, Murphy, 1976). Thus, even in such close-knit environments, where one is truly connected to nature and dependent on others to survive, we still
find individuals who live only for themselves. Nevertheless, among the 499 living on the island, only one Eskimo was called a kunlangeta which is a prevalence of about 0.2% (Murphy, 1976). In contrast, the label psychopathy according to current diagnostic tools may apply to about 0.6% - 1.2% of Western society (Coid et al., 2009, 2012). Similarly, the prevalence of antisocial traits in different rural villages in Taiwan is near zero, reaching a maximum of 0.3%. This is considerably lower than the prevalence of 1.3% as found in the nearby metropolitan area of Taipei (Hwu et al., 1989). Explanations for this phenomenon emphasize that the anonymity, lack of social control, social inequality, emphasis on personal control, competitive atmosphere, and hierarchical structure of individualistic societies might more readily incite psychopathic development at lower levels of genetic risk or that psychopaths are more likely to thrive in such a society (Lykken, 1995; Stout, 2006).

Offenders diagnosed as psychopaths make up around 15-20% of the prison population but commit more than 50% of all serious felonies in Western society. Compared to nonpsychopathic offenders, they also commit twice as many crimes on average, commit a greater variety of crimes, begin committing crimes at much younger ages, and are more violent during the act (DeLisi, 2009; Hare, 1993; Porter et al., 2001, 2003). After release they are three to four times more likely to recidivate and recidivate violently than non-psychopathic criminals (Douglas et al., 2006, 2008; Hemphill et al., 1998). Some scholars have advanced that psychopathy is the purest and best explanation for antisocial behavior and even went as far as to argue that psychopathy is the unified theory of crime (DeLisi, 2009).

Paradoxically, despite their heightened risk for criminality and violence, psychopaths, especially primary variants, are adept at impression management, and know how to present themselves in a positive light or how to manipulate and play off those around them in order to escape detention, punishment, or substantially shorten their prison sentences (Babiak and Hare, 2007). Despite factual knowledge of higher recidivism rates and higher risk for future violence, psychopathic sex offenders were still two to three times more likely to receive early (conditional) release from long-term prison sentences than their non-psychopathic counterparts (Porter et al., 2009). In a similar vein, offenders with the highest levels of psychopathic traits and recidivism rates actually received the most favorable evaluations from the facilitators of a rehabilitation program (Seto and Barbaree, 1999). These findings again
underscore the substantial discrepancy between the outward appearance and inner deviance of psychopathic offenders. All in all, psychopathy is a serious problem to societal harmony, especially in individualistic cultures.

The societal problem is that we still do not have a coherent view on what psychopathy precisely entails—which intrapsychic dynamics, behavioral expressions, and etiological pathways characterize such a personality profile. Although Hervey Cleckley sought the delimitate the psychopathy construct back in the 1940’s, and was quite successful in his endeavor (Cleckley, 1941), in the decades thereafter, the construct has again been convoluted and a number of contrasting definitions have gained ground.

Nowadays, subjects diagnosed as psychopathic are characterized by a large variety of divergent behavioral profiles and etiological pathways leading to this disturbance. It is thus critical to divide these subjects into distinct and more homogeneous groups to better understand the underlying mechanisms at work. The diagnosis or inclusion of false-positives but also false-negatives is still a frequent problem encountered in both clinical and research settings. Since we do not have a clear-cut understanding of how psychopathy may be expressed in affect and behavior and how it crucially differentiates from other conditions, we are naturally crippled in our efforts to understand these individuals or handle them in society, let alone develop successful prevention programs or treatments.

Furthermore, it has been repeatedly demonstrated that psychopathy is strongly determined by genetic background. Uncovering the biological contributions to this type of pathology will greatly facilitate the development of specialized pharmacological but also behavioral and psychological therapy. The neurobiological risk-factors, and especially monoaminergic processes, that contribute to the etiology of psychopathy are just beginning to be uncovered and are potentially viable for understanding some of the major pathologies associated with this condition, an important target for the design of psychotropic medications, and thus an important direction of future research.

However, the wide-spread inconsistency and disagreement on what should be regarded as psychopathic has naturally compromised research that aims to uncover its etiological underpinnings and thereby also hindered the development of specialized treatments. For example, some reviews argue that primary psychopathy is associated with a highly stable serotonergic functioning which engenders socio-emotional deficiency, while secondary psychopathy is associated with reduced serotonergic functioning, which
engenders neuroticism, detachment, and reactive aggression (Yildirim and Derksen, 2013). In sharp contrast, others argue that it is primary psychopathy which is associated with reduced serotonergic functioning and reactive aggression while secondary psychopathy is not (Fanning et al., 2014). Upon closer inspection of the definitions used in these papers, it becomes clear that both use widely divergent operationalizations of primary psychopathy (fearlessness/socio-emotional deficiency versus Machiavellian egocentricity).

Therefore, before specific psychological and pharmacological treatments can be designed or pre-emptive measures taken to reduce the impact of psychopathy on society, it is paramount that we first reach consensus on what psychopathy is, which personality styles comprise this heterogeneous group, how these subtypes associate with external correlates, which etiological mechanisms play an important role in their development, and how certain neurobiological alterations may contribute to such etiological processes.

II. Goal and Methods of this Thesis

The main goal of this thesis is to provide the scientific community with novel theoretical insights into the biological, social, and psychological processes that together shape the etiology of a psychopathic personality profile. On the basis of comprehensive review and structural analysis, new theoretical models have been constructed regarding the conceptualization, categorization, and etiology of psychopathy.

The methods applied to reach the hypotheses and theoretical models in this thesis may be termed as “qualitative meta-analysis” (see Schreiber et al., 1997). Qualitative meta-analysis entails the systematic review and structural analysis of the literature regarding the different facets of a certain relationship (e.g., dopamine and impulsivity) in order to identify consistent correlations, evaluate possible causal mechanisms, and eventually, commence new theories. By constantly switching from a thorough review of causal mechanisms on the level of socio-biology to a more general understanding of the functional relevance of those mechanisms for psychology, a holistic perspective is constructed on the etiology of psychopathy as rooted in a matrix of interdependent biological, environmental, and psychological influences.
The ambition is to integrate theory and research from neurobiological and psychological sciences in order to place this work in a broader conceptual framework and promote synergy across fields.

III. Overview of this Thesis

My ambition with this thesis is to slowly acquaint the reader with the larger matrix of interdependent relationships that can shape the etiology of either primary or secondary psychopathy.

Chapter 1 will begin with the clarification of the psychological traits, behavioral patterns, and etiological processes that are convergent with the psychopathic condition from those that are divergent and incompatible. Psychopathy has been operationalized in a variety of ways throughout history and its potential relationship to external constructs (e.g., criminality, impulsivity, fear) or differentiation from similar disorders (e.g., primary vs. secondary psychopathy) is a source of ongoing debate. Chapter 1 strives to give an overview of the history of the psychopathy construct and examine and compare its various conceptualizations and corresponding operationalizations.

After discussing the various conceptualizations and operationalizations of psychopathy more specifically, Chapter 2 will focus on the much needed differentiation between primary and secondary psychopathy. These divergent conditions are still frequently conflated in science and practice. Although primary and secondary psychopathy may show outward resemblances and achieve equally high scores on diagnostic instruments assessing psychopathic traits, they should be treated as distinct conditions with different etiological processes underpinning their development. To provide a more detailed view on corresponding etiological pathways, I will also discuss the putative alterations in relevant neural circuitry in primary as compared to secondary psychopathy and examine the potential relationships between these biological alterations and the observed traits.

Continuing with the chapters 3, 4 and 5, I will examine in greater detail the different bio-social risk mechanisms undergirding the development of primary and secondary variants of psychopathy. Here, it is discussed how different hormonal and monoaminergic systems (testosterone, serotonin, dopamine) and their (dys)functionality at important neural modules
(amygdala, striatum, frontal cortex) can contribute to the etiology of psychopathy and increase the risk for life-course persistent antisocial behavior. A main focus of this section is to delineate how biological alterations brought about by genetic variation might interact with early social experiences. These bio-social influences that occur early in development (conception to three years of age), interactively shape the physiological response patterns and give rise to the unique psychodynamic landscape of the developing human organism, thereby forming the first building blocks of personality. In this stage of early childhood development, the emergent psychodynamic landscape consists mainly of the intensity and duration of physiological responses to social, emotional, and reinforcing events (Id), the associative networks linking these internal drives and emotions to external stimuli (Ego/object relations), and the first evolving abilities of cortical modules to intuitively appraise and regulate these lower-order limbic processes (first steps toward Superego development; self-regulation, self- and other-awareness, emotional empathy).

Finally, the thesis is concluded with chapter 6 where I will discuss new ways of viewing the constructed hypotheses and offer some ideas on how to improve our understanding of the psychopathy construct and the biological and psychological factors that may contribute to its etiology. The second part of this chapter discusses the critiques that might be expressed towards contemporary ways of viewing the relationship between biology and psychology. The main argument is that socio-biology, which most theories are currently based on, does not dictate our psychological outcome and the effect of such risks on eventual behavior is strongly modified by identity. In order to improve our understanding of mental disorders, we need to learn to let go of absolutes within the social sciences (i.e., serotonin deficiency leads to depression) and learn to work creatively with the psychopathology that is presented. The brain is organic matter, and although its molecular functions are tightly controlled by certain absolute laws, its infrastructure and interconnectivity is established through an equally organic, intuitive, and random process. Therefore, it is important to further investigate the processes by which social influences such as unique life experiences, family structure, gender roles, peer interactions, subculture identification, and cultural values can crystallize the unemotional, unattached, and reward-seeking psychodynamic landscape into conscious behavioral patterns that evolve around the purposeful and selfish pursuit of power, money, status, and
social control. In contrast to the psychological processes that develop early in childhood and mediate the unconscious connections between internal processes and external events, later developing abilities during adolescence and adulthood constitute our more consciously and socially aware identity; our purposeful rather than intuitive manner of relating to our environment.
CHAPTER 1
UNMASKING THE ELUSIVE PSYCHOPATH
The Checkered History of the Psychopathy Construct
ABSTRACT

Psychopathy as a disorder of morality and emotion has been recognized as far as the dawn of the western calendar. Nonetheless, throughout the first 1800 years, psychopathic behavior was ascribed to paranormal entities, and psychopathic individuals were described as evil or demonic. Since the entrance of Phillipe Pinel into the stage, who argued for neutrality when assessing mentally disordered patients, a large number of conceptualizations have been incepted. Two of the most influential that were introduced during the mid 20th century are the Cleckley’an and McCord’ian operationalizations of psychopathy. However, these definitions are not convergent and differ mainly in the level of aggressive and impulsive pathology ascribed to psychopathy. Similarly, in the last few decades a number of different conceptualizations have been introduced that disagree on a number of issues regarding psychopathy. In addition to the longer standing DSM operationalization of the antisocial personality disorder, the most prominent among these operationalizations is the Psychopathy Checklist-Revised (PCL-R) as introduced by Robert Hare. However, in the last two decades a number of complaints arose with regard to the construct validity of the PCL-R and it has been repeatedly argued that the PCL-R conflates a number of psychopathic subgroups into one overarching diagnostic category while at the same time excluding equally psychopathic patients who are calculated, controlled, and fore-sighted. For this reason a number of other measures have been introduced such as the Psychopathic Personality Inventory by Scott Lilienfeld and the Triarchic Psychopathy Measure by Christopher Patrick. In this chapter I will critically review the strengths and shortcomings of each of these contemporary measures to assess psychopathy.

The critical discussion on the history of psychopathy and on the validity of the various psychopathy instruments stated in this chapter have been peer-reviewed and published as; Yildirim, B.O., & Derksen, J.J.L. (2015). Clarifying the Heterogeneity in Psychopathic Samples; Towards a New Continuum of Primary and Secondary Psychopathy. Aggression and Violent Behavior, 24, 9-41.
As far back as the dawn of the Western calendar, more than 2000 years ago, different scholars, philosophers, and clergy men have written timeless pieces on the subject of immorality. Ancient religious scriptures such as the Bible or Koran, fictional literature such as Roman and Greek mythology, and a plethora of other historical scripts, parables, and fables from different geographical regions, include characters who might be considered psychopathic according contemporary definitions. In these ancient scriptures, psychopathic features are often prominent in portrayals of notorious warriors, tyrannical rulers, self-serving noblemen, fraudulent villains, corrupt clergy men, evil witches, and demonic entities.

In the New Testament, which is now over 2000 years old, St. Paul sends two letters to young priests to warn them about people whom he describes as “hypocritical liars, whose consciences have been seared as with a hot iron” (1 Timothy 4: 2). People whose “minds and consciences are corrupted. They claim to know God, but by their actions deny him” (Titus 1:15-16). St. Paul further defines these individuals in terms of their “defective or deficient conscience, their duplicity, their callousness and, importantly, their potential to cause great harm to congregations” thereby introducing a primer on the subject that is closely related to current conceptualizations (Dein, 2012).

Also, these religious scripts and ancient myths tell various stories in
which murder and vengeance are depicted as part of the fabric of life. A well-known example comes from the book of Genesis, which tells the story of Cain who murdered his brother Abel out of spite that God accepted Abel’s offer while refusing his. Another ancient story is the Roman myth about the foundation of Rome. According to this story, Rome is founded by the demigod Romulus who slayed his brother Remus due to a disagreement on where to establish and how to rule the new city. After killing his brother, Romulus founds and governs the new city, naming it Rome, after himself. Other fictional characters with psychopathic traits throughout history include Shakespeare’s Iago in the play of Othello (1601) Henrik Ibsen’s character Peer Gynt (1867), and Ferenc Moln’s character Liliom (1909) (Cleckley, 1941, 1988).

In short, psychopathic characters have appeared in a steady stream of literature and folklore from all cultures and ages. See Cleckley (1941, 1988), Piechowski-Jozwiak and Bogousslavsky (2013), and Kiehl and Hoffman (2011) for more examples of psychopathic characters in literature and fiction throughout the ages.

Philosophical efforts to understand psychopathic personalities can also be traced back to ancient times. During the 1st century B.C., Theophrastus, a student of Aristotle, was the first to attempt a systematic study into human personality styles. In his renowned work, Characters, he passionately describes thirty different moral types and illustrates their defining behaviors with various examples. One of these types, termed the unscrupulous man, bears some resemblance to modern concepts of psychopathy;

“The Unscrupulous Man will go and borrow more money from a creditor he has never paid...When marketing he reminds the butcher of some service he has rendered him and, standing near the scales, throws in some meat, if he can, and a soup-bone. If he succeeds, so much the better, if not, he will snatch a piece of tripe and go off laughing” (cited in Widiger et al., 1991, pp. 63).

Later in the 4th century A.D., the scholar and theologian Saint Jerome would be the first to write on the subject of conscience. He introduced the term synderesis to describe our inherent human ability to sense the difference between good and evil;

“That spark of conscience which was not quenched even in the heart of Cain...that makes us, too, feel our sinfulness when we are overcome by evil,
desire, or unbridled spirit...and yet in some men we see this conscience overthrown and displaced; they have no sense of guilt or shame for their sins”
(cited in Stout, 2005, pp. 27)

After a long period of relative disinterest in the topic of conscience or deviant behavior, it regained new attention at the end of the 18th century when doctors, philosophers, and scientist returned to age-old arguments concerning free-will, and started pondering on the question whether certain transgressors are capable of understanding the consequences of their acts (Millon, 2011). In the interval that spanned nearly 1500 years, the popular idea that prevailed was that mental disorder, coined *insanity* in those times, is by definition related to intellectual retardation. In other words, ‘mind’ was equated with ‘reason’, and only a disintegration of rational thinking and reasoning would therefore be judged as insanity. Due to their excellent cognitive capabilities and apparently normal appearance, psychopathic personalities were generally not considered insane or pathologically ill before the 19th century but rather ‘evil’ or ‘demonic’ in a more spiritual sense.

### 1.1 Historical Perspectives on Psychopathy

19th century conceptualizations

Beginning at the end of the 18th century, paranormal and spiritual explanations for deviant behavior slowly started to make place for more rational and philosophical discussions on the nature of consciousness and free-will. Psychological concepts regarding psychopathy that were developed throughout the 19th century have went through innumerable reformulations up until contemporary times.

Let us start at the beginning, when psychiatry as we know it, was first incepted. This journey commences in 1801 when the French psychiatrist Philippe Pinel was shocked by the inhumane conditions of mentally handicapped patients and decided to stand up for a more compassionate approach to mental disorders. He argued that physicians should get rid of judgmental labels, such as evil or insane, and free patients from their deprived and shackled conditions (see figure 1.1). Pinel was thus among the first to
adopt a more humanistic view on mental disorders, and to propose that one should try to understand the inner workings of psychiatric patients rather than condemning them to a life of isolation and confinement (Pinel, 1806).

Out of his neutral observation, Pinel discovered that some patients were outwardly unimpaired in cognitive abilities but nonetheless demonstrated a severe disruption of the moral faculties (Pinel, 1806). These patients engaged foolhardily in impulsive, aggressive, and destructive acts despite an excellent intellectual understanding of the futility and counterproductiveness of their behavior. He referred to these cases as exhibiting manie sans délire, thereby suggesting that, contrary to popular belief in those times, madness could exist without retardation or psychosis. Pinel also introduced the term la folie raisonnante (rational insanity) to particularly describe patients who got carried away by instincțe fureur (instinctive fury) (Pinel, 1806).

However, Pinel’s descriptions mainly depict hostile, angry, and explosive individuals, and might thus especially pertain to what we now would term secondary rather than primary psychopathy (more on this in chapter 2). Primary psychopathic individuals often present a believable facade of normalcy and are not carried away by emotion (Cleckley, 1941, 1988).

In the following decades, the American psychiatrist and founding

Figure 1.1 Let good deeds be remembered; in addition to arguing for moral neutrality when assessing antisocial patients, Pinel more generally fought for a more humane psychological approach to the custody, treatment, and care of psychiatric patients, similar to the current notion of ‘ethics’. He is often regarded as the ‘father’ of modern psychiatry.
father Benjamin Rush continued with Pinel’s initial deductions. He concluded that certain individuals show an alienation of the mind, which referred to the insufficient integration of moral faculties into the overall personality (Dinitz, 1986). According to Rush, this moral deficiency led these patients to live an unreliable and parasitic life without the slightest sense of shame or concern over personal or communal welfare.

Later in 1835, the English psychiatrist James Crowley Prichard used the insights of Pinel and Rush to devise a broad category of mental disorders marked by what he termed moral insanity or moral imbecility (Prichard, 1835). The term “morally insane” quickly gained ground and was widely used throughout the 19th century to refer to individuals with obvious afflictions to their inner socio-emotional processes but who presented with normative reasoning capacity and intact reality testing. However, moral insanity as used by Prichard included a wide variety of personality disordered individuals rather than psychopathic or antisocial individuals more specifically. That is, during the 19th century, ‘moral’ did not necessarily refer to morality but to socio-emotional processes more generally (Millon, 2011; Whitlock, 1982). The term moral insanity was the forerunner of what we would now term ‘personality disorder’. Prichard described this form of psychopathology as;

“...a form of mental derangement in which the intellectual functions appear to have sustained little or no injury, while the disorder is manifested principally or alone in the state of feelings, temper, or habits. In cases of this nature the moral or active principles of the mind are strangely perverted or depraved; the power of self-government is lost or greatly impaired and the individual is found to be incapable, not of talking or reasoning upon any subject presented to him, but of conducting himself with decency and propriety in the business of life” (cited in Millon, 2011, pp. 426).

Unfortunately, moral insanity as defined by Prichard was a particularly laden and derogatory term that would permeate philosophy and clinical practice for the next 60 years. Prichard thus parted with the morally neutral attitude for which Pinel so passionately argued, and instead suggested that antisociality and criminality should be condemned because such behaviors indicated a “reprehensible defect in character” (Millon, 2011).

Then in 1876, the famous Italian criminologist and physician Cesare Lombroso published his work L’uomo Delinquente (The Delinquent Man)
wherein he first introduced the notion of the *born criminal* (Lombroso, 1876). Lombroso argued that criminality is unmistakably rooted in constitution, and that deviant individuals can be reliably identified by *physical stigmata*, such as a sloping forehead, ears of unusual size, asymmetry of the face, excessive length of arms, and other such peculiarities. He further adopted the notion of Prichard and described the born criminal as a *moral imbecile* who is guiltless, aggressive, boastful, impulsive, and generally insensitive to social rejection or physical pain.

The actual terms *psychopathy* and *psychopathic* were first introduced by the German psychiatrist Julius Ludwig Koch towards the end of the 19th century. Koch’s concept of *psychopathic inferiority*, first proposed in 1889 in his book *Kurzgefaßter Leitfaden der Psychiatrie* (A Concise Guide of Psychiatry), largely replaced the term moral insanity in the literature (Koch, 1889). A couple years later, during the 1890’s, Koch published *Die Psychopathischen Minderwertigkeiten* (Psychopathic Inferiorities) wherein he detailed and classified various mental disorders characterized by social or emotional malfunctioning (Koch, 1893). Similar to the concept of moral insanity, Koch’s psychopathic inferiorities included a wide variety of personality disturbances of which only a small portion would be considered psychopathic in the modern sense of the word (Millon et al., 1998). In fact, psychopathic inferiority was differentiated from psychotic states and gross intellectual deficits but otherwise included “all mental irregularities whether congenital or acquired” (Millon, 2011, pp.427).

Koch further separated the psychopathic inferiorities into multiple subtypes of increasing severity and stated the importance of clarifying whether the “inferiority” was due to genetics or upbringing. He was thus among the first to incite the question of nature versus nurture with regard to psychopathology. Just before the end of the 19th century, Koch critically reviewed Lombroso’s initial propositions and wrote an essay titled *The Question Of The Born Criminal*. Herein he divided habitual criminals into the “mentally healthy” and “mentally abnormal”, the latter being described as being “psychopathic” in character. Because Koch’s differentiation of criminal subtypes closely parallels contemporary contrasts between primary and secondary psychopathy, I will describe his contribution in more detail in chapter 2.
Early to mid-20th century conceptualizations

At the beginning of the 20th century, in 1904, the German psychiatrist Emil Kraeplin introduced the first comprehensive system to reliably classify mental disorders. His writings can be regarded as a precursor to contemporary efforts at differentiating mental disorders into separate diagnostic categories.

With the publication of the seventh edition of his important work *Psychiatrie: Ein Lehrbuch* (Psychiatry: A Textbook) Kraeplin was the first to use the term *psychopathic personalities* to refer specifically to deviant individuals rather than personality disorders in general. He subdivided these psychopathic personalities into four subcategories (i.e., born criminals, the unstable criminals, morbid liars and swindlers, and pseudoquerulants) (Kraeplin, 1912). In later editions, Kraeplin also added other categories, such as the *excitable*, *eccentric*, and *instinctual* criminals, thereby bringing the total to seven antisocial subtypes. His categorizations and descriptions are surprisingly consistent with contemporary definitions. Due to space restrictions I will describe his four initial categories in more detail.

The first category, *born criminals*, are described as cases “with abnormal endowment gradually merging into disease” (pp. 517, Kraeplin, 1912). This subtype closely resembles criminal, violent, and disinhibited variants of primary psychopathy as operationalized in contemporary literature;

“Even in early youth there are conspicuous moral defects, such as a lack of sympathy, shown by barbarous cruelty to animals, malicious teasing, illtreatment of their playmates, and general unresponsiveness to kindness. Later there develops pronounced selfishness without sense of honor or proper affection for parents, brothers, and sisters. Here belong those monstrous children who even at the tenderest age try to murder the members of their family for trivial reasons, and then report in a stupid, matter-of-fact way the details of their plans, and show obvious regret at their failure. Attempts at education are fruitless, since the most important incentives — love and ambition — are lacking. Force alone is able to suppress the manifestations of their unbridled selfishness, but it is soon met by duplicity, cunning, deceit, callousness, stubbornness, and a disposition to lie. Development throughout is selfish. Patients manifest affection toward parents, relatives, and companions only when they anticipate some advantage from it” (pp. 518, Kraeplin, 1912).
Kraeplin further added that “from this class of morally defective individuals the majority of professional criminals originate” (pp. 519). These professional criminals were defined as crafty, glib, calculating, and manipulative career criminals with a particular short-sightedness to their acts.

The category of morbid liars and swindlers were also described by Kraeplin as being deceitful, selfish, and deficient in conscience, similar to the category of born criminals, but differed in that they displayed lower levels of impulsivity and aggression and were instead out to con others through skillful manipulation and impression management. This category thus represents a more controlled and “successful” subtype of primary psychopathy as conceptualized today;

“...Thirst for adventures leads these patients to undertake adventurous journeys, during which they employ their gift for lying to make credulous people believe their fabulous tales concerning themselves, their past history, and their future prospects, and to lure money from their pockets. They know how to conceal their real personality so that it is often impossible to expose them. They are especially apt to pose as scions of a famous family, who have been compelled by various circumstances to flee and to conceal themselves, but they have the prospect of securing great riches. They know how to establish the probability of all this by all sorts of dodges, such as forged letters and papers. They swindle every one possible by relating to them pathetic stories. They present themselves as colleagues, turn up under different names, and use high-sounding titles to order merchandise of all kinds...Many patients simply wander about acquiring a livelihood by irregular but respectable occupations, boast and lie for no other purpose than the mere pleasure derived from their falsehoods and impressions which they make on their surroundings.” (pp. 528-529, Kraeplin, 1912).

The remaining categories of pseudoquerulants and unstable criminals were designated those individuals who were primarily driven by an inability to control their urges and emotions, rather than a hunger for material gains. The unstable criminals are described as exhibiting “instability” and “weakness of will” in all domains of life, which is most consonant with the notion of borderline personality disorder (BPD) or unstable forms of secondary psychopathy as described in modern literature;

“In emotional attitude the patients show abrupt changes, at times being elated and confident, and at others spiritless, sensitive, or pessimistic.
They are very easily aroused to enthusiasm, and as readily disheartened. There is usually an increased irritability, sensitiveness, and peevishness. They are offended and dispirited upon slight provocation, are suspicious and prejudiced, but one can easily put them into good humor again. Very often their relations with their relatives become strained. The patients often become dissatisfied and embittered, the cause of which in their opinion never lies in their own behavior, but in the unkindness of their people.” (pp. 521-522, Kraeplin, 1912).

The last category, termed pseudoquerulants, mainly resembles antisocial personality disorder (ASPD) or detached forms of secondary psychopathy as described by later theorists such as Theodore Millon (2011) and Stephen Porter (1996). Kraeplin (1912) described this category as being hostile, egoistic, paranoid, and belligerent individuals who are characterized by primitive defense mechanisms such as denial and projection, have a biased and hostile worldview, and are always out to quarrel with others;

“Judgment is also biased, irrelevant, tends to exaggerations, is in many ways perverse and influenced by intense feelings. Hence persons and conditions are often incorrectly judged...This marked personal influence over apprehension, memory, and judgment arises from an increased emotional irritability. The patients are very passionate and become greatly excited over trifles. They regard every real or apparent infringement upon their rights as gross injustice, which they believe themselves justified in combating with the keenest weapons. They are, therefore, revengeful and persistent in their hostility, regard every opposition as a personal matter, are always ready to impute to their adversaries dishonorable motives, and to carry on their fight in every possible way. Associated with their passion there is a marked egotism. Patients regard themselves as especially intelligent and superior to their environment, and are also disposed to consider their own affairs as matters of public importance — that they themselves are champions of an important cause. Hence even trifling affairs lead to longdrawn-out litigations, because they feel under obligation to fight to the finish for their rights. The combination of sensitiveness with recklessness and arrogance inevitably involves patients in many difficulties and conflicts with their environment.” (pp. 531-532, Kraeplin, 1912).

Continuing in 1925, Wilhelm Reich used Freud’s insights on the trilateral architecture of the human mind (i.e., Id, Ego, Superego) and
introduced the concept of the *impulsive personality*. Rather than detailing specifics of categories, such as his forerunners, Reich attempted a more general description of etiological mechanisms underpinning the development of antisocial traits, such as egocentrism, impulsivity, and aggression. Reich main premise was that impulsive personalities develop because the Superego fails to gain adequate power over the Ego’s “unyielding controls”. Consequently, the individual cannot “adequately restrain the Id’s seduction when faced with instinctual temptations, hence resulting in the free expression of impulses” (pp. 431, Millon, 2011). Reich further differentiated these impulsive personalities from neurotic characters, and contended that these latter personalities are more easily recognized as disturbed, whereas impulsive individuals may present with outward normality and apparent rationality. His theory that antisocial behavior is reflective of a defective or deficient Superego eventually became one of the most popular and influential views of the 20th century regarding the explanation of criminal behavior.

A third prominent theorist during the first decades of the 20th century who also played a key role in furthering the concept of psychopathy was Kurt Schneider. However, in contrast to Kraeplin and in line with earlier conceptions by Koch, the term psychopathic was used by Schneider to describe personality disorders more generally. In 1923, Schneider published his influential book *Die Psychopathischen Persönlichkeiten* (The Psychopathic Personalities) wherein he argued that the psychopathic condition could be defined as an abnormal personality in the broadest sense of the word (Schneider, 1923). In his view, abnormal personalities were individuals who suffered from their own maladaptive ways or caused suffering to society because of it. Schneider also asserted that delinquency is often incorrigible and that many such deviants are constitutionally inclined to progress into criminality from an early age on. Schneider’s portrayal of criminally inclined personalities, termed the *active affectionless psychopaths*, bears close resemblance to the descriptions of Koch’s “psychopathic criminal” and Kraeplin’s “born criminal” and is surprisingly coherent with contemporary views on primary psychopathy;

“We mean personalities with a marked emotional blunting mainly but not exclusively in relation to their fellows. Their character is a pitiless one and they lack capacity for shame, decency, remorse, and conscience. They are ungracious, cold, surly, and brutal in crime...The social moral code is known, understood but not felt and therefore personality is indifferent to it” (cited in Millon, 2011, pp. 430).
As reflected by the checkered history of its conceptualization, up until the mid-20th century, there existed little consensus among scholars on what the term psychopathy entailed or how it differentiated with outwardly similar conditions.

Luckily, in 1941, the American neuropsychiatrist Hervey Cleckley (figure 1.2) released his now seminal work *The Mask of Sanity* in which he provided the scientific and psychiatric community with lively and vivid descriptions of a large number of psychopathic cases, and elaborated his efforts with a list of sixteen traits that he suggested to exemplify the psychopathic personality (see table 1.1). The concept of psychopathy had expanded considerably since Koch's initial insight, and by the mid 20th century encompassed a large diversity of conditions. In response to these inconsistencies, Cleckley strived to clarify and delimitate the psychopathy concept.

Together, his sixteen criteria paint the picture of a personality profile defined by a host of pathological traits across the affective, cognitive, interpersonal, and behavioral domains (see table 1.1). These traits were initially extrapolated from a group of patients on whom the psychological board, at the hospital where Cleckley worked, was unable to reach consensus. These patients did not fit in any of the established diagnostic labels within the neurotic and psychotic domains of psychopathology. The first version of Cleckley's work in 1941 was based mainly on his experience with these adult male and hospitalized psychopaths, but later editions included a much more diverse group of patients such as females, adolescents, and people who had never been admitted to a psychiatric institution (Cleckley, 1941, 1955, 1988).

Cleckley's description and explanation of psychopathy pertains exclusively to primary forms of the disorder as described in modern literature.

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**Figure 1.2**
Hervey Cleckley, M.D.
(1903-1984)
His writings have strongly influenced how we think about this condition today. Cleckley repeatedly emphasized that despite an absence of neurotic or psychotic symptoms, psychopathy results in severely maladaptive behavioral patterns, usually observed only in the most pathological of psychiatric conditions such as schizophrenia.

First and foremost, Cleckley argued that psychopaths appear insouciant and are likely to make a persuasive and distinctly positive first impression of robust mental health. They seem well-adjusted to society, content with themselves, morally reputable in mind, and authentically sincere in conduct. Their opinions on life are accompanied by seemingly sincere emotions. They discuss their ambitions with enthusiasm, convictions with firmness, family life with tenderness and warmth, and their outlook on life with optimism. As Cleckley simply stated; “he looks like the real thing” (pp. 382, Cleckley, 1955).

Moreover, these individuals evince a poise and calmness in their behavior that is generally unseen in psychiatric patients. Signs of delusion, irrational thinking, “nervousness”, or any other psychoneurotic manifestations are bound to be absent, thereby giving off the impression of unshakable confidence, emotional stability, and sound rational insight. More than the average person, the psychopath “is likely to seem free from social or emotional impediments, from the minor distortions, peculiarities, and awkwardnesses that are so common, even among the successful” (pp. 382, Cleckley, 1955). According to Cleckley, psychopathic subjects display “excellent logical reasoning”, and are able to intellectually reason the consequences of antisocial acts, outline admirable long-term plans, and criticize their former mistakes (Cleckley, 1988). Most people who come into contact with a psychopathic individual not only see a healthy, confident, and well-adjusted person but also one with high abilities.

However, looks can be deceiving and in no other psychiatric condition does this saying ring more true than in psychopathy. Cleckley even devoted the title of his book to this most peculiar but defining feature. Beneath the veneer of apparent adjustment and sincerity, the affective landscape of the psychopath is barren, unpassionate, uncaring, and indifferent. His deviant mental landscape is slowly but surely revealed over time when his maladaptive, egocentric, and irresponsible behaviors start to accumulate, and the observer starts to notice the abyss that lies between his own and the psychopath’s understanding of agreements, values, rules, and morality in general.

Psychopaths have no sense of responsibility or loyalty whatsoever,
“no matter how binding the obligation, how urgent the circumstances, or how important the matter” (pp. 385, Cleckley, 1955). They are unreliable, untruthful, and insincere to the extreme, and their profound egocentricity, guiltlessness, and lovelessness extents to all areas of their lives. Cleckley described the egocentricity observed in these individuals as “nothing short of astonishing”. The psychopath’s loyalty to close family members is spurious and conditional, his fondness for friends casual and superficial, and his sexual relations undifferentiated, impersonal, and full of perversions. Although psychopaths might fake affection towards a certain woman or simulate parental devotion to their children, often with particular skillfulness, these affections are always self-serving and dependent on the condition that these external objects satisfy some need of the psychopath himself.

The psychopath’s profound inability for true love and attachment—much more serious than observed in any other condition—is consistent with a general poverty in all of his affective reactions. “Vexation, spite, quick and labile flashes of quasi-affection, peevish resentment, shallow moods of self-pity, puerile attitudes of vanity, absurd and showy poses of indignation, are all within his emotional scale…but mature, wholehearted anger, true or consistent indignation, honest, solid grief, sustaining pride, deep joy, genuine despair, are

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<th>Cleckley’s criteria for the psychopathic personality</th>
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<td>1) Superficial charm/Good “intelligence”</td>
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<td>2) Absence of psychotic symptoms</td>
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<td>3) Absence of “nervousness” and neurotic symptoms</td>
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<td>4) Unreliability</td>
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<td>5) Untruthfulness and insincerity</td>
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<td>6) Lack of remorse or shame</td>
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<td>7) Inadequately motivated antisocial behavior</td>
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<td>8) Poverty in affective reactions</td>
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<td>9) Pathological egocentricity and incapacity for love</td>
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<td>10) Poor judgment and failure to learn by experience</td>
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<td>11) Specific loss of insight</td>
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<td>12) Interpersonal unresponsiveness</td>
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<td>13) Fantastic and uninviting behavior</td>
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<td>14) Suicide rarely carried out</td>
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<td>15) Trivial and impersonal sex-life</td>
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<tr>
<td>16) Failure to follow any life-plan</td>
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Table 1.1
reactions not likely to be found within his scale” (pp. 397, Cleckley, 1955).

Whenever psychopathic subjects are confronted with their deceit or punished for unruly behaviors, they will usually deny all responsibility and redirect the blame onto others. However, they will often go through an idle ritual of saying that much of their trouble is their own fault (Cleckley, 1988). Cleckley particularly stressed the skillfulness and apparent sincerity with which psychopaths can argue and exculpate themselves out of any difficult situation, making an impression of being genuinely sorry, remorseful, and guilty. However, despite their many despicable behaviors, cruel exploits, and senseless destruction of others’ trust, psychopaths are simply impervious to shame or remorse, unable to feel regret or guilt, and blind to such matters as “personal values”.

No matter how revolting their acts, psychopaths manage to keep cool and absolutely free from signs of embarrassment, nervousness, or self-awareness. They could not care less about how their behavior affects others around them, not even family members, spouses, or friends, who often desperately try to help them attain a more adaptive lifestyle and repeatedly come to their aid whenever they are in trouble again. “No matter how well he is treated, no matter how long suffering his family, friends, the police, hospital attendants, and others may be, he shows no consistent reaction of appreciation except superficial and transparent protestations” (pp. 404, Cleckley, 1955).

Finally, psychopaths are described by Cleckley as prone to misconduct but their motivation to act antisocially or deceitfully is often inadequate, senseless, and ill-considered. The psychopath “will commit theft, forgery, adultery, fraud, and other deeds for astonishingly small stakes and under much greater risks of being discovered than will the ordinary scoundrel” (pp. 390, Cleckley, 1955). No matter how many times the psychopath is reprimanded for such misdemeanors, and no matter how difficult these punishments make life (incarceration, institutionalization), psychopaths are unable to change their maladaptive ways. They will squander many good opportunities to make money through a desired job, to achieve rapprochement with family members, or even to attain lasting freedom from prisons or psychiatric wards. Despite their sound and rational reasoning, psychopaths fail miserably in gaining any form of deeper insight into their own condition, rarely seen in even the most disordered neurotic and psychotic patients. Moreover, such a deficiency of insight “is harder to comprehend than the schizophrenic’s deficiency, for it exists in the full presence of what are often assumed to be qualities by which
insight is gained” (pp. 401, Cleckley, 1955).

To explain the etiological mechanisms that undergird a psychopathic personality style, Cleckley introduced the term semantic aphasia. Semantic aphasia entails that although the faculties of language and the ability to speak it remain unimpaired superficially, the ability to truly understand and resonate with what one is saying is absent. Patients with semantic aphasia can converse about moral and ethical constructs, but their words are neither connected to internalized principles or values, nor do they automatically conjure up the appropriate affect, thereby remaining hollow of real content. Thus, semantic aphasia provides an explanation of why psychopaths evince a profound loss of insight into their own emotional deficiency despite their excellent rational skills and intellectual understanding. These patients can eloquently speak the words of regret, guilt, and remorse but do not know, or better said, ‘feel’ their deeper meaning:

“What we take as evidence of his sanity will not significantly or consistently influence his behavior. Nor does it represent real intention within, the degree of his emotional response, the quality of his personal experience much more reliably than some grammatically well-formed, clear, and perhaps verbally sensible statement produced vocally by the autonomous neural apparatus of a patient with semantic aphasia can be said to represent such a patient’s thought or carry a meaningful communication of it” (pp. 440, Cleckley, 1955).

These initial insights of Cleckley were the first stepping stones towards a reliable and valid understanding of the complex disorder that is psychopathy. Cleckley’s work mainly describes the primary psychopathic condition and he had much less to say about the more impulsive and violent secondary psychopath. Despite Cleckley efforts to delimitate the psychopathy construct to include only primary variants of psychopathy, subsequent scholars have again muddied the waters by describing the condition in such broad terms that not only primary but also secondary psychopaths were included. One example is the description given by the McCords. Finally, with the introduction of the DSM, we have even arrived at a state that not only psychopaths but also ordinary criminals are sometimes being diagnosed as being “psychopathic”. I will now discuss these developments in more depth.
1.3 William and Joan McCord: “The Psychopath” (1964)

A subsequent contribution to the conceptualization of psychopathy was made by the sociologist William McCord, and his wife; criminologist Joan McCord. In their book *The Psychopath: An Essay on the Criminal Mind* (1964), the McCords described psychopathy along a number of pathological traits similar to Cleckley, but rather than sixteen, included only five traits to set such individuals apart from the ordinary man and criminal (see table 1.2). They broadly defined the psychopath as “an asocial, aggressive, highly impulsive person who feels little or no guilt and is unable to form lasting bonds of affection with other human beings” (pp. 3).

Comparable to Cleckley, who focused on affective deficiencies to explain the condition, the McCords defined “lovelessness” and “guiltlessness” as being the central differentiating features that set psychopaths apart from ‘ordinary’ criminals;

“Similarly, the psychopathic disorder melds, at the borderline, into other forms of criminal or mentally disordered behavior. Consequently, the much abused term “psychopathic” should be reserved only for those extreme cases upon which most qualified persons would agree. Unless an individuals exhibits the two critical psychopathic traits - guiltlessness and lovelessness - he should not be categorized as psychopathic”

In this short excerpt it is also made clear that the McCords viewed psychopathy

<table>
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<th>McCords conceptualization of “The Psychopath”</th>
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<tr>
<td>1) The psychopath is asocial</td>
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<td>2) The psychopath is driven by uncontrolled desires</td>
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<td>3) The psychopath is aggressive</td>
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<td>4) The psychopath feels little guilt “guiltlessness”</td>
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<tr>
<td>5) The psychopath has a warped capacity for love “lovelessness”</td>
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Table 1.2
as a more severe variant of personality disorder than observed in most mentally
disordered criminals. Indeed, the psychopath is not described by the McCords
as a peculiar and separate class to ordinary criminals, as Cleckley explained the
condition, but as those criminals who, because of a more profound
traumatization, rejection, and abuse in their childhoods, are simply more severely disturbed in their affective development than are other criminals.

Apart from the core personality traits of guiltlessness and lovelessness,
which may also indicate hostile callousness in the context of irritability rather
than emotional insouciance as Cleckley described it, the McCords focused
largely on behavior to define psychopathy. According to them, psychopaths
behave in a “dangerously disruptive manner” and are impervious to rules, no
matter how important. They further argued that much of the psychopath’s
antisocial behavior is caused by a need for immediate gratification and pleasure.
Psychopaths resemble the socially and morally undeveloped infant; “absorbed
in himself, craving only his pleasure” and “preoccupied by his own insecurities”
(pp. 9).

Indeed, while Cleckley focused on neither impulsivity nor aggression to
define psychopathy, the McCords adamantly contended that the psychopath’s
impulsivity and aggression goes far and beyond that of the ordinary criminal
and might be qualified as undifferentiated and “explosive”. They even went as
far as to state that “the psychopath’s asociality often expresses itself in brutal
aggression” (pp. 10, italics added). Thus, in the McCords view, psychopaths are
overtly aggressive and dysfunctionally impulsive by definition. One explanation
for this discrepancy is that Cleckley worked in a psychiatric hospital, whereas
the McCords mainly gained their insights within the criminal justice system.
It is therefore understandable that the McCord’ian definition portrays a more
maladjusted, aggressive, and impulsive pattern.

Other important differences that set the McCord’ian operationalization
apart from the Cleckley’an, is the exclusion of adaptive features such as low
neuroticism, absence of psychotic symptoms, and good “intelligence”. By
failing to include adaptive features of the disorder and by focusing mainly
on outward behavioral expressions rather than latent personality features, the
McCord’ian conceptualization conflates primary and secondary psychopathic
criminals into a single overarching category of overtly violent and impulsive
individuals. In contrast, the Cleckley’an definition pertains to primary
psychopathy more specifically.
1.4 Diagnostic and Statistical Manual of Mental Disorders (1952 - Present)

During the first serious attempt in 1952 to create a categorization system and manual for the classification of psychiatric disorders (Diagnostic and Statistical Manual of Mental Disorders), the new overarching category of *sociopathic personality disturbances* was introduced and subdivided into separate diagnostic entities (1st ed.; DSM-I; American Psychiatric Association -APA-, 1952). One of these subtypes, termed the *antisocial reaction*, most closely resembled the Cleckley’an concept of psychopathy:

000-x61 Antisocial reaction

“This term refers to chronically antisocial individuals who are always in trouble, profiting neither from experience nor punishment, and maintaining no real loyalties to any person, group, or code. They are frequently callous and hedonistic, showing marked emotional immaturity, with lack of sense of responsibility, lack of judgment, and an ability to rationalize their behavior so that it appears warranted, reasonable, and justified. The term includes cases previously classified as “constitutional psychopathic state” and “psychopathic personality”. As defined here the term is more limited, as well as more specific in its application” (pp. 38, APA, 1952).

The intentions of the DSM-I task force were to replace the stained psychopathy term, which had been convoluted by its many divergent operationalizations, with a more neutral one. However, the diagnostic category of “sociopathic disturbance - antisocial reaction” was nearly synonymous with earlier operationalizations of psychopathy. Moreover, the DSM-I referred to these cases as being “previously classified as constitutional psychopathic state and psychopathic personality” (pp. 38). Naturally, in the years following the publication of the DSM-I, there arose increasing confusion regarding the terms sociopathy and psychopathy and both were used interchangeably in scientific literature and clinical practice.

Because of this terminological confusion, the DSM-II (APA, 1968) once more changed the diagnostic label. Instead of sociopathic disturbance, it
was now called *antisocial personality*, but the criteria and description remained largely the same. One small difference is that the DSM-II included “low frustration tolerance” in the description and additionally commented that “a mere history of repeated legal or social offenses is not sufficient to justify this diagnosis” (pp. 43, APA, 1968).

The operationalization of the antisocial personality in subsequent editions, starting with the DSM-III, was chiefly influenced by the work of American researcher Lee Nelkin Robins. In the 1960’s, Robins examined the juvenile antecedents of adult antisocial behavior and detailed these findings in her book *Deviant Children Grown Up* (1966). She had managed to obtain a large number of discarded records from the St. Louis Municipal Child Guidance Clinic, pertaining to delinquent and deviant children who had been admitted some decades earlier, during the 1920’s and 1930’s. After inspecting their detailed nurse and psychologist observations, Robins followed up on these children to study their adult development. She successfully located over 80% of the subjects in their forties and assessed their adult personality and behavioral patterns.

What makes Robins’ contribution so important is that the findings from this *single* follow-up study were used as the prime foundation for the construction of a new diagnostic category in the DSM-III. Undoubtedly in line with the Zeitgeist of the behavioristic era, spanning the last decades of the 20th century, the DSM-III task force concluded that including latent personality traits as criteria invites subjectivity and reduces the reliability of classification. Instead, they now suggested to focus solely on observable behavior. Since Robins’ study adhered to a similar philosophy, and focused largely on the factual observation of behavior, it was considered the perfect study for this aim. In fact, the DSM-III task force voted to base its diagnostic guidelines *exclusively* on the findings of Robins’ follow-up study. Different researchers and scholars protested fiercely to this narrow view, and, during the construction of the DSM-III, a number of alternative models were suggested but to no avail (e.g., Millon, 2011).

With its publication in 1980, the DSM-III introduced the new diagnostic category of *antisocial personality disorder* (ASPD) (APA, 1980). To the annoyance of many scientists and clinicians in the field, this new diagnostic category conflated psychopathy and other types of antisocial deviancy into one overarching diagnostic group of overtly impulsive, aggressive, deceitful, and criminal individuals. As decided during its construction, the criteria for ASPD
excluded latent personality domains such as cognitive abilities (e.g., failure to learn from experience, rationalization of behavior), interpersonal relatedness (e.g., absence of empathy and loyalty), and affective reactions (e.g., emotional immaturity, hedonistic). Making matters even worse, the DSM-III listed a large number of arbitrary transgressions and misdemeanors (e.g., three or more days of lateness or absence from work, three or more traffic arrests, intoxicated driving, pimping, selling drugs, ten or more sexual partners within one year, etc.) under each behavioral criterion (e.g., impulsiveness, irresponsibility etc.) from which the diagnostician had to choose to justify a positive score. These specific misdemeanors and behaviors were directly derived from Robins’ detailed observations.

An important member of the DSM-III task force, Theodore Millon, opposed fiercely to the narrow view of ASPD as being defined through highly specific criminal behaviors gathered in a single follow-up study. In 1978, two years before the DSM-III was to be published, Millon wrote a passionate and well-justified critique at the final draft version of the ASPD diagnostic criteria;

“I have never felt comfortable with the write-up for the antisocial personality disorder. I very much agree with those who contend that the focus given is oriented too much toward the “criminal personality” and not sufficiently toward those with similar propensities who have avoided criminal involvements. More importantly, the write up fails to deal with personality characteristics at all, but rather lists a series of antisocial behavior that stem from such characteristics...The list comprising the antisocial diagnostic criteria is merely a sequence of picayunish specifics (e.g., thefts, three or more traffic arrests, etc.). These details make us delude ourselves that we are a mature empirical science when, in actuality, they derive from the data of one, highly biased study...It is these more general traits that I would like to see us list as diagnostic criteria. If there is some value in specifying particular illustrations to exemplify them, then, and only then, should we list such details” (pp. 424, Millon, 2011).

In line with these critiques by Millon (2011), American psychologist Scott Lilienfeld contended that the DSM-III definition of ASPD as a substitute for Cleckley’an psychopathy presented some serious conceptual issues (Lilienfeld, 1994). He argued that behavior based approaches such as the DSM-III provide “only a handful of indicators for each criterion and do not permit the diagnostician to consider other indicators” (pp. 21). Therefore, when psychopathy is defined through closed concepts, such as
specific behavioral expressions, it presupposes that all psychopaths should show that behavior, or in other terms, that the behavior is directly reflective of the underlying personality. In that sense, the DSM-III commits the error of conflating behavioral expressions such as antisociality with associated personality dispositions to show that behavior, such as low fear or impulsivity. In contrast, personality based approaches acknowledge that similar predispositions, such as lack of fear or tendency to act impetuously, can be expressed through a myriad of ways.

Nonetheless, this trend of focusing on behavior rather than personality in the diagnosis of ASPD, continued in subsequent versions of the DSM, up to the recent DSM-5 published in 2013. Although the DSM-IV (APA, 1994) substantially reduced the number of specific behaviors listed under each criteria, as Millon requested, the general criteria that were listed still pertained largely to observable behaviors while ignoring other domains of personality (see table 1.3 for diagnostic criteria). When referring to ASPD, the DSM-IV even went as far as to state that “this pattern has also been referred to as psychopathy, sociopathy, or dissocial personality disorder” (pp. 702, 4th ed., text rev; DSM-IV-

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<th>DSM-IV/ DSM-IV-TR (axis II) and DSM-5 (section II) criteria for Antisocial Personality Disorder (ASPD)</th>
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A. There is a pervasive pattern of disregard for and violation of the rights of others occurring since age 15 years, as indicated by three (or more) of the following:

1. Failure to conform to social norms with respect to lawful behaviors as indicated by repeatedly performing acts that are grounds for arrest
2. Deceitfulness, as indicated by repeated lying, use of aliases, or conning others for personal profit or pleasure
3. Impulsivity or failure to plan ahead
4. Irritability and aggressiveness, as indicated by repeated physical fights or assaults
5. Reckless disregard for safety of self or others
6. Consistent irresponsibility, as indicated by repeated failure to sustain consistent work behavior or honor financial obligations
7. Lack of remorse, as indicated by being indifferent to or rationalizing having hurt, mistreated, or stolen from another

B. The individual is at least age 18 years.
C. There is evidence of Conduct Disorder with onset before age 15 years.
D. The occurrence of antisocial behavior is not exclusively during the course of Schizophrenia or a Manic Episode.

Table 1.3
TR; APA, 2000), which is a confusing and incorrect statement.

Similar to Lilienfeld, the American behavioral geneticist David Lykken argued that because similar patterns of behavior can arise due to divergent psychological processes, the classification of people based on their antisocial actions rather than their psychological dispositions, even though this is preferable and required in court, is much less attractive to psychiatry or science (Lykken, 2006). Identifying an ASPD with the DSM-III or the DSM-IV is as non-specific and scientifically unhelpful as diagnosing a “neurological disorder” or “infection” in a sick patient (Lykken, 2006). Antisocial behavior can arise through a myriad of etiological pathways that are underpinned by different psychological and biological processes. In fact, violent and antisocial samples are equally diverse as members of the general population (Lykken, 2006). The DSM-IV diagnostic category of ASPD has for these reasons never been attractive as a substitute for psychopathy.

Over the two decades that the DSM-IV (APA, 1994) and DSM-IV-TR (APA, 2000) were in usage, the diagnostic criteria for personality disorders were more generally criticized for disproportionate diagnostic comorbidity, instability of the disorders over time, excessive heterogeneity within diagnoses (e.g., 256 ways to diagnose BPD), lack of model variance, and poor convergent and discriminant validity across personality disorders (Clark, 2007; Skodol et al., 2011; Widiger and Trull, 2007).

Initially, it appeared as though the DSM-5 was going to address many of the substantiated critiques expressed at its predecessors. In response to extensive research, a large range of scholars suggested to improve the assessment of personality disorders by using dimensional constructs (i.e., negative affectivity, antagonism, detachment, psychotism, disinhibition) rather than categorical models, and by including additional items concerning latent personality traits such as self-identity and other-relatedness (Clark, 2007; Millon et al., 2004; Schmeck et al., 2013; Widiger and Trull, 2007).

In line with these suggestions, the DSM-5 personality disorders workgroup proposed an alternative system for the diagnosis of ASPD (see table 1.4). This new model includes both latent personality traits (egocentrism, lack of empathy, incapacity for intimacy, etc.), as well as behavioral expressions. Furthermore, whereas the ‘old’ diagnostic criteria for ASPD effectively classify someone as exhibiting the condition when only three of the seven listed traits are present (see table 1.3), the new diagnostic criteria are more thorough (see table 1.4), and likely to capture exclusively those with serious antisocial
DSM-5 (section III) criteria for Antisocial Personality Disorder (ASPD)

A. Moderate or greater impairment in personality functioning, manifested by characteristic difficulties in two or more of the following four areas:

1. **Identity**: Egocentrism; self-esteem derived from personal gain, power, or pleasure.
2. **Self-direction**: Goal setting based on personal gratification; absence of prosocial internal standards, associated with failure to conform to lawful or culturally normative ethical behavior.
3. **Empathy**: Lack of concern for feeling, needs, or suffering of others; lack of remorse after hurting or mistreating another.
4. **Intimacy**: Incapacity for mutually intimate relationships, as exploitation is a primary means or relating to others, including deceit and coercion; use of dominance or intimidation to control others.

B. Six or more of the following seven pathological personality traits:

1. **Manipulativeness** (an aspect of Antagonism): Frequent use of subterfuge to influence or control others; use of seduction, charm, glibness, or ingratiating to achieve one’s ends.
2. **Callousness** (an aspect of Antagonism): Lack of concern for feelings or problems of others; lack of guilt or remorse about the negative or harmful effects of one’s actions on others; aggression; sadism.
3. **Deceitfulness** (an aspect of Antagonism): Dishonesty and fraudulence; misrepresentation of self; embellishment or fabrication when relating events.
4. **Hostility** (an aspect of Antagonism): Persistent or frequent angry feelings; anger or irritability in response to minor slights and insults; mean, nasty, or vengeful behavior.
5. **Risk-taking** (an aspect of Disinhibition): Engagement in dangerous, risky, and potentially self-damaging activities, unnecessarily and without regard for consequences; boredom proneness and thoughtless initiation of activities to counter boredom; lack of concern for one’s limitations and denial of the reality of personal danger.
6. **Impulsivity** (an aspect of Disinhibition): Acting on the spur of the moment in response to immediate stimuli; acting on a momentary basis without a plan or consideration of outcomes; difficulty establishing and following plans.
7. **Irresponsibility** (as aspect of Disinhibition): Disregard for – and failure to honor – financial and other obligations and commitments; lack of respect for – and lack of follow - through on - agreements and promises.

**Note.** The individual is at least 18 years of age.

Specify if:

**With psychopathic features:**
Specifiers: Low anxiousness (Negative Affectivity domain), Low withdrawal (Detachment domain), High attention seeking (Antagonism domain).

Table 1.4
personality disturbances.

However, the American Psychological Association (APA) Board of Trustees decided at the last moment that both models should be retained in the DSM-5 in order to “preserve continuity with current clinical practice, while also introducing a new approach that aims to address numerous shortcomings of the current approach to personality disorders” (pp. 761, 5th ed.; DSM-5; APA, 2013). While the old model is currently placed in the main section meant for actual diagnosis (section II), the new approach is included in a separate appendix-like section (section III) titled *Alternative DSM-5 Model for Personality Disorders* (APA, 2013). This section is reserved for models and measures that are still “emerging” and need further research to merit replacement of the old diagnostic criteria (APA, 2013).

Preliminary findings indicate that although the DSM-5 section III criteria for ASPD adequately capture the coldheartedness, impulsive antisociality, meanness, and disinhibition domains of psychopathy, and do a better job at indexing core psychopathy traits compared to the DSM-IV-TR and DSM-5 Section II criteria, they still fall short in assessing the boldness/fearless dominance domain of psychopathy (Anderson et al., 2014; Crego and Widiger, 2014; Few et al., 2015; Strickland et al., 2013). Apart from risk-taking and manipulativeness, which are both positively associated to the boldness/fearless dominance domain of psychopathy \( (r \approx 0.40 – 0.70) \), none of the other traits included in the main criteria set correlate significantly with these integral psychopathy facets, and hostility even shows a small negative correlation \( (r \approx -0.15) \) (Anderson et al., 2014; Crego and Widiger, 2014; Strickland et al., 2013). However, regarding the items included in the DSM-5 as psychopathy specifiers, especially low anxiousness and low withdrawal, different studies reported significant correlations with boldness and fearless dominance scores (Anderson et al., 2014; Crego and Widiger, 2014; Few et al., 2015). Nonetheless, the variance of fearless dominance and boldness scores explained by these specifiers is small (only low anxiousness shows a consistent correlation), and it has been suggested to include additional trait facets of the Personality Inventory for DSM-5 (PID-5) as psychopathy specifiers, such as intimacy avoidance, restricted affectivity, grandiosity, and low submissiveness (Anderson et al., 2014; Few et al., 2015; Strickland et al., 2013). In its current form, the DSM-5 section III category of ASPD may pertain particularly to the McCord’ian rather than Cleckley’an conceptualization and more closely relate to secondary rather than primary variants of psychopathy.
In the same year that the DSM-III task force introduced ASPD as a new diagnostic category, the Canadian psychologist and researcher Robert D. Hare rejuvenated the efforts of Hervey Cleckley and developed the Psychopathy Checklist (PCL). The ambition to develop this diagnostic instrument arose when Hare realized that there were no reliable tools to identify psychopathic subjects for his research project. Most psychological tests available at the time relied on self-reporting which Hare considered unreliable in a population bent to present themselves in a better light to achieve prison freedoms or parole (Hare, 1993). Moreover, these self-report questionnaires, including the Socialization Scale of the California Personality Inventory (CPI So), Millon Clinical Multiaxial Inventory Antisocial Personality Disorder (MCMI APD), Self Report Psychopathy Scale (SRP), Minnesota Multiphasic Personality Inventory Psychopathic Deviate (MMPI Pd), and Eysenck Personality Questionnaire Psychoticism Scale do not assess Cleckley’s or primary psychopathy, but rather index criminal behavior, rebelliousness, impulsivity, and aggression as related to antisocial deviancy more generally (Harpur et al., 1989; Lilienfeld and Fowler, 2006).

The characteristic features of psychopathy as included in the PCL were initially extrapolated from the experience and analytic research of Hare with incarcerated criminals, combined with the vivid case examples and sixteen criteria of Cleckley. The first PCL edition consisted of 22 items but after determining the correlation of each item with the cumulative score of the rest, two items that were not sufficiently inter-correlated were dropped in the revised edition; PCL-R (see table 1.5). The PCL-R is ideally scored through both biographical information (collected in institutional files or medical dossiers) and a lengthy semi-structured interview that must be held by a trained interviewer. In circumstances that the interview cannot be held, however, the PCL-R can also be scored by using collateral information alone (Hare, 2003). In sharp contrast to the DSM, which exclusively includes observable behaviors to increase reliability, the high inter-rater reliability of the PCL-R demonstrates that latent personality traits such as callousness, manipulativeness, and
grandiosity can also be reliably assessed (Hare, 2003). Nevertheless, some studies have recently criticized PCL-R inter-rater reliability and argued that it can vary across different contexts (i.e., research vs. therapeutic), especially with regard to items assessing latent personality features (Edens et al., 2010).

After its construction and validation, the PCL-R was quickly adopted world-wide and used in incarcerated settings to assess psychopathic traits and predict dangerousness, recidivism risk, and treatment potential. It is currently recognized as the state-of-the-art diagnostic tool or gold standard for such

<table>
<thead>
<tr>
<th>Psychopathy Checklist-Revised items</th>
</tr>
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<tbody>
<tr>
<td><strong>Factor 1 “Interpersonal &amp; Affective facet”</strong></td>
</tr>
<tr>
<td><strong>Interpersonal facet:</strong></td>
</tr>
<tr>
<td>1) Glib/Superficial charm</td>
</tr>
<tr>
<td>2) Grandiose sense of self-worth</td>
</tr>
<tr>
<td>3) Pathological lying</td>
</tr>
<tr>
<td>4) Conning/Manipulative</td>
</tr>
<tr>
<td><strong>Affective facet:</strong></td>
</tr>
<tr>
<td>5) Shallow affect</td>
</tr>
<tr>
<td>6) Callous/Lack of empathy</td>
</tr>
<tr>
<td>7) Lack of remorse or guilt</td>
</tr>
<tr>
<td>8) Failure to accept responsibility for own actions</td>
</tr>
<tr>
<td><strong>Factor 2 “Antisocial &amp; Lifestyle facet”</strong></td>
</tr>
<tr>
<td><strong>Lifestyle facet:</strong></td>
</tr>
<tr>
<td>9) Parasitic lifestyle</td>
</tr>
<tr>
<td>10) Need for stimulation/ Proneness to boredom</td>
</tr>
<tr>
<td>11) Irresponsibility</td>
</tr>
<tr>
<td>12) Impulsivity</td>
</tr>
<tr>
<td>13) Lack of realistic, long term goals</td>
</tr>
<tr>
<td><strong>Antisocial facet:</strong></td>
</tr>
<tr>
<td>14) Revocation of conditional release</td>
</tr>
<tr>
<td>15) Poor behavioral controls</td>
</tr>
<tr>
<td>16) Juvenile delinquency</td>
</tr>
<tr>
<td>17) Early behavioral problems</td>
</tr>
<tr>
<td>18) Criminal versatility</td>
</tr>
<tr>
<td><strong>Independent items</strong></td>
</tr>
<tr>
<td>19) Promiscuous sexual behavior</td>
</tr>
<tr>
<td>20) Many short-term relationships</td>
</tr>
</tbody>
</table>

Table 1.5 Factor structure derived from Hare, 2003.
purposes, but exclusively for individuals with extensive criminal records such as prison inmates and forensic inpatients (e.g., Vitacco et al., 2005; Westen and Weinberger, 2004). In the last two decades, different PCL-R derivatives have been developed for the assessment of psychopathic traits in other samples such as psychiatric patients and community subjects (PCL-Screening Version = PCL-SV) or in children and adolescents (PCL-Youth Version = PCL-YV). These later instruments are strongly correlated with the PCL-R \((r = 0.80)\), show similar external correlates, and are thus suggested to capture a similar construct (Hart et al., 1995; Neumann et al., 2006). Collectively, I will refer to these tools as the PCL instruments.

The PCL-R contains a total of twenty items (i.e., traits), and the PCL-YV eighteen, while the PCL-SV is a shortened version and only comprises twelve items. These items can be scored on a 0–2 point likert scale (0 = does not apply, 1 = is present but not dominant, 2 = dominant personality trait or behavioral pattern). Because of the high cut-off point for diagnosing psychopathy (minimum score of 30 on the PCL-R and PCL-YV and 18 on the PCL-SV), this diagnosis can only be made when the individual receives a maximum score on at least 75% of the items. In so doing, the PCL instruments only diagnose individuals as psychopathic if the associated pathology is severe and leads to significant social, emotional, interpersonal, and behavioral malfunctioning. This is in sharp contrast to the more lenient and behavior-based DSM criteria. Thus, the prevalence of ASPD as diagnosed with the DSM criteria is high among incarcerated criminals (50-80%), whereas the prevalence of psychopathy as diagnosed with the PCL-R is much lower (around 25%), indicating that PCL-R derived psychopathy is a more specific and severe pattern of antisocial deviancy (Hart and Hare, 1989; Hare, 2003; Widiger et al., 1996).

Since its first introduction, studies with the PCL instruments in different settings and populations have consistently revealed a dominant two-factor-four-facet structure underlying their items (see table 1.5) (Benning et al., 2003; Flores-Mendoza et al., 2008; Hare, 2003; Harpur et al., 1988, 1989; Hill et al., 2004; Kosson et al., 2013; Neumann et al., 2006; Sevecke et al., 2009). Factor 1 summarizes the callous, unscrupulous, and unemotional manipulation of others and overlaps with the Cleckley’an definition, whereas factor 2 contains items relating to an irresponsible, impulsive, and delinquent lifestyle, pertains more closely to secondary psychopathy, and is largely convergent with the traits listed under the label of ASPD/BPD from the
DSM-IV-TR and DSM-5 Section II (Blackburn, 2007; Blackburn et al., 2008; Cooke et al., 2004; Hare, 1991, 2003; Nioche et al., 2010; Skeem et al., 2003, 2007; Verona et al., 2001).

These two factors are moderately related ($r \approx 0.50$), but nonetheless distinct constellations (Hare, 2003; Skeem and Cooke, 2010a). The major difference is that factor 1 is uniquely related to emotional deficiencies, instrumental/goal-directed aggression, and has been associated with both adaptive and maladaptive behavioral patterns (e.g., competitive achievement orientation, emotional resilience to stress and threat, high socioeconomic status, deliberate risk-taking, professional success, and social dominance), whereas factor 2 is uniquely related to a lack of behavioral controls, reactive/impulsive aggression, and has mainly been associated with maladaptive behavioral patterns (e.g., institutional and authority care before the age of 16, violence, expelled from school, impetuous risk-taking, run away from home, psychiatric admission, suicide attempts, being convicted and incarcerated, homelessness, financial problems) (Babiak et al., 2010; Babiak and Hare, 2007; Blackburn et al., 2008; Blair, 2006a, 2006b, 2010; Board and Fritzon, 2005; Coid et al., 2012; Colledge and Blair, 2001; Fowles and Dindo, 2006; Hall and Benning, 2006; Hall et al., 2004; Hare, 2003; Kennealy et al., 2010; Patrick, 2006; Poythress and Skeem, 2006; Reidy et al., 2011; Skeem et al., 2003, 2007; Verona et al., 2001; Woodworth and Porter, 2002).

When both factors are treated as belonging to a singly unitary construct, Hare’s operationalization of psychopathy differs substantially from Cleckley’s and in many ways parallels the McCord’ian definition (aggression, criminality) (Blackburn et al., 2008; Skeem et al., 2003, 2007; Skeem and Cooke, 2010a). One important point of divergence between the PCL-R and the Cleckley’an conceptualization is the source material from which these definitions were originally extrapolated. Although many of Cleckley’s patients were convicted criminals, admitted by the courts on the suspicion of mental illness, his conceptualization was also extrapolated from a great number of psychopathic cases who were neither criminal nor violent, but were admitted by their hopeless families unable to deal with their erratic, reckless, and unreliable behavior. In contrast, the PCL-R items were extrapolated exclusively from incarcerated criminals through statistical analysis rather than qualitative observation. Since the PCL-R items were chosen to index psychopathy as
a unitary construct, and because the initial candidate pool included more deviancy related items that assessed maladjustment, the positive adjustment indicators did not show high internal consistency and dropped out in the selection process (Patrick, 2006; Skeem et al., 2011). As a consequence, the PCL-R does index a uniform construct but this is not Cleckley’an or primary psychopathy. Rather, the PCL-R items are uniformly indicative of deviancy and maladjustment.

Especially factor 2, the “antisocial lifestyle” factor of the PCL-R, includes many behavioral traits indicative of life-course persistent maladjustment that are absent from Cleckley’s list. For example, Cleckley only included one item that assessed overt antisocial behavior, named “inadequately motivated antisocial behavior”. Moreover, when describing this item, Cleckley focused in particular on the underlying motivation for this behavior, rather than asserting that antisocial behavior itself is a defining feature of the condition;

“He will, in fact, commit such deeds [theft, forgery, adultery, fraud] in the absence of any apparent goal at all. Yet we do not find the regularity and specificity in his behavior that is apparent in what is often called compulsive stealing or other socially destructive actions carried out under extraordinarily pressures which the subject, in varying degrees, struggles against” (pp. 390; Cleckley, 1955).

In sharp contrast, the PCL-R includes many antisocial, impulsive, or aggressive behaviors as characteristic of psychopathy, such as revocation of conditional release, poor behavioral controls, impulsivity, juvenile delinquency, early behavioral problems, and criminal versatility. In fact, factor 2 contains more items (ten) compared to factor 1 (eight), indicating that the PCL-R weighs social deviancy and impulsivity more strongly than the interpersonal and affective traits in the diagnosis of psychopathy (Skeem and Cooke, 2010a, 2010b). Different researchers and clinicians have criticized the construct validity of factor 2 in the assessment of psychopathy and have asserted that due to the inclusion of these items, the PCL-R portrays a much more deviant, criminal, and maladjusted pattern than Cleckley initially intended (Cooke and Michie, 2001, Cooke, Michie, and Hart, 2006; Lilienfeld, 1994; Patrick, 2006; Skeem and Cooke, 2010a, 2010b).

Also, despite that it is somewhat tacitly assumed that factor 1, the “interpersonal/affective” factor of the PCL-R, is largely convergent with
Cleckley’s definition, there are still some important differences between both trait constellations. That is, factor 1 includes some malignant personality traits that are absent from Cleckley’s list, such as cunning manipulation and grandiose sense of self-worth, while redefining other items, such as superficial charm, in more devious terms.

For example, explaining the trait “grandiose sense of self-worth”, Hare contends that psychopathic inmates come over as “arrogant, shameless braggarts - self-assured, opinionated, domineering, and cocky” (pp. 38, Hare, 1993). Cleckley did not put much of an emphasis on this aspect of grandiosity, and although he did notice that psychopaths can be utterly self-centered and ignorantly boastful rather than domineeringly arrogant, he also emphasized that their interpersonal conduct is often characterized by a certain agreeableness, cordiality, and apparent sincerity.

In a similar vein, the wording of Cleckley’s criteria differs substantially from that of the PCL-R, even with traits that are named similarly such as “superficial charm”. When reading the corresponding text to the criterion of superficial charm, it can be identified that Cleckley intended this item to be an indicator of positive psychological adjustment (cordial, intelligent, outwardly sincere, likable, well-adjusted, happy, and “looks like the real thing”), whereas the PCL-R wording conjures up the image of a self-absorbed narcissistic individual (glib, insincere, slick, boastful, macho, fake, and a “too good to be true” social presentation) (Patrick, 2006). Indeed, Cleckley coupled this criterion to ‘good intelligence’ (see table 1.1). As discussed, during the development of the PCL-R, Hare removed indicators of positive adjustment because these items did not show high internal correlations. Therefore, for the items to be included in the PCL-R, such as superficial charm, the diagnostic text accompanying such traits would have been written in such a way that they complemented an overall deviant personality.

Furthermore, in removing indicators of positive adjustment, the PCL-R tacitly approves that despite pronounced neurotic symptoms, such as anxiety, depression, and suicidal tendencies, a subject may still be diagnosed as psychopathic as long as he meets most of the other criteria. In accordance, PCL-R total scores show a weak positive relationship to neuroticism ($r = 0.15$), negative emotionality ($r = 0.30$), and even suicide (Lynam and Derevensky 2006, Patrick, 2006; Verona et al., 2001). Traits that are unanimously seen as being antithetical to the construct of primary psychopathy. The fact that the PCL-R does not include any indicator of emotional stability, low neuroticism, good
mental health, or fearlessness is considered by many researchers to impact its construct validity in assessing primary psychopathy in particular (Lilienfeld and Andrews, 1996; Schmitt and Newman, 1999; Skeem et al., 2007; Skeem and Cooke, 2010).

Given these shortcomings, Skeem et al. (2011) and Skeem and Cooke (2010a, 2010b) have recently criticized the PCL-R’s monopoly in the field of psychopathy assessment. While there have been several endeavors to develop psychopathy measures over the years, none have emerged as major alternatives to the PCL-R. Skeem et al. (2011) express concerns that “the measure has, effectively, usurped the construct” and “contributed to mono-operation bias - that is, the error of operationalizing a construct in only one way” (pp. 102). As a consequence of this conflation, the scientific field has learned a great deal about the criminal psychopath as defined by the PCL-R, but not necessarily about the nature and boundaries of the psychopathy construct. Instead of focusing heavily on one instrument to define such a relevant clinical condition with so much impact on society, future studies should also include other instruments and cross validate the correlations of these instruments with external constructs.

In sum, although the specificity of the PCL-R is such that it differentiates psychopathic individuals from the larger and highly heterogeneous group of ASPD diagnosed through the DSM, there is still much heterogeneity in the PCL-R derived psychopathic population. Different researchers and clinicians have suggested and empirically supported that individuals diagnosed as psychopathic with the PCL-R can be further differentiated into primary and secondary subtypes who differ substantially regarding self-esteem, impulsivity, neuroticism, angry hostility, incentive motivation, aggression, externalizing behavior, and harm avoidance (e.g., Blackburn et al., 2008; Hicks et al., 2004; Porter, 1996; Skeem et al., 2003, 2007). Chapter 2 will extensively discuss the heterogeneity observed within PCL-R diagnosed samples and make the crucial distinction between primary and secondary psychopathy.
In light of the criticism that the PCL instruments omit adaptive features of primary psychopathy and weigh social deviancy equally if not more heavily than the interpersonal/affective features, it has been argued that these tools should not be used in community samples. The argument is that such samples are less likely to be characterized by life-course persistent antisociality and more prone to show the adaptive features of the condition (Lilienfeld and Andrews, 1996; Patrick et al., 2009; Skeem and Cooke, 2010a). Moreover, the extensive scoring procedure of the PCL instruments, and their heavy reliance on collateral information, make them less preferable in settings where diagnosticians do not have access to reliable background information, or where time is of the essence (Alterman et al., 1993; Lilienfeld and Andrews, 1996).

In pursuit of an instrument to assess psychopathic traits in more well-adjusted samples, different self-report measures emerged in the decades following the release of the PCL-R (see Lilienfeld and Fowler, 2006). However, these questionnaires including the Self Report Psychopathy Scale (SRP-II) and the Levenson Primary and Secondary Psychopathy Scales (LPSP) are plagued by the recurring issue of construct validity—they index a more global antisociality construct and Machiavellian egocentrism that characterizes secondary psychopathy more specifically, similar to factor 2 of the PCL-R, and do not properly assess key attributes of the primary psychopath, such as low neuroticism, fearlessness, lovelessness, and charm (Lilienfeld and Fowler, 2006; Ross et al., 2009).

To curtail these issues, Lilienfeld and Andrews (1996) decided to introduce a new and empirically founded self-report measure that indexes latent personality traits rather than overt behavior. Since research with the PCL-R indicated that psychopathy is a multidimensional construct, and that different types of psychopathy may exist that are underpinned by divergent etiological pathways, Lilienfeld and Andrews chose to develop their questionnaire without assuming or requiring the items to cohere around a unitary higher order construct (Patrick et al., 2009). Beginning their endeavor, they wrote a list of personality-based items which assessed features of
psychopathy defined as crucial by prominent scholars in the field. Applying an exploratory approach to test construction, Lilienfeld and Andrews (1996) used preliminary responses to the test as a basis for further revisions, thus moving back and forth between the construction and validation of the items.

Out of this endeavor, the Psychopathic Personality Inventory (PPI) was born (Lilienfeld and Andrews, 1996). The PPI initially included 187 items but in order to lower its reading level and eliminate psychometrically problematic or culturally specific items, 33 items were removed and the PPI revised version (PPI-R) now comprises 154 items (Lilienfeld and Widows, 2005). Overall, the PPI shows solid convergent validity when compared to other measures of psychopathy and antisocial deviancy such as the Self-Report Psychopathy Scale-Revised (SRP-R) \((r = 0.91)\), interviewer ratings of the degree of Cleckley’an psychopathy \((r = 0.60)\), PCL-R total scores \((r = 0.39 – 0.58)\), DSM-IV ASPD scores \((r = 0.57)\), and DSM-5 Section III ASPD scores \((r = 0.49 – 0.79)\) (Anderson et al., 2014; Benning et al., 2005c; Berardino et al., 2005; Lilienfeld and Andrews, 1996; Malterer et al., 2010; Poythress et al., 1998, 2010).

When factor-analyzed, the PPI item pool can be organized around eight replicable facets which can be clustered into three superordinate factors (see table 1.6) (Benning et al., 2003; Benning et al., 2005c). The first factor (PPI-I), termed \textit{fearless dominance} includes the three subfacets; social potency (able to manipulate and influence others), fearlessness (a willingness to take physical risks and an absence of anticipatory anxiety), and stress immunity (resilience, emotional stability, and absence of tension in anxiety provoking situations) (Benning et al., 2003, 2005c). The second factor (PPI-II) named \textit{impulsive antisociality} includes four subfacets; Machiavellian egocentricity (a ruthless willingness to manipulate and take advantage of others), impulsive non-conformity (reckless, rebellious, and unconventional), blame externalization (blames others and rationalizes own transgressions) and carefree nonplanfulness (an insouciant attitude toward the future) (Benning et al., 2003, 2005c; Lilienfeld and Fowler, 2006). Interestingly, while the two PCL-R factors are moderately to highly correlated, the overarching PPI factors of fearless dominance (PPI-I) and impulsive antisociality (PPI-II) are found to be weakly correlated (Neumann et al., 2013), with some studies even reporting orthogonality (Benning et al., 2003; Marcus et al., 2013).

Empirical studies with the PPI report that especially the fearless dominance factor (PPI-I) parallels the Cleckley’an conceptualization and is most consonant with notions of primary psychopathy. Indeed, PPI-I is
negatively related to measures of neuroticism, harm avoidance, and social sensitivity, such as anxiety, hostility, depression, emotional lability, empathy, self-consciousness, vulnerability, social withdrawal, and behavioral inhibition (BIS), while showing positive correlations to measures of positive affectivity, reward sensitivity, and self-esteem, such as narcissism, excitement seeking, assertiveness, gregariousness, risk-taking, motivational drive, fun-seeking, and behavioral activation (BAS) (Anderson et al., 2014; Benning et al., 2003, 2005a, 2005b; Blonigen et al., 2005; Derefinko and Lynam, 2006; Douglas et al., 2008; Falkenbach et al., 2014; Maples et al., 2014; Patrick et al., 2006; Ross et al., 2009). Finally, PPI-I is also related to various indicators of adaptive adjustment such as high socio-economic status, conscientiousness, perseverance, achievement, well-being, and educational level (Benning et al., 2003; Maples et al., 2014). This pattern of correlations suggests that the PPI-I properly indexes the low fearfulness, reduced empathy, and high reward-seeking considered to exemplify primary psychopathy, while also capturing some of the more adaptive traits as identified by Cleckley, such as positive emotionality, well-being, resilience, and a sound mind.

Somewhat counterintuitively, PPI-I displays inconsistent associations with the personality domain of agreeableness, which is operationalized through behaviors that are perceived as kind, sympathetic, cooperative, warm, and considerate (Thompson, 2008). Some studies report a weak negative correlation ($r = -0.13$) (Benning et al., 2005c) while others fail to find a significant relationship (Maples et al., 2014; Ross et al., 2009). Furthermore, PPI-I is negatively related to hostility or anger ($r = -0.11$) and only shows a weak positive association with physical aggression ($r = 0.12$) (Anderson et al., 2014; Falkenbach et al., 2014) These findings indicate that individuals who score high on PPI-I might show some narcissistic and dominant traits but are largely neutral regarding interpersonal behavior, being neither cooperative and altruistic nor necessarily hostile and alienated in their social conduct, which is coherent with Cleckley’s initial descriptions. In fact, some studies have even found that the PPI-I is associated with altruistic heroism, and that primary psychopaths may indeed be more likely to behave both heroically and antisocially, dependent on the circumstances (Smith et al., 2013).

Furthermore, Hare’s conceptualization of the core psychopathic personality, reflected by factor 1 of the PCL instruments, captures a more malignant, callous, grandiose, and aggressive pattern than PPI-I. As such, PPI-I correlates modestly to factor 1 of the PCL-R ($r = 0.19 - 0.25$) (Malterer et al., 2006).
## Psychopathic Personality Inventory

<table>
<thead>
<tr>
<th>Facets</th>
<th>Example items (r = reversed scoring)</th>
</tr>
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<tbody>
<tr>
<td><strong>Factor 1 “Fearless Dominance”</strong></td>
<td></td>
</tr>
<tr>
<td>Social Potency</td>
<td>- Even when others are upset with me, I can usually win them over with my charm.</td>
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<tr>
<td></td>
<td>- If I really wanted to, I could convince most people of just about anything.</td>
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<tr>
<td></td>
<td>- People are almost always impressed with me after they first meet me.</td>
</tr>
<tr>
<td>Fearlessness</td>
<td>- I would find the job of movie stunt person exciting.</td>
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<tr>
<td></td>
<td>- Looking down from a high place gives me “the jitters.” (r)</td>
</tr>
<tr>
<td></td>
<td>- I think that it might almost be exciting to be a passenger on a plane that appeared certain to crash, yet somehow managed to land safely.</td>
</tr>
<tr>
<td>Stress Immunity</td>
<td>- When I want to, I can usually put fears and worries out of my mind.</td>
</tr>
<tr>
<td></td>
<td>- When I’m in a frightening situation, I can “turn off” my fear almost at will.</td>
</tr>
<tr>
<td></td>
<td>- I can remain calm in situations that would make many other people panic.</td>
</tr>
<tr>
<td><strong>Factor 2 “Impulsive Antisociality”</strong></td>
<td></td>
</tr>
<tr>
<td>Machiavellian Egocentricity</td>
<td>- I could make an effective “con artist” if the situation required it.</td>
</tr>
<tr>
<td></td>
<td>- If I want to, I can influence other people without their realizing they are being manipulated.</td>
</tr>
<tr>
<td></td>
<td>- I sometimes lie just to see if I can get someone to believe me.</td>
</tr>
<tr>
<td></td>
<td>- To be honest, how much I like someone depends a lot on how useful that person is to me.</td>
</tr>
<tr>
<td>Impulsive Non-conformity</td>
<td>- I’ve never really cared much about society’s so called “values of right and wrong.”</td>
</tr>
<tr>
<td></td>
<td>- I would enjoy hitch-hiking my way across the United States with no prearranged plans.</td>
</tr>
<tr>
<td></td>
<td>- I get restless and disappointed if my life becomes too routine.</td>
</tr>
<tr>
<td>Blame Externalization</td>
<td>- People have often criticized me unjustly (unfairly).</td>
</tr>
<tr>
<td></td>
<td>- I generally feel that life has treated me fairly. (r)</td>
</tr>
<tr>
<td></td>
<td>- I feel that very few people have ever understood me.</td>
</tr>
<tr>
<td>Carefree Nonplanfulness</td>
<td>- I weigh the pros and cons of major decisions carefully before making them. (r)</td>
</tr>
<tr>
<td></td>
<td>- I often make the same errors in judgment over and over again.</td>
</tr>
<tr>
<td></td>
<td>- I generally prefer to act first and think later.</td>
</tr>
<tr>
<td><strong>Factor 3 “Coldheartedness”</strong></td>
<td></td>
</tr>
<tr>
<td>Coldheartedness</td>
<td>- I am a guilt-prone person. (r)</td>
</tr>
<tr>
<td></td>
<td>- I am so moved by certain experiences (e.g., watching a beautiful sunset, listening to a favorite piece of music) that I feel emotions that are beyond words. (r)</td>
</tr>
<tr>
<td></td>
<td>- Seeing a poor or homeless person walking the streets at night could really break my heart. (r)</td>
</tr>
</tbody>
</table>

Table 1.6 The PPI Factors and corresponding facets. Factor structure derived from Benning et al., 2003.
2010; Poythress et al., 2010), which is mainly explained by the unique variance in the interpersonal facet \((r = 0.3)\), while showing no relationship to the more malevolently defined affective facet (Benning et al., 2005a).

Because PPI-I is closely associated with narcissism \((r = 0.52)\), and does not correlate highly with antisocial behavior, different researchers have questioned its construct validity in assessing core psychopathy traits and in differentiating psychopathic from nonpsychopathic subjects (Lynam and Miller, 2012; Maples et al., 2014; Neumann et al., 2013). However, Maples et al. (2014) reported that compared to other questionnaires specifically designed to index narcissism (i.e., narcissistic personality inventory-16), PPI-I showed much stronger negative associations to neuroticism, sensitivity to punishment, and negative affect, while also showing higher positive correlations with extraversion, openness, positive affect, and mental health. Furthermore, as discussed above, deviant personality traits, such as criminality, impulsivity, and aggression, are not integral to psychopathy (Cleckley, 1941; Cooke and Michie, 2001; Poythress and Hall, 2011; Skeem and Cooke, 2010). Nonetheless, one trait that is consistently related primary psychopathy, but does not correlate to PPI-I, is moral utilitarianism (Gao and Tang, 2013). Despite this shortcoming, PPI-I may currently be the most valid self-report scale to assess primary psychopathic features as introduced by Cleckley and differentiate such individuals from secondary psychopaths and other personality disordered groups (narcissistic, ASPD) (see also Cox et al., 2013).

Similar to factor 2 of the PCL-R, PPI-II mainly comprises items that are indicative of maladjustment to society and predictive of behavioral deviancy. PPI-II has been associated with impulsivity, aggressiveness, deceitfulness, irresponsibility, anxiousness, antisocial and criminal behavior, substance abuse problems, suicidal ideation, and high levels of both externalizing and internalizing symptomatology (Benning et al., 2003, 2005a, 2005b; Blonigen et al., 2005; Derefinko and Lynam, 2006; Douglas et al., 2008; Patrick et al., 2006; Ross et al., 2009). Similar to factor 2, PPI-II may index personality features that are more closely related to secondary variants of psychopathy (Cox et al., 2013; Hicks et al., 2012). However, contrary to factor 2, PPI-II adopts a personality based approach and does not directly assess deviant or criminal behavior, but rather gauges the presence of personality traits underlying such a lifestyle, including impulsivity, recklessness, rebelliousness, and selfishness. As such, factor 2 is modestly related to the PPI-II \((r = 0.35)\) (Benning et al., 2005a; Malterer et al., 2010; Poythress et al., 2010).
The third factor consists of the independent facet of coldheartedness (unsentimentality and a lack of imaginative capacity), which was initially meant to index callousness, lovelessness, and absence of empathy (Benning et al., 2003, 2005c). However, it has been hypothesized that because nearly all items of the coldheartedness scale are reverse keyed, the item content reflects sentimentality, imaginativeness, and affective responsiveness, more so than callousness or cruelty (Benning et al., 2003). Indeed, coldheartedness is most strongly related to the personality domain openness to experience, especially one of its facets termed “absorption”. Absorption primarily assesses aspects of consciousness rather than socio-emotional functioning, and refers to the degree to which people can lose themselves in tasks, are hypnotically suggestible, or become sentimental from aesthetics and art. The coldheartedness facet of the PPI may thus index propensities that are separate from the other subscales, and perhaps unrelated to both primary as well as secondary psychopathy.

Finally, there are some notable short-comings when using self-report measures in psychopathic populations that should be mentioned here (see also Lilienfeld and Fowler, 2006). First, psychopaths lie and are good at impression management. In addition, the nature of their lies is bound to be influenced by situational variables (e.g., motivated to give a good impression for a job interview but a disturbed impression for an insanity plea). Hare (1993) even described a psychopathic inmate who had obtained his own MMPI manual, scoring keys, and different books on its interpretation in order outsmart the psychologist and give the psychological profile that was needed for the situation (e.g., depressed and anxious at admission but gradually increasing in mental health as time passed thus reflecting treatment progress). Second, psychopaths have no insight into the seriousness of their own condition and might thus fail to grasp that they are unemotional or to understand the impact of their behavior on others. Indeed, Lilienfeld and Fowler (2006) argue that because psychopathic individual have little experience with emotional processes or moral feelings such as guilt, they may mislabel certain feelings;

“they may learn to refer to “guilt” when they experience negative affect after committing an antisocial act and receiving punishment for it, even though they are actually experiencing regret (displeasure upon getting caught) rather than remorse. From this perspective, psychopaths’ reporting of many emotions may be inaccurate but not insincere.” (pp. 110, Lilienfeld and Fowler, 2006).
Christopher Patrick: 
The Triarchic Model (2009 - Present)

In response to the checkered history of the psychopathy construct and because of its multidimensional nature, Christopher Patrick and his two colleagues Don Fowler and Robert Krueger (2009) asserted that psychopathy is best conceptualized through distinct phenotypic domains, rather than as a unitary construct. Since there is still much uncertainty on the development of psychopathy, its various subtypes, and its expression in children, future investigations into its etiology may benefit by deconstructing psychopathy into more elemental phenotypic constructs that have clear psychological and neurobiological referents (Patrick et al., 2009).

In an attempt to integrate historical conceptualizations with modern operationalizations, Patrick et al. (2009) identified three recurring themes in the literature; *boldness*, *meanness*, and *disinhibition* (see figure 1.3). These three constructs, although interrelated, can be measured and understood separately as they reflect separate developmental processes and are phenotypically distinct. Thus, these phenotypic traits are proposed not as pertaining to a unitary higher order construct, but as configural building blocks expressed in varying degrees by different psychopathic individuals (Skeem et al., 2011). To operationalize these three constructs, Patrick (2010) developed the The Triarchic Psychopathy Measure (TriPM), which is a 58-item self-report inventory.

*Boldness* is described by Patrick et al. (2009) as a benign and “pure” phenotypic expression of genotypic fearlessness. It is defined as the nexus of fearless dominance, low anxiety, and thrill/adventure seeking (Skeem et al., 2011). Boldness may be expressed through adaptive features, such as emotional stability, low internalizing symptomatology, leadership/authority, social poise, assertiveness, persuasiveness, bravery, and venturesomeness, but also through less adaptive proclivities, such as narcissism, low BIS, manipulativeness, risk-taking, and thrill seeking (Anderson et al., 2014; Patrick et al., 2009; Sellbom and Phillips, 2013; Stanley et al., 2013; Strickland et al., 2013). Boldness is further described as integral to the Cleckley’an conceptualization of primary psychopathy and is largely parallel with the fearless dominance factor of the PPI-R (PPI-I) (Patrick et al., 2009; Skeem et al., 2011). Accordingly, boldness
is most strongly related to PPI-I ($r = 0.61 - 0.77$), while showing no significant associations to PPI-II or the separate facet of coldheartedness (Anderson et al., 2014; Sellbom and Phillips, 2013). In other words, boldness is phenotypically distinct from disinhibition, impulsivity, or callousness, and emergent from different etiological mechanisms (i.e., fearlessness in boldness, disaffiliation in callousness, and low self-control in disinhibition) (Anderson et al., 2014; Patrick et al., 2009).

However, it must be noted that the construct validity of boldness as operationalized by the TriPM is not entirely clear, and it may be questioned whether this scale is uniquely related to primary psychopathy. Since most items on the boldness scale are to some degree indicative of admirable personal traits, such as resilience (“I am well equipped to deal with stress”) and self-confidence (“I don’t think of myself as talented”—reverse keyed), but also admirable social traits, such as persuasiveness (“I have a knack for influencing people”), poise (“it’s easy to embarrass me”—reverse keyed), and leadership (“I’m a born leader”), it is imaginable that narcissistic individuals would also show high scores on this dimension while not necessarily being psychopathic. Indeed, the boldness scale has been associated quite substantially with narcissism ($r = 0.64$) (Sellbom and Phillips, 2013). This is somewhat expected since primary psychopaths are by definition narcissistic due to a profound cognitive and

**Figure 1.3** The Triarchic conceptualization of psychopathy (Patrick et al., 2009).
affective egocentrism (Hare, 1993). However, the opposite is not true, and although narcissists like to view themselves as fearless, resilient, revolutionary, and influential, their self-confidence is often not based in reality. In sharp contrast with primary psychopathy, narcissists can be quite neurotic, are unable to handle criticism, desperately seek for attention, and have an obsessive need to validate their self-worth (Miller et al., 2013; Vaknin and Rangelovska, 2010; Wright et al., 2013). It is thus paramount that future studies examine to what degree boldness is able to separate narcissistic from primary psychopathic individuals.

Meanness is defined as being similar to boldness regarding underlying genotypic dispositions of fearlessness, but arises when this temperament is additionally met with genotypic disaffiliation or an abusive and neglectful environment which may push “genotypic fearlessness in the direction of phenotypic meanness” (pp. 932, Patrick et al., 2009). Characteristic behavioral manifestations of meanness include arrogance and verbal derisiveness, defiance of authority, lack of close personal relationships, aggressive competitiveness, physical cruelty to animals and people, instrumental aggression, strategic exploitation of others for gain, and thrill seeking through destruction (Patrick et al., 2009; Skeem et al., 2011). For example, both boldness and meanness are associated with low BIS scores but meanness is additionally related to a more severe lack of empathy, Machiavellianism, and higher levels of antisociality (Sellbom and Phillips, 2013; Stanley et al., 2013). Furthermore, empathy or empathetic concern show a weak negative but non-significant association to boldness ($r = -0.15$) but are significantly related to meanness ($r = -0.60$) (Sellbom and Phillips, 2013; Stanley et al., 2013). Also, contrary to boldness, meanness is related to the coldheartedness ($r = 0.67$) and the impulsive antisociality factor (PPI-II) of the PPI-R ($r = 0.60$), callousness as measured through different questionnaires ($r = 0.60$), and the affective and antisocial facets of the PCL-R ($r = 0.20$) (Patrick, 2010; Sellbom and Phillips, 2013; Stanley et al., 2013).

Therefore, whereas boldness was constructed to assess core psychopathy features as defined by Cleckley, meanness is intimately connected to antisocial attitudes and behavior, and more closely related to conceptualizations of psychopathy derived from criminal offender samples, such as those by Hare and the McCords (Patrick et al., 2009).

As discussed, due to the fact that the PCL-R was extrapolated from
offender samples, it is uniformly indicative of maladjustment and antisocial deviancy. Thus, factor 1 of the PCL-R naturally indexes a more malignant phenotypic expression of genotypic fearlessness (e.g., callousness, cunning, and lovelessness) that is intimately linked to an antisocial lifestyle (factor 2), and more closely related to meanness, rather than boldness. More specifically, when factor 1 is subdivided into its facets, the interpersonal facet shows the strongest associations with boldness \((r = 0.27)\), whereas the affective facet shows the highest correlations to meanness \((r = 0.25)\) (Patrick, 2010).

However, meanness is not exclusive to primary psychopathy and may also arise in neurotic and irritable individuals if exposed to sufficient levels of adversity, abuse, and trauma (secondary psychopathy). Indeed, meanness has been positively associated with hostility, anhedonia, depressivity, social withdrawal, and suspiciousness (Strickland et al., 2013). Constructs that are intimately connected to emotionality. Related to this suggestion, Patrick et al. (2009) assert that phenotypic meanness can manifest as a predatory and unemotional pursuit of self-serving goals in the context of a fearless temperament (primary psychopathy), but can also manifest as hostility, anger, and reactive aggression in the context of an irritable temperament (secondary psychopathy). Therefore, similar to boldness, the meanness scale may not pertain uniquely to primary psychopathy, and a variety of personality styles, including secondary psychopaths, may show high scores on this dimension.

Disinhibition is defined by Patrick et al. (2009) as the “nexus of impulsivity and negative affectivity” (pp. 925, italics added). Disinhibition is originally described through behaviors that are closely related to neuroticism, such as irritability, oppositionality, substance abuse, emotional dysregulation, anger, and hostility. Accordingly, it is positively related to neuroticism \((r = 0.32)\) (Stanley et al., 2013). It is, thus, unclear how this dimension relates to primary psychopathy, which is characterized by fearlessness and low neuroticism, rather than to secondary psychopathy more specifically. Patrick et al. (2009) assert themselves that “contemporary researchers in the field would generally not view disinhibition or externalizing as equivalent to psychopathy”, and, “it is when externalizing tendencies are coupled with dispositional boldness or meanness that a diagnosis of psychopathy would be considered applicable” (pp. 926).

Reviewing the Triarchic Model, Skeem et al. (2011) also assert that “disinhibition occurring in the context of psychopathy may have a distinctive appearance and perhaps arise from different sources, compared to disinhibition
per se” (pp. 106). Indeed, because strong emotional reactions can fuel impulsive and aggressive behaviors, disinhibition in the context of primary psychopathy may be predominantly related to cognitive and motivational risk endophenotypes that impair self-control and result in impetuous risk-taking behaviors (i.e., hypersensitivity to anticipated rewards, need for excitement/novelty, inability to inhibit dominant behavioral tendencies, frustration intolerance, hyposensitivity for potential punishment, and inability to plan ahead) (Buckholtz et al., 2010; Gao et al., 2011; Gao and Raine, 2010; Hartzler and Fromme, 2003; Ishikawa et al., 2001; Snowden and Gray, 2010; Swogger et al., 2010).

Unfortunately, these risk factors are insufficiently reflected in the TriPM and thus, similar to the boldness and meanness scales, the construct validity of the disinhibition scale when applied as a measure of primary psychopathy is unclear. For example, nearly all items of the TriPM disinhibition scale are ambiguous and index short-sighted behavior that can arise due to negative urgency and hostile impulsivity (more closely associated with secondary psychopathy and neuroticism), as well as reward hyperfocus and impetuous risk-taking (associated with psychopathy in general). Some items even have an emotional connotation, such as “people often abuse my trust”. In accordance, the disinhibition scale has been equally strongly associated to anxiousness, emotional lability, separation insecurity, anhedonia, and depressivity (all $r \approx 0.30 - 0.40$), as to risk-taking ($r \approx 0.35$) (Anderson et al., 2014; Strickland et al., 2013). It has been demonstrated that psychopathy is mainly associated with risk-taking, even in the face of punishment, but not so much with other forms of impulsivity (Takahashi et al., 2014). It would thus have been more appropriate to include items such as “when I focus on something I want, I lose track of the potential risks involved” or “I cannot let go of a goal once I have set my mind on it, regardless of whether I hurt other people in the process” or “sometimes I like to stir up some chaos just for the sake of sensation”, in order to specifically assess the disinhibition as related to primary psychopathy rather than disinhibition more generally related to neuroticism and secondary psychopathy.
CHAPTER 2
TOWARDS A NEW CONTINUUM OF PRIMARY AND SECONDARY PSYCHOPATHY
A Matter of Deficiency versus Disturbance
ABSTRACT

Psychopathic individuals identified through contemporary instruments vary considerably in personality and etiological background, which creates confusion in practice and inconsistency in data. The goal of this chapter is to clarify this heterogeneity and introduce a new typology to narrow down psychopathic subcategories. Towards this end, I will review cluster-analytic studies to identify more homogeneous categories. In line with the existing literature, the psychopathic population is broadly divided into a primary and secondary category which diverge crucially in personality and etiology. Secondary psychopathy may be situated on a continuum with the antisocial or borderline personality disorder because it represents a more severe but not qualitatively different form of environment-contingent emotional disturbance (e.g., prefrontal cortex malfunctioning, serotonin deficiency, impaired predictive allostasis), whereas primary psychopathy is an unique condition that is strongly rooted in a constitutionally defined emotional deficiency (e.g., limbic hyporesponsivity, serotonin hyperstability, dampened reactive allostasis). However, both primary and secondary psychopathic samples show high levels of within-group heterogeneity and may be placed on their own continuum of, respectively, self-control and affect instability. Concluding, a new continuum will be introduced of primary psychopathy (controlled to disinhibited) and secondary psychopathy (detached to unstable) and it will be discussed how these subtypes may differ on a number of psychopathy measures, personality profiles, and endophenotypic pathways.

The psychopathic categorizations and deduced hypotheses stated in this chapter have been peer-reviewed and published as; Yildirim, B.O., & Derksen, J.J.L. (2015). Clarifying the Heterogeneity in Psychopathic Samples; Towards a New Continuum of Primary and Secondary Psychopathy. Aggression and Violent Behavior, 24, 9-41.
W hen Koch first introduced the concept of the habitual criminal at the end of the 19th century, he made an interesting proposition that is still highly relevant today. In his essay titled *Die Frage Nach Dem Geborenen Verbrecher* (The Question About The Born Criminal, 1894), Koch posed the philosophical question whether habitual criminals are born or made. His premise was that all psychopathic inferiorities, including those leading to “moral insanity”, can be fundamentally divided into separate groups based on how their antisocial pathology had developed; the “mentally healthy” and the “mentally abnormal”. According to Koch, the mentally abnormal were characterized by a congenital weakness which had provoked them into a criminal lifestyle, whereas the mentally normal types had largely acquired their inclination towards crime through destructive experiences;

“It is true that the childhoods of some psychopaths were characterized by material and emotional deprivation and physical abuse, but for every adult psychopath from a troubled background there is another whose siblings are normal, conscientious people with the ability to care deeply for others” (Robert Hare)

“Insanity that leads to crime is either constitutional or acquired, in the latter case due to some environmental impact in an otherwise healthy individual...I do not understand why so much literature establishes the existence of constitutional Moral Insanity (idiocy) while the existence of acquired Moral Insanity is largely denied” (pp. 37, Koch, 1894).
His assertion that some criminals are born and others made is comparable to our contemporary differentiation between primary and secondary psychopathy. Koch was thus among the first to incite the question of nature versus nurture when analyzing the antecedents of antisocial behavior.

The term *sociopathy* was first introduced by the German Psychiatrist Karl Birnbaum in 1909, who contended that the adjective of “socio” rather than “psycho” is a more appropriate description of the majority of criminal cases (Millon, 2011). Birnbaum proposed that not all delinquents are constitutionally inclined to criminality, but that many such behaviors reflect the operation of immature mental states, or acquired patterns of conduct that have evolved primarily as a reaction to destructive societal experiences. Thus, similar to Koch, Birnbaum suggested we should clearly differentiate etiological processes rooted in either nature or nurture when analyzing immoral behavior. However, as Koch had already complained, the notion that social conditioning plays an important part in the development of antisocial behavior faded to the background in light of the strong prevailing Zeitgeist that such behaviors are primarily determined by constitution. A view that was inextricably linked to the concept of moral insanity as introduced by Prichard some 75 years earlier.

In the same year that Cleckley published his important work on the psychopathic personality, another significant contribution to the conceptualization and categorization of psychopathy was made by the American psychiatrist Benjamin Karpman (1941). Karpman argued for the need to differentiate subtypes of psychopathy based on etiological antecedents. He recognized that phenotypical similarities, such as egocentrism, callousness, deviousness, and antisociality, can arise due to differing etiological pathways, mediated in varying degrees by constitutional or social influences. This theory fitted nicely with earlier distinctions made by Koch and Birnbaum:

“Symptomatic psychopathy includes all those reactions that on the surface bear close resemblance to what we call psychopathic behavior, except that in these cases it is not difficult to elicit psychogenesis which is behind the psychopathic indulgence; idiopathic psychopathy (anethopathy) includes psychopathic reactions for which it is impossible to find any psychogenic factors” (abstract, Karpman, 1941).

In other words, Karpman’s *idiopathic psychopathy* referred to those with a heritable affective defect that had hindered conscience formation. As Karpman put it, these individuals are characterized by the “instinctive emotional
organization of a subhuman animal” (p. 533)—a fearless and predatory character. In contrast, *symptomatic psychopathy* referred to those who have mainly become psychopathic due to an environmentally acquired affective disturbance that had skewed conscience formation and resulted in deep-seated neurotic conflicts (Karpman, 1941). Therefore, the callousness and hostility observed in symptomatic psychopathy was seen as an emotional adaptation to parental rejection and abuse, and therefore more amenable for treatment (Karpman, 1941). Karpman’s theoretical insights are impressively consistent with empirical research from the last decade.

In 1975, the British psychologist Ronald Blackburn subjected the personality profiles (assessed with the Minnesota Multiphasic Personality Inventory - MMPI) of non-psychotic male offenders to cluster analysis and identified two subtypes of psychopathy that resembled the idiopathic and symptomatic groups of Karpman. The two groups with equally pronounced psychopathic traits displayed significant differences on a number of personality measures, with the most notable differences being found regarding neuroticism. The psychopathic group with low levels of neuroticism was labeled by Blackburn as exhibiting *primary psychopathy* and the other group with high levels of anxiety and depression was labeled *secondary psychopathy* (Blackburn, 1975; Blackburn et al., 2008; Lykken, 1995; Skeem et al., 2003, 2007).

In the years following Blackburn’s empirical identification, both Don Fowles (1980) and David Lykken (1995) elaborated on the concepts of primary and secondary psychopathy, and focused on the etiological mechanisms underpinning each disorder. Their insights were based on the biopsychological theory of personality proposed by Gray (1987). This theory posits that humans have three separate systems that interactively control affective and motivational processes; two opposing motivational influences that mediate behavioral reactions to environmental cues and a fight-flight-freeze system responsible for organizing behavior in response to unconditioned stimuli of salience. One motivational influence is the behavioral inhibition system (BIS), which serves to increase arousal to cues of punishment or non-reward and inhibit behavior to such contingencies (i.e., passive avoidance). The other system is termed the behavioral activation system (BAS) and serves to increase arousal to reward-anticipatory cues thereby initiating behavioral approach modules to such contingencies (e.g., incentive motivation). All three systems are paramount for evolutionary fitness since organisms need to navigate their world in a manner such that they avoid potential pain (e.g., predators, danger), approach pleasure
(e.g., eating, sexual intercourse), and react appropriately to immediate threats and challenges in order to survive and reproduce.

According to Lykken (1995) and Fowles (1980), primary psychopathy arises mainly due to an hyporesponsive fight-flight-freeze system (fearlessness) and low levels of BIS (low anxiety, low avoidance), thereby resulting in attenuated appraisal and low avoidance of danger, risk, and otherwise aversive events. Conversely, secondary psychopathy evolves primarily out of an unusually active BAS, thereby increasing the risk of impulsive responding to reward-anticipatory cues (impulsive, risk-taking). Lykken (1995) further proposed that both a low BIS but normal BAS, as well as a normal BIS but high BAS, can lead to troubles in avoiding potential punishment. However, the primary psychopath, due to his low BIS, would be expected to additionally show a low stress and anxiety sensitivity, whereas the secondary psychopath would be expected to show high scores on neuroticism and anxiety because “the lure of temptation would be likely to cause him to select a stressful and disquieting lifestyle” (pp. 122).

Finally, the forensic psychologist Stephen Porter (1996) also developed an explanatory theory on the differences between primary and secondary psychopathy. In his essay *Without Conscience or Without Active Conscience?* Porter argues that two distinct etiological pathways, one primarily constitutional and one environmental, can “culminate phenotypically as a psychopathic personality” (pp. 180). Similar to Blackburn and Lykken, Porter’s proposition is that the fundamental psychopath is born without the capacity for strong affect. In contrast, however, Porter described secondary psychopathy as a form of dissociative disorder rather than a personality disorder. He hypothesized that secondary psychopaths have experienced a “de-activation” or dissociation of affect. That is, in response to repeated rejection and abuse, he argued, the youngster learns to de-activate his basal inborn capacity towards love, empathy, and attachment in order to protect himself from further pain. This brings about a dissociation of cognition and affect, and skews the development of conscience. Whereas most scholars argued that psychopathic subtypes are likely to differ regarding neuroticism and impulsivity, Porter described the fundamental and secondary psychopath as phenotypical twins. Porter argued that, rather than showing a propensity towards neuroticism, the secondary psychopath is also affectionless due to the dissociation of emotion and cognition.
2.1 The Levenson Self-Report Psychopathy Scale (LSRP): A Valid Tool for Differentiating Primary from Secondary Psychopathy?

To assess primary and secondary forms of psychopathy, Levenson and colleagues developed the Levenson Self-Report Psychopathy Scale (LSRP) which is a 26-item self-report measure designed to assess psychopathic traits in community samples (Levenson et al., 1995). Because of its easy administration and scoring, the LSRP has gained much popularity in the differential assessment of primary and secondary psychopathy and has become common practice for such purposes. However, there are some notable issues with the construct validity of this instrument, especially with regard to its primary psychopathy scale (PP scale).

Rather than assessing emotional deficiencies, the PP scale describes an egocentric, callous, and manipulative mindset more globally (i.e., Machiavellianism), which is related to both primary and secondary psychopathy (Ali et al., 2009; Karpman, 1941; Kämmerle et al., 2014; McHoskey et al., 1998; Ross et al., 2009; Seibert et al., 2011; Sellbom, 2011; Skeem et al., 2003). Furthermore, the PP scale has been positively associated with traits that are antithetical to primary psychopathy, such as stress reaction ($r = 0.09$), anxiety ($r = 0.16$), trait neuroticism ($r = 0.17$), attachment anxiety-avoidance ($r = 0.18$), borderline personality disorder (BPD) ($r = 0.27$), cluster C personality traits ($r = 0.16$), and emotional dysregulation ($r = 0.23$) (Burns et al., 2015; Levenson et al., 1995; Miller et al., 2008; Salekin et al., 2014). In addition, the PP scale is also associated with an aggressive humor style, reactive aggression, angry hostility, and feeling socially excluded—all indicating a particular bitterness and neurotic antagonism towards others (Fanning et al., 2014; Masui et al., 2013; Miller et al., 2008; Seibert et al., 2011). Finally, PP is more strongly related to factor 2 and facets of PPI-II (especially Machiavellian egocentricity) rather than factor 1 and facets of PPI-I (Brinkley et al., 2001; Lilienfeld et al., 2004; Ross et al., 2009; Seibert et al., 2011; Sellbom, 2011). These results suggest that the PP scale might be a better indicator of secondary psychopathy, and Machiavellian egocentricity more generally, rather than primary psychopathy more specifically. Indeed, the PP scale was associated with
reduced serotonergic functioning, which is related to neuroticism and reactive aggression and specifically characterizes secondary psychopathy (Fanning et al., 2014; Yildirim and Derksen, 2013; but see chapter 3). Nevertheless, primary psychopaths, especially those who are more disinhibited, disaffiliated, or violent, are likely to also show high scores on the PP scale.

Conversely, the secondary psychopathy scale (SP) assesses a self-defeating, impulsive, and disillusioned mentality more generally, and has been closely associated with BPD ($r = 0.44$), emotional dysregulation ($r = 0.70$), trait anxiety ($r = 0.69$), state anxiety ($r = 0.28$), and neuroticism ($r = 0.43$) more specifically (Ali et al., 2009; Burns et al., 2015; Miller et al., 2008; Ridings and Lutz-Zois, 2014). Making matters more confusing, the SP scale has also been closely related to Machiavellianism (Ali et al., 2009; Jakobwitz and Egan, 2006; McHoskey et al., 1998; Seibert et al., 2011), and shows similar associations with criminality and violence as the PP scale (Brinkley et al., 2004), which calls into question the discriminant validity between the SP and the PP scale.

One possibility is that the SP scale indexes a more fearful and dysregulated subtype of secondary psychopathy associated with BPD and ASPD pathology and high anxiety. Conversely, the PP scale may capture both a more detached subtype of secondary psychopathy, which is mainly related to NPD and ASPD pathology, as well as disinhibited subtypes of primary psychopathy (see synthesis section for typology). Therefore, I will not rely on data with the LSRP scale to differentiate primary from secondary psychopathy. Instead, to validly identify primary and secondary psychopathic subtypes and infer their external correlations, I will focus below on cluster-analytic studies since these usually include additional measures of neuroticism and anxiety to differentiate these conditions.

2.2 Differential Diagnostic Imperatives: Primary versus Secondary Psychopathy

The PCL-R has greatly facilitated research into the psychopathic personality. Nonetheless, a less desirable side effect has been the conflation of the PCL-R with the construct of psychopathy (Skeem and Cooke, 2010a; Skeem et al., 2011). In other words, our contemporary understanding of the physiological and behavioral correlates of psychopathy are largely a reflection of what the
PCL-R, but also PCL-YV and PCL-SV, measures and correlates with. However, these PCL instruments must be seen as solely classifying a syndrome—they merely group together superficial expressions of latent personality traits rather than revealing the underlying etiological peculiarities that have resulted in these traits. A number of different pathways may result in outwardly similar phenotypes, and PCL-R derived psychopathic individuals may thus differ crucially on constructs that are specific to their unique etiology. Therefore, although the specificity of the PCL-R is such that it differentiates psychopathic individuals from the broader and more heterogeneous group of antisocial personality disorder (ASPD) diagnosed through the DSM, there is still much heterogeneity among the individuals it classifies as being a psychopath. As contended in chapter 1, the PCL instruments are not coherent with the Cleckley’s definition of primary psychopathy but rather conflate personality features characteristic to both primary and secondary psychopathy into one overarching criteria set. Thus, psychopathic individuals as identified through PCL instruments can be further differentiated into primary and secondary subtypes who show divergent etiological backgrounds, and differ regarding relevant personality domains such as neuroticism, fear, and impulsivity.

**Primary and secondary psychopathy in youngsters**

Cluster-analytic studies with the PCL-YV in youngsters have identified distinct psychopathic subtypes. Despite similar PCL-YV scores (mean score ≈ 30) and premeditated instrumental aggression, secondary psychopathic youth reported higher levels of neuroticism overall (i.e., physiological anxiety, worrying, hostility, depression, social concerns, and global psychological distress), psychosocial immaturity, impulsive aggression, and lower levels of self-control and responsibility, compared to primary psychopathic youth (Kimonis et al., 2011). In addition, secondary psychopathic youngsters showed higher levels of emotional and attentional problems and were more attentive to emotionally distressing pictures during neuropsychological testing, suggesting more sensitive emotional processing (Kimonis et al., 2012).

Vincent et al. (2003) also parsed potential subtypes of adolescent offenders but the group that scored high on all facets, named the *psychopathy cluster*, was treated as a homogeneous group because of a similar PCL-YV score. Since the researchers did not differentiate the "psychopathy" cluster into
separate subtypes based on external constructs such as anxiety or self-esteem, they may have failed to properly distinguish between primary and secondary psychopathy.

Other studies in children and adolescents have used the callous and unemotional scales of *The Antisocial Process Screening Device* (Frick and Hare, 2001) or the *Inventory of Callous-Unemotional Traits* (Frick, 2004) to assess psychopathic traits. Callous-unemotional traits are largely convergent with the affective facet of the PCL-YV (Lee et al., 2003). Beginning with the youngest sample studied, Humayun et al. (2014) reported that children who showed high levels of anxiety in addition to callous-unemotional traits (secondary psychopathy) had more adjustment problems at age seven (peer problems, antisocial behavior) than youth who displayed elevated scores on callous-unemotional traits exclusively (primary psychopathy). Another study by Fanti et al. (2013), in a large sample of non-institutionalized adolescents, also reported two variants of psychopathy among youth high in callous-unemotional traits and conduct problems; “secondary” high-anxious variants and “primary” low-anxious variants. Both groups were more likely to be male and showed equally high levels of callous-unemotional traits, impulsivity, and sensation seeking. However, primary psychopathic adolescents showed lower levels of anxiety, narcissism, and conduct problems, and higher levels of self-esteem, compared to the secondary group.

The most recent study by Docherty et al. (2015) identified three variants of psychopathy, with the primary subtypes showing the lowest levels of psychopathology overall, including both internalizing and externalizing pathology, and the secondary subtypes showing the highest levels. A third cluster, possibly a variant of the secondary psychopath, was called the fearful cluster, and scored in between the other two categories on most domains of psychological functioning.

All together, these studies in youngsters demonstrate that primary and secondary psychopathy may already be differentiated as young as childhood. In this context, primary psychopathic juveniles, regardless of legal status (incarcerated, institutionalized, or community), are emotionally stable, fearless, and self-assured, while the secondary group is impetuous, neurotic, and generally show more severe psychopathology and externalizing symptomatology.
In response to comprehensive review, Skeem et al. (2003) concluded that two psychopathic subtypes likely exist who show equally pronounced PCL-R traits, but differ on several other domains of personality. In particular, secondary variants display more severe forms of impulsivity, violence, and higher levels of trait-anxiety and depression. Secondary psychopaths also demonstrated higher scores on both objective measures of emotionality, such as autonomic arousal, as well as on subjective measures, such as ratings of anger and aggression (e.g., Blackburn and Lee-Evans, 1985, but see Skeem et al., 2003 for further references). Indeed, secondary psychopathy is strongly associated with borderline personality disorder (BPD), indicating that this group may be particularly dysregulated in emotions and more prone to hostility, hate, and paranoia. Similarly, primary psychopathy is mainly related to overt forms of narcissism (i.e., grandiose narcissism), characterized by social poise, assertiveness, and self-assurance, while secondary psychopathy may be more closely related to covert forms of narcissism (i.e., vulnerable narcissism) and more maladaptive personality dynamics such as neurotic conflicts, stress vulnerability, narcissistic fury (violence), and discontentedness with life in general (Skeem et al., 2003). Finally, it has been repeatedly demonstrated that primary subtypes mainly show high scores on factor 1 of the PCL-R and a strong genetic component to their pathology, while the secondary group mainly displays high scores on factor 2 and a stronger relationship with childhood abuse (Skeem et al., 2003). The conclusions from this review and the results of others (e.g., Blackburn et al., 2008; Ishikawa et al., 2001) with regard to associated personality pathology in primary and secondary psychopathy are schematized in figure 2.1.

Different studies in adult incarcerated male samples have largely supported these initial suggestions by Skeem and colleagues. The first of these, conducted by Hicks et al. (2004), identified two separate clusters of imprisoned criminals that could be diagnosed as being psychopathic using the PCL-R (mean PCL-R score of the whole sample = 32). One cluster, termed the emotionally stable psychopaths were characterized by high levels of agency (social potency, well-being, achievement) and low levels of stress vulnerability, whereas the second group, termed aggressive psychopaths were characterized by high negative emotionality, low constraint, and high levels of social detachment. A year later, Newman et al. (2005) further elaborated that primary psychopathy

1. Emotional Lability
2. Antisocial Personality
3. Chronic Impulsivity
4. Aggression
5. Criminal Behavior
6. Impaired Empathy
7. Callousness
8. Racketeering
9. Narcissism
10. Paranoia
11. Schizotypy
12. Borderline Personality
13. Antisocial Personality
(defined as PCL-R > 30 and low anxiety) is associated with a weak BIS but unrelated to BAS, whereas secondary psychopathy (defined as PCL-R > 30 and high anxiety) showed the opposite—high BAS with an average BIS. These findings accord with earlier theories stating that primary psychopaths are less fearful of threat and avoidant of punishment, while secondary psychopaths are more impulsive, hedonistic, and short-sighted (Lykken, 1995). Although not specifically analyzed, BIS scores were more variable in the secondary psychopathy group (SD = 0.97 vs. 0.83) while BAS scores were more variable in the primary psychopathy group (SD = 0.98 vs. 0.84) indicating that primary and secondary samples may show a higher variability regarding BAS and BIS scores respectively (Newman et al., 2005).

A comprehensive cluster-analysis by Skeem and colleagues in 2007, conducted in a male prison sample, provides further insight into the differences between primary and secondary psychopathy. Secondary psychopathic inmates manifested significantly more pathological personality traits (borderline, dependent, and avoidant), higher levels of neuroticism and social withdrawal (higher levels of irritability, stress susceptibility, lack of assertiveness), and a poorer clinical functioning (substantially higher levels of major mental illnesses). There were also some positive outcomes associated with secondary psychopathy such as higher response rates to therapeutic interventions, which is in accordance with Karpman’s initial propositions. In that same year, Swogger and Kosson (2007) also identified two separate clusters of incarcerated offenders who showed high PCL-R scores but could be distinguished regarding levels of anxiety (total PCL-R = 28.65 and 25.27 respectively). In line with previous studies, they reported that the secondary psychopathic group showed higher levels of psychopathology, including more pronounced drug dependency, negative affectivity, and lower levels of social poise or assertiveness.

Another study by Blackburn et al. (2008) used cluster-analysis in a violent forensic male sample, and identified four psychopathic clusters with equally high PCL-R scores (PCL-R ≈ 26). One group presented with particularly high scores on the interpersonal/affective traits exclusively (termed controlled psychopathy by the authors), and three clusters presented with high scores on both factors (termed primary, secondary, and inhibited psychopathy). Both the primary and controlled subgroups showed low levels of internalizing pathology and social withdrawal, low prevalence of paranoid, avoidant, dependent, and BPD traits, and low levels of childhood sexual and physical abuse, whereas the secondary and inhibited subgroups exhibited high scores on
all these variables. The primary and controlled criminals may have represented subcategories of primary psychopathy who are at decreased risk for anxiety and depression and higher in self-confidence and impulse control, whereas the secondary and inhibited clusters may have represented subcategories of secondary psychopathy, who are often abused as a child, and show high levels of both internalizing and externalizing pathology, including high levels of impulsivity and hostility (Blagov et al., 2011; Fanti et al., 2013; Hicks et al., 2004; Karpman, 1941; Kimonis et al., 2011; Lykken, 1995; Porter, 1996;
A more recent study by Poythress et al. (2010) also examined BIS/BAS functioning in PCL-R clusters but found slightly different results from that of Newman et al., (2005). They identified three clusters with a mean PCL-R score above the cutoff point 30; a primary, secondary, and a fearful cluster. Similar to Newman’s findings, the primary cluster showed the lowest levels of anxiety and harm avoidance, and the highest number of commission errors on a passive avoidance task—all indicative of a low BIS. However, contrasting the earlier findings of Poythress et al. (2010), primary psychopathy was also related to the highest BAS scores, indicating that subsamples of primary psychopaths may parallel and even surpass secondary types in BAS scores. Nonetheless, the secondary cluster showed the highest levels of externalizing symptomatology, impulsivity, aggressive disciplinary problems, and a trend towards higher levels of violent recidivism suggesting that the BAS elevations in secondary psychopaths may be of a more pathological nature, and more likely to result in dysfunctional forms of impulsivity.

To replicate the findings by Poythress et al. (2010), and examine whether similar cluster could be identified using less time-consuming self-report measures, Cox et al. (2013) cluster-analyzed a large sample of ASPD diagnosed inmates with the Psychopathic Personality Inventory (PPI; Lilienfeld and Andrews, 1996; Lilienfeld and Widows, 2005). In line with Poythress, they identified three clusters termed primary, secondary, and fearful psychopathy. Again, the secondary cluster scored higher on measures of internalizing symptomatology and impulsivity, while showing lower levels of interpersonal dominance compared to the primary cluster. Similarly, primary psychopathy was related to the lowest scores on carefree nonplanfulness and highest on fearlessness, social potency, Machiavellian egocentricity, and stress-immunity facets of the PPI, suggesting a less emotional and more egocentric, calculated, manipulative, and deliberate approach to life. Unexpectedly, however, primary psychopaths showed the highest level of externalizing symptomatology and were more prone to recidivism compared to all other groups. Therefore, cluster-analyzing the PPI may bring forth primary subtypes that are more prone to problematic externalizing behavior than secondary subtypes, whereas an opposite pattern may be found when cluster-analyzing the PCL-R. Finally, it is also interesting to note that the fearful cluster showed a near identical pattern of scores compared to the secondary cluster but differed exclusively in levels of fearlessness on the PPI. As discussed below in the synthesis section,
the fearful cluster may constitute a specific group of highly neurotic secondary psychopaths as asserted by Blackburn and Karpman.

Hicks et al. (2010) noted that most of the cluster-analytic studies were conducted with male samples and questioned whether similar subtypes could be identified in female prisoners. Cluster-analyzing a female incarcerated sample brought forth similar psychopathic profiles as found in males. That is, secondary psychopathic females were also characterized by higher levels of negative emotionality and lower levels of behavioral constraint compared to the primary cluster. In addition, they found that secondary psychopathic females displayed an early onset of antisocial and criminal behavior, greater substance use and abuse, more violent behavior and institutional misconduct, and more mental health problems (post-traumatic stress disorder and suicide attempts). Contrastingly, primary psychopathic females showed few distinguishing personality features compared to controls (i.e., female prisoners low on psychopathy) but were “prolific criminals especially regarding nonviolent crimes, and exhibited relatively few mental health problems despite substantial exposure to traumatic events” (abstract). Therefore, primary and secondary psychopathy show comparable external correlates in both genders, which possibly reflects similar etiological mechanism. Still, more research in female samples is needed to validate such preliminary claims.

A final way of dissociating the constructs related with either primary or secondary psychopathy in incarcerated or institutionalized samples is through examination of the external correlates of the PCL-R factors. As asserted and evinced by Skeem et al. (2003, 2007), factor 1 shows slightly stronger correlations with primary psychopathy while factor 2 is more strongly related to secondary subtypes.

Factor 1 is associated with an attenuated threat responsiveness (i.e., emotional hyporesponsivity), low baseline prevalence of internalizing disorders (e.g., anxiety, depression), low levels of BIS, and normal to high levels of BAS, whereas factor 2 is related to normal or even heightened emotional responsiveness to threats, high prevalence of internalizing disorders (i.e., anxiety and depression), high levels of BAS, and normal to high levels of BIS (Beauchaine et al., 2009; Blagov et al., 2011; Blair et al., 2005; Claes et al., 2014; Cook, 2010; Fowles and Dindo, 2006; Herpertz et al., 2001; Newman et al., 2005; Poythress and Skeem, 2006; Skeem et al., 2003, 2007; Verona
et al., 2001, 2012; Wallace et al., 2009; Wallace and Newman, 2008). These findings have been replicated in children and adolescents with psychopathic traits (Feilhauer and Cima, 2012; Frick et al., 1999; Frick and White, 2008; Kimonis et al., 2012; Viding et al., 2012).

Also, impulsivity and behavioral disinhibition have been found to be strongly associated with factor 2, and are a hallmark of secondary psychopathy, but show weak to non-significant correlations with factor 1 (Blackburn et al., 2008; Colledge and Blair, 2001; Feilhauer et al., 2012; Fowles and Dindo, 2006; Newman et al., 2005; Skeem et al., 2003, 2007; Wallace and Newman, 2008; Wallace et al., 2009). These results evince that some primary psychopathic individuals (i.e., those who mainly show high scores on factor 1) are likely to show markedly lower levels of impulsivity compared to their more criminal and disinhibited counterparts (Blackburn et al., 2008; Gao and Raine, 2010; Ishikawa et al., 2001; Poythress and Hall, 2011; Skeem and Cook, 2010a; Wilkowski and Robinson, 2008).

Finally, factor 1, and primary psychopathy more specifically, are exclusively related to heightened instrumental aggression and goal-driven antisocial behaviors that are characterized by premeditation and absence of emotion. In contrast, factor 2, and secondary psychopathy more specifically, have been repeatedly related to heightened reactive aggression and impulse-driven antisocial behaviors that are characterized by low self-control and emotional dysregulation (Blair, 2006a; Hare, 1993; Kennealy et al., 2010; Mitchell et al., 2006; Newhill et al., 2012; Porter and Woodworth, 2006; Poythress and Skeem, 2006; Skeem et al., 2003, 2007; Woodworth and Porter, 2002).

Taken together, it has been consistently reported that psychopathic subtypes can be differentiated on the basis of several psychological traits regardless of their equally pronounced scores on different psychopathy measures such as the PCL-R or PPI. Cluster-analytic studies in prison or forensic samples support a distinction of individuals scoring high on these measures into a primary subgroup (low anxiety), and a secondary subgroup (high anxiety). These subtypes are identified in both male and female prisoners. Secondary psychopathy is generally related to more severe social maladjustment and higher levels of both internalizing and externalizing psychopathology. For example, reactive aggression, impulsivity, and violent criminality are more closely related to secondary than primary psychopathy. Nonetheless, some studies report that secondary psychopaths may have a greater potential for
growth and improvement following psychological therapy, likely because the neural mechanisms for emotional growth are still present.

*Primary and secondary psychopathy in adult community samples*

In contrast to these investigations in forensic or prison samples, four studies have examined the existence of psychopathic subtypes in community samples. Coid et al. (2012) were the first to cluster-analyze PCL-SV scores in a large community sample. Psychopathic personalities were categorized into a *successful* and *criminal* cluster. Furthermore, in agreement with incarcerated samples, the authors reported a third group of *non-psychopathic criminals* who showed high levels of antisocial, lifestyle, and affective but not interpersonal traits and could represent secondary psychopathy more specifically. However, as identified through cluster-analysis by both Blackburn et al. (2008) and Poythress et al. (2010), some violent individuals attain high scores on all four facets of the PCL-R, including interpersonal traits (and would, therefore, be clustered into the criminal psychopathy subcategory of the Coid study), but present with high levels of neuroticism and harm avoidance. Indeed, Coid et al. (2012) found that a very large proportion of the criminal psychopathic cluster displayed affective or anxiety disorders (90.9%, $p < 0.01$ and 63.6%, $p < 0.01$ respectively). This study may therefore have unintentionally lumped the primary and secondary psychopathic subjects into one cluster since they did not differentiate the highest scoring PCL-SV group into separate subtypes based on external constructs, such as trait-anxiety or internalizing symptomatology.

Drislane et al. (2014) also used model-based cluster analysis to identify subtypes of psychopathy in men who scored ≥ 95th percentile on the *Triarchic Psychopathy Measure* (TriPM; see Patrick et al., 2009). These subjects were selected from a larger community sample of over 4000 males who were evaluated for service in the Finnish military. Similar to incarcerated samples, the best fitting model identified a primary and secondary cluster. Secondary psychopathic participants reported high levels of internalizing problems including anxiousness, depression, and somatization, and scored higher on the disinhibition facet relative to the primary group, whereas primary psychopathic individuals showed higher rates of violent crimes and particularly high scores on the boldness facet (capacity to remain calm and focused in pressured or
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<th>Domains</th>
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<th>Secondary Psychopathy</th>
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<td><strong>Psychopathy Measures</strong></td>
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<td>Low on SP scale</td>
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<td>Therapy potential</td>
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Table 2.1 *Summary of theoretical differentiations between primary and secondary psychopathy.*
See also chapter 1 for a more in depth discussion of the different psychopathy measures.
threatening situations, rapid recovery from stressful events, high self-assurance and social efficacy, and a tolerance for unfamiliarity and danger; Patrick et al., 2009).

Finally, Falkenbach et al. (2014) conducted a cluster-analytic study with the PPI in a large sample of college students. They also identified a primary and secondary cluster who scored very high on the PPI and four clusters who showed low scores. Compared to the secondary cluster, the primary cluster showed higher scores on the PPI-I, overt narcissism, and positive affectivity, while displaying lower scores on the PPI-II, anxiety, anger, aggression, BIS, negative affectivity, and BPD traits. However, both groups were equal regarding BAS scores indicating that while primary psychopathy is consistently related to a lower BIS as Fowler and Lykken hypothesized, it does not necessarily relate to lower levels of BAS. In extension to these findings, Broeran et al. (2014) also reported in a large sample of community males that while primary and secondary subtypes were both related to high levels of BAS, primary psychopathy was specifically associated with a low BIS score and a low fight-flight-freeze system activity (low fear sensitivity).

In sum, similar to incarcerated samples, community samples also provide evidence for the existence of multiple personality styles who score high on measures of psychopathy but still diverge regarding internalizing symptomatology, fearlessness, disinhibition, aggression, and violence. See table 2.1 for a final overview of the putative emotional, behavioral, and psychopathological differences between primary and secondary psychopathy.

2.3 An Evolutionary Model on the Etiology of Primary and Secondary Psychopathy

Linda Mealey; cheating as an evolutionary stable strategy

In response to the emerging wealth of data on the phenotypical expression and etiology of primary and secondary psychopathy, Linda Mealey (1995) developed a sociobiological model to explain their evolutionary roots. Since both conditions are marked by a severe emotional pathology, she argues that we must first define emotions. A basic differentiation can be made between
primary *basic emotions* such as fear, anger, and disgust, and secondary or tertiary *complex emotions* such as shame, guilt, sympathy, and love (Izard, 1991). Primary emotions are clearly related to survival, independent of culture or socialization, and instinctively programmed into the human physiological system through genes, whereas secondary emotions such as social emotions are more dependent on learning and socialization and thus more variable across cultures and individuals (Ekman, 1971). Whereas the primary emotions are universal to both humans as well as many other animals, the secondary emotions have evolved in response to specific evolutionary pressures (Mealey, 1995).

Secondary emotions such as remorse, shame, guilt, and pride can be seen as devices that have crucially contributed to the evolution of human social cooperation. The evolutionary imperative for humans to cooperate in order to overcome otherwise unsurmountable obstacles (e.g., hunting big predators), ensure group survival (e.g., sharing food, defending against external threat), and efficiently divide responsibilities, has incited the evolution of increasingly complex social skills (Lykken, 1995). Within this social repertoire, our communicative skills are the single most crucial determinant of our social effectiveness. We communicate our thoughts and emotions through our conscious language but also—and maybe even more importantly—through body language and facial expressions (Dimberg, 1988; Richerson and Boyd, 2010). Through our social emotions we let others know how we feel about what we did, or what we intent to do, and these expressions help others to decide our trustworthiness, predict our likely future behavior, and evaluate their willingness to either befriend and cooperate with us or to reject and exclude us from the group (Frank, 1988; Hirshleifer, 1987). We signal shame and remorse after defecting on others so that they know that we feel bad about our behavior and will not do it again. Similarly, we signal pride after successful cooperation so that others know we feel positive about cooperating and will likely do it again. Furthermore, we cooperate with others, even when it benefits us more to defect on the short-term, simply because we know that in doing so we will attain a better social reputation which will be more beneficial in the long-term (i.e., others will be more likely to cooperate with us whenever we need them) (Mealey, 1995). This need for social reciprocity and status is so deeply seated that most humans will feel an unconsciously driven but compelling need to return favors or attain a favorable social reputation (Cialdini, 2000; Lykken, 1995).
However, our inner thoughts and intentions are by definition hidden from others and they can only know about what we think and feel through what we express outwardly. This paves the way for deception (Caldwell, 1986). According to Mealey (1995), the fact that individuals can signal cooperation and appear trustworthy beforehand and then defect when it is their turn to reciprocate has enabled the emergence of an evolutionary niche of individuals who take advantage of this ‘weakness’ in the chain of human evolution. These are the cheaters of human society: the psychopaths (Mealey, 1995). Mealey (1995) argues that primary psychopathy in particular is an evolutionary stable strategy (ESS) meaning that “as long as evolutionary pressures for emotions as able communication devices leading to long-term, cooperative strategies coexist with counterpressures for cheating, deception, and “rational” short-term selfishness, a mixture of phenotypes will result, such that some statistical equilibrium will be approached” (pp. 525). In other words, as long as most people are trustworthy and cooperating, there will always be a small group of individuals who take advantage of this human tendency through cheating. Both groups would remain of equal size so that a persistent equilibrium can exist between cheaters and cooperators.

Mealey (1995) further argues that the tendency to acquire a life-strategy of cheating can evolve out of divergent etiological pathways. This behavior can come about either (1) as a genetically based, individual difference in the use of a cheating strategy (i.e., primary psychopathy), or (2) as an environmentally-contingent strategy, leading to cheating when the individual is evolutionary disadvantaged to overcome obstacles towards survival and reproduction any other way (e.g., low intelligence, low SES, less resources, less social abilities) (i.e., secondary psychopathy). Both Mealey’s theoretical suggestions are critically discussed below.

Cheating in primary psychopathy; genetic variation in social sensitivity

In Mealey’s view, primary psychopaths are individuals who have a genotype that predisposes them to acquire and be reinforced for displaying antisociality. She states that there will always be a small and unchanging baseline frequency of these individuals in every culture, no matter what the sociocultural or socioeconomic conditions (Mealey, 1995).

Interestingly, the different heritable features attributed to primary
psychopathy are just the traits a cheater would need to prosper; (1) less interference by social emotions or anxiety about punishment when making decisions (boldness/utilitarianism), (2) ability to fake internal states and convince others (charming/persuasive), (3) less need for social attachment and less responsive to human suffering (callousness), and (4) a mentality that beliefs great success can be achieved without needing others (self-esteem/optimism/grandiosity) (Hare, 1993). The endophenotype mediating these traits is believed to be a genetically based emotional deficiency, fearlessness, and stress immunity (Blair, 2006a, 2006b; Lykken, 1995; Yildirim and Derksen, 2013).

To understand how emotional deficiency can predispose towards a cheater strategy, we must ask ourselves; why do the majority of people act prosocial? Why do they care to achieve a desirable social reputation and maintain close attachments to their social group? And why are they so afraid to lose their reputation or social attachments? Of course, there is Mealey’s rather rational answer pertaining to evolutionary fitness as discussed above—to ensure that others will help them in return when they are in need. However, it has been established that most human decision-making, especially regarding social or emotional choices, is much more strongly influenced by quick emotional associations rather than time consuming rational analyses (Damasio, 1994; Eimontaite et al., 2013; Naqvi et al., 2006). A more plausible answer to the question why humans will be more likely to cooperate rather than cheat is because we need others and thus unconsciously fear losing them, which is a likely punishment for cheating (Lykken, 1995). Not only because others can help us out with life challenges that we cannot surmount our own but also because love, friendship, and attention are directly related to our psychological and physical well-being (Schore, 2001a). This is especially true in modern society where we do not necessarily need others to survive and where most of us can achieve financial independence.

As Alan Schore (2009) argued; “in a secure attachment relationship the regulatory processes of affect synchrony that co-create positive arousal and interactive repair of negative arousal allow for the emergence of efficient self-regulation. Thus, attachment represents biological regulation between and within organisms” (pp.3). In agreement, the availability of social support and secure attachment is associated with more adaptive coping behaviors, lower levels of stress-induced psychopathology, and improved regulation of HPA-axis responses to laboratory stressors (Cohen and Wills, 1985; Ditzen et al., 2007; Heinrichs et al., 2003; Kim et al., 2010; Meuwly et al., 2012; Quirin
et al., 2008). In this manner, our social relations serve to regulate our self-esteem and mental health and keep us ‘balanced’ amidst changing and stressful environments. Since we develop strong social attachments in order to co-create positive emotional states (sharing, in-group forming, affect synchrony) and benefit from mutual regulation and cooperation during times of stress or threat (helping, soothing, team-work), we try to act in ways that ensure our proximity to these attachments (Schore, 2001a). Simply stated, humans need love, support, camaraderie, and attention to maintain their psychological equilibrium and thrive in difficult circumstances.

Thus, we are inherently inclined to organize mutually supportive groups and motivated to act according the norms and values of our own group to avoid punishment in the form of love withdrawal, abandonment, and social exclusion (Lykken, 1995). This also holds for deviant attachments that foster antisocial rather than prosocial behavior. For example, when our social experiences have taught us that antisociality and aggression are accepted ways to acquire and maintain social status (in deviant neighborhoods) and ensure proximity to our social attachments (deviant peer groups/gangs), we must still stay loyal to our own subgroup to achieve social status and secure rewarding bonds (Lykken, 1995). Criminals who are not psychopathic will usually fear losing the respect and reputation they have built up among their deviant peers and may just as well become depressed when this happens. This is why most criminals have a code, a certain list of rules to adhere to in order to remain respected.

However, strengthening emotional regulation or dampening emotional responsivity effectively dampens homeostatic disruptions to socially aversive events, such as abandonment, rejection, punishment, and exclusion, and naturally reduces the need for social attachment to regulate internal states—ultimately engendering socio-emotional detachment (Yildirim and Derksen, 2013). Just like homeothermic organisms (i.e., warm-blooded) differ from ectothermic organisms (i.e., cold-blooded) in that they can dynamically regulate body temperature in response to changing environments making them less dependent on environmental sources of heat, emotionally stable individuals differ from unstable individuals in that they have a more effective and dynamic regulation of internal states in response to changing social environments, stressors, and salient events, making them less dependent on social attachments for stress-regulation. For example, increased stress responses to laboratory stressors has been related to increased prosocial behaviors and improved social
cognition, likely enabling these stress-responsive individuals to seek out and befriend conspecifics in order to regulate their stress experience (Smeets et al., 2009; Von Dawans et al., 2012). Therefore, lower stress or threat responsivity may be naturally related to a lower need for social attachments to regulate internal states resulting in higher socio-emotional detachment, thereby easing the way to a cheater strategy through the aforementioned features (boldness, callousness, utilitarianism).

Whether a cheating strategy actually emerges in any given emotionally deficient individual depends on social experiences, cultural values, intelligence, and socioeconomic resources. Individuals born with such a fearless temperament may also develop adaptive life-strategies that can further society and help mankind. I thus strongly disagree with Mealey’s view that genes may directly determine life strategies and that there exists a peculiar genotype that leads directly to cheating behavior. Although genes might direct behavior towards certain experiences and although most emotionally deficient individuals may express some primary psychopathic traits such as boldness, narcissism, and social potency, I believe that it is the social environment through which these genetic effects are eventually crystallized into antisocial patterns (i.e., cheating). The following chapters will specifically discuss how genes and environment work together in contributing to psychopathic behavior.

_Cheating in secondary psychopathy; environmentally-contingent adaptation_

Contrastingly, secondary psychopaths acquire a cheating strategy through more environmentally determined pathways. The development of personality can be seen as the unfolding of a particular life strategy in response to evolutionary relevant environmental cues (Millon et al., 2004). Mealey views secondary psychopathy as an adaptation to cues of social (reduced social skills), economic (financial impoverishment), and cognitive disadvantage (low intelligence) resulting in the adoption of alternative strategies to overcome one’s evolutionary disadvantage (Mealey, 1995). She thus argues that one of the more important variables that can lead to adopting a cheating strategy, especially in males, is being competitively disadvantaged with respect to the ability to obtain resources and mating opportunities.

According to Mealey (1995), childhood factors such as abuse and
neglect lead to cheating strategies because such experiences preclude youth to develop effective social skills to compete with others. Similarly, low intelligence also confers a competitive disadvantage. Therefore, Mealey suggests that secondary psychopathy is an adaptation to a disadvantage of resources and skills, and serves to enhance competitive fitness through cheating on those who are better equipped to win the game of life.

However, this is again a somewhat simplistic and rational idea since the greater majority of males who live in the lower socio-economic classes, who are not intelligent or socially skilled, and who struggle hard to maintain, do not adopt a cheating strategy and remain loyal to those around them. Although Mealey argues that these differences arise due to different temperamental styles that react differently to this disadvantage—a view that is partly shared by me—I still view her explanation as a too rational explanation on how secondary psychopathy is related to evolutionary mechanisms.

A more plausible explanation is that humans are biologically endowed to adapt not only to the quality of resources available that could confer an evolutionary advantage, but much more importantly to the quality of social relationships that they will experience throughout life. During our evolutionary history from hominids to humans in the Pleistocene—a time period notorious for its volatility and unpredictability—our species has encountered a wide variety of harsh circumstances that we had to adapt to. Some required cooperation whereas other environments required everyone to fend for himself (Lykken, 1995). Those ancestors who were able to abandon the constraints of social impulses in times of persisting stress and uncertainty—including the ability to pair-bond—may have had greater success in transmitting their genes (Belsky et al., 1991; Lykken, 1995).

Evolution has therefore selected for those qualities that enabled the evolving hominids to adapt flexibly to the social environment they were born into. Herein lies the concept of neural Darwinism. Neural Darwinism states that those neurons which achieve the appropriate input during development will grow and prosper, whereas those who do not will atrophy and die (Edelman, 1987). This ‘use it or lose it’ principle enables humans to develop and strengthen only those neural modules and connections that are adaptive in the environment they are born into. The human physiological system is shaped according evolutionary cues it receives about its environment and in so doing facilitates behavioral adaptation to these circumstances (Belsky et al., 1991). Indeed, rudimentary forms of prosocial as well as antisocial behaviors are part
of every normal infant’s and toddler’s repertoire, and which orientation will survive and develop into an adult life-strategy depends on what is (implicitly) punished and what is rewarded by the environment, but also simply through imitation of parental behaviors (Lykken, 1995; Paulus, 2014).

Social epidemiologist Richard Wilkinson elegantly summarized this principle in the Zeitgeist 3 documentary:

“However, this early sensitivity isn’t just an evolutionary mistake. It exists again in many different species. Even in seedlings there is an early adaptive process to the kind of environment they are growing up in. For humans, the adaptation is to the quality of social relationships. So early life—how much nurturing, how much conflict or how much attention you get—is a ‘taster’ of the kind of world you may be growing up in. Are you growing up in a world where you have to fight for what you can get, watch your back, fend for yourself, and learn not to trust others. Or are you growing up in a society where you depend on reciprocity, mutuality, cooperation, and where empathy is important, where your security depends on good relations with other people. That needs a very different emotional and cognitive development. That’s what the early sensitivity is about. Parenting is thus quite unconsciously a system of passing on that experience to children” (29:37, Joseph, 2011).

Evolution may have endowed higher order social animals such as humans the ability to adapt to the social environments they are born into through increased plasticity of neural pathways corresponding to social behavior. In harsh, unloving, and untrustworthy environments, long-term evolutionary fitness is more efficiently achieved by detaching oneself to close bonds (callousness, lovelessness), by being opportunistic, manipulative, competitive, and on-guard for potential threat, and by fiercely protecting acquired resources and one’s social status (reactive aggression) (Belsky et al., 1991; Lykken, 1995). One might say that the brain ‘freezes’ into a trait-like fight-or-flight modus operandi.

In support of this hypothesis, the majority of human infants are born with an astonishing plasticity of their neural pathways, in particular those underpinning social and moral behavior. So called “plasticity” genotypes that decrease stability/increase flexibility of physiological processes have been found to predispose towards emotional and behavioral dysregulation and increase the risk for secondary psychopathic/reactive aggressive phenotypes, but only
when additionally exposed to stressful life-events and adverse social experiences (Caspi et al., 2010; Davidson et al., 2000; Hariri and Holmes, 2006; Holmes, 2008; Homberg and Lesch, 2011; Whitaker-Azmitia, 2001, 2010; Yildirim and Derksen, 2013). However, rather than reflecting a proper impairment in brain functioning, heightened neuroticism and aggression mediated through these sociobiological mechanisms could thus actually reflect evolutionary adaptations to a threatening and resource-scarce worldview.

2.4 Core Etiological Mechanisms in Primary versus Secondary Psychopathy

Both primary and secondary variants of psychopathy show substantial heritability (Hicks et al., 2012) but these genetic components play different roles in their etiology (Blackburn et al., 2008; Cook, 2010; Hicks et al., 2012; Kimonis et al., 2012; Mealey, 1995; Skeem et al., 2003, 2007).

For example, empirical research in the last decade has indicated that “plasticity” genotypes which are associated with endophenotypes integral to secondary psychopathy, such as emotional lability, approach motivation/reward-sensitivity, and irritability, only result in antisocial development when additionally exposed to abusive and stressful environments, whereas the same genotypes can also increase propensity towards prosocial and socially adapted behavior in positive environments (Bakermans-Kranenburg and Van Ijzendoorn, 2006; Bakermans-Kranenburg et al., 2008; Belsky et al., 2009; Belsky and Beaver, 2011; Cicchetti et al., 2012; Munafò et al., 2008; Propper, et al., 2007; Reif et al., 2007; Sheese et al., 2007). Indeed, except for Lykken (1995) who suggested a strong genetic component, most scholars have argued that despite some temperamental abnormalities, the etiology of secondary psychopathy is mainly explained by destructive social experiences that have disturbed socio-emotional development (Blackburn et al., 2008; Karpman, 1941; Mealey, 1995; Porter, 1996).

Contrastingly, the emotional deficiency and corresponding fearlessness that underpin the development of primary psychopathy is mainly rooted in constitution (Baker et al., 2009; Beaver et al., 2011; Blair, 2006a, 2006b; Hicks et al., 2012; Karpman, 1941; Porter, 1996; Ribeiro da Silva et al., 2012; Skeem et al., 2003, 2007; Yildirim and Derksen, 2013). Studies which have assessed
primary psychopathic traits (e.g., low neuroticism, fearlessness, insouciance, callous/unemotional traits) reported that shared and non-shared environmental factors, including those found within the family (parental permissiveness, attachment, socialization), were either unrelated or marginally related to between-twin differences in such traits (e.g., Beaver et al., 2013; Viding et al., 2005, 2008; Viding and Larson, 2010; Waldman and Rhee, 2006). In accordance, socialization seems to have a much larger effect on different risks for antisocial behavior found in secondary psychopaths, such as neuroticism, impulsivity, and hostility, rather than those found in primary psychopaths such as emotional deficiency and fearlessness, likely because the neural mechanism through which these latter risks are mediated is more strongly determined by constitution and less susceptible to environmental influences (Blair, 2006a, 2010; Hall et al., 2004; Hare, 1993; Harpur et al., 1989; Reidy et al., 2011; Viding et al., 2005, 2008).

Nevertheless, it must be noted that neither primary nor secondary variants are entirely related to genetics or environment. More specifically, secondary psychopathy and the associated impulsive antisociality has been related to childhood abuse/trauma and low socioeconomic status, whereas primary psychopathy and the associated interpersonal/affective traits have been associated with parental neglect, maternal disengagement, and low maternal care (Beaver et al., 2012; Blackburn et al., 2008; Coid et al., 2012; Cook, 2010; Hicks et al., 2012; Ishikawa et al., 2001; Kimonis et al., 2012, 2013a, 2013b; Graham et al., 2012; Poythress et al., 2006, 2010; Ribeiro da Silva et al., 2012; Skeem et al., 2003). For example, incarcerated youth with secondary psychopathy were more often characterized by sexual abuse, whereas those with primary psychopathy were more likely to have been neglected (Kimonis et al., 2013b). In a similar vein, the only environmental variable that showed an effect on primary psychopathic features was maternal disengagement (Beaver et al., 2012).

It might, therefore, be more adequate to state that the emotional deficiency associated with primary psychopathy and rooted in temperament is more naturally related to antisocial behavior when the absence of protective factors, such as maternal warmth and engagement, rewarding social network, and undivided parental attention, do not counterbalance such inherent tendencies (e.g., Lykken, 1995). In contrast, the temperamental irritability, neuroticism, and reward responsivity as associated with secondary psychopathy may only result in antisocial development in the presence of risk factors that
increase social stress levels to destructive heights, such as trauma, rejection, and abuse (e.g., Porter, 1996; Yildirim and Derksen, 2013).

**Biobehavioral pathways to primary psychopathy; deficiency**

As shortly described above, the etiology of primary psychopathy is predominantly rooted in genetic contributions that dampen spontaneous emotional responses to social cues or immediate threat, and thereby attenuate the natural aversion to risk, punishment, and novelty (emotional deficiency), impede emotional empathy or the development of self-conscious moral emotions (guilt/shame), and eventually preclude the proper integration of affect into a developing model of morality (deficient conscience) (see Blair, 1995, 2006a, 2006b; Cook, 2010; Fowles and Kochanska, 2000; Kochanska, 1991, 1993; Larsson et al., 2006; Lykken, 1995; Meffert et al., 2013; Ribeiro da Silva et al., 2012; Viding et al., 2005, 2008; Yildirim and Derksen, 2013).

Core characteristics that are common to all primary psychopaths can be summarized as; (1) lower levels of psychological and physiological stress/fear responsiveness (fearlessness), (2) dampened empathy-related neural and physiological responses to, and reduced recognition and psychological appraisal of, socio-affective stimuli (callous insouciance), (3) less emotional interference during moral judgments and decision-making (moral utilitarianism), and (4) a particular talent at manipulating, deceiving, and persuading others (social potency) (Benning et al., 2005a, 2005b; Blair, 2006a, 2006b; Blair et al., 2002, 2003; Carré et al., 2013; Cima et al., 2008, 2010; Contreras-Rodríguez et al., 2014; Deeley et al., 2006; Glenn, 2011a, 2011b; Glenn et al., 2009, 2011; Gordon et al., 2004; Harenski et al., 2009, 2010, 2014a, 2014b; Hicks et al., 2004; Iria and Barbosa, 2009; Jones et al., 2009; Justus and Finn, 2007; Kiehl et al., 2001; Koenigs et al., 2011; Kosson et al., 2002; Lykken, 1995; Mahmut et al., 2008; Marsh and Cardinale, 2012, 2014; Marsh et al., 2011; Montagne et al., 2005; Patrick et al., 1993; Porter et al., 2009; Seto and Barbaree, 1999; Sobhani and Bechara, 2011; Sprengelmeyer et al., 1999; Stadler et al., 2011; Tassy et al., 2013; Vanman et al., 2003; Viding et al., 2012; Winslow et al., 2012; Young et al., 2012). Contrary to these emotional patterns that operate below consciousness and mediate the development of core psychopathic features, conscious cognitive appraisals of what is considered morally wrong or right are consistently found to be intact, and sometimes even enhanced, in
psychopathy (Aharoni et al., 2012; Cima et al., 2010; Link et al., 1977; Tassy et al., 2013). As the title of one of these studies aptly states, “psychopaths know right from wrong but do not care” (Cima et al., 2010).

The neural signature of this emotional deficiency has been ascribed to a genetically determined attenuation of amygdalar reactivity (e.g., Blair, 2006a, 2006b; Blair et al., 2005). Longitudinal studies have, indeed, provided support for extremes of temperamental emotionality and fearfulness based on amygdalar reactivity, namely the low- and high-responsive temperament which show high stability from infancy to adulthood (Kagan and Snidman, 2004; Kagan et al., 2007; Schwartz et al., 2003). At four-months-old, a large number of infants were assessed for their amygdalar reactivity through the intensity of the freeze response to an unexpected stimulus (i.e., unexpected change in taste of food). Subsequently, these infants were followed up at ages

\[ Figure 2.2 \] Different subcortical and cortical brain regions implicated in the etiology of primary and secondary psychopathy. Cortical regions are numbered according corresponding Brodmann Area.
2, 4, 7, 11, and 15 and tested on a variety of behavioral and physiological measures. Children with low responsive temperaments in the first year of life (lower amygdalar reactivity), were more sociable and less inhibited towards an unfamiliar researcher and peer, smiled more often, showed less signs of tension/ nervousness, and more often reported to be “happy” at the time of all the follow-ups (Kagan and Snidman, 2004). Physiologically, these children at age 11 and then as adolescents at age 15 showed the lowest levels of cortical arousal to expected and unexpected aversive stimuli, lowest resting heart rate, more dynamic regulation of heart rate, and the least amygdalar reactivity to unfamiliarity (Garcia-Coll et al., 1984; Kagan et al., 1978, 1988, 1994, 2007; Kagan and Moss, 1962; Schwartz et al., 1999, 2003; Snidman, 1989). Amygdalar reactivity to novelty and associated measures of fear have been found to stay intact into early adulthood, such that children categorized as having low amygdalar reactivity in their second year, also showed the least amygdalar reactivity to novel faces as young adults (mean age = 21.8) (Schwartz et al., 2003).

However, this amygdalar deficiency is not equally present in both hemispheres of the brain. That is, adolescents with callous-unemotional traits and adults with the interpersonal/affective features of psychopathy most consistently display right-hemisphere fronto-amygdalar structural abnormalities and hyporeactivity to aversive stimuli or when processing moral emotions (Carré et al., 2013; Fairchild et al., 2013; Glenn et al., 2009; Gordon et al., 2004; Harenski et al., 2009, 2010, 2014a, 2014b; Jones et al., 2009; Kiehl et al., 2001; Kosson et al., 2002; Marsh et al., 2011; Marsh and Cardinale, 2012, 2014; Müller et al., 2008; Tiihonen et al., 2000; Viding et al., 2012; Yang et al., 2010). Interestingly, Marsh et al. (2014) recently reported that extraordinarily altruistic individuals (those who donated a kidney to a complete stranger) displayed an enlargement and enhanced responsivity of the right amygdala to fearful facial expressions, which is the exact opposite of what is found in primary psychopathy. In accordance, low-responsive children and adolescents display a left-ward bias in resting brain activity, which has been associated with behavioral approach and reduced anxiety, whereas high-responsive youngsters show a right-ward bias, which is associated with behavioral inhibition and increased anxiety (Balconi and Mazza, 2009, 2010; Coan and Allen, 2003; Fox et al., 1995; Harmon-Jones and Allen, 1997; Hecht, 2011; Kagan and Snidman, 2004).

In a similar vein, Hecht (2011) concludes that prosocial behavior, as
Primary versus secondary psychopathy

well as feelings of empathy, guilt, and fear are mediated predominantly by regions within the right hemisphere, whereas impulsivity, stimulation-seeking, aggression, and risk-taking are tightly linked to left hemisphere activity. Therefore, while the core features of primary psychopathy have been repeatedly and consistently associated to right hemisphere hyporesponsivity, the antisocial and impulsive traits have been mainly related to left hemisphere hyperactivity (see Hecht, 2011).

The right fronto-amygdalar circuitry is involved in the initial, fast, and possibly intuitive detection of peripheral and affectively salient or otherwise relevant stimuli and results in somatic arousal in response to these stimuli. This largely intuitive process is followed by a more detailed, prolonged, and cognitive evaluation of the stimulus by the left fronto-amygdalar complex after it is brought within the central field of attention (Costafreda et al., 2008; Hardee et al., 2008; Morris et al., 1996, 1999, 2002; Sergerie et al., 2008; Skuse et al., 2005; Wright et al., 2001). Coherent with this inter-hemispheric lateralization of fronto-limbic functionality, primary psychopathic subjects are mainly impaired in spontaneous emotional reactions to (peripheral) aversive stimuli. That is, when they are verbally instructed to consciously direct attention or to deliberately induce the appropriate emotion (thereby soliciting left-hemisphere capacities) their initial hyporesponsivity and insensitivity is no longer observed (Meffert et al., 2013; Newman et al., 2010).

In short, without the parallel fluctuations of the right amygdala-prefrontal circuitry, goal-directed motivation and decision making may be devoid of socio-emotional considerations and depend solely on predicted instrumental outcomes and ongoing reward feedback (trial-and-error learning). This neurophysiological profile could then contribute to social insensitivity, egocentrism, risk-taking, boldness, and an aggressive pursuit of reward, and may also increase the risk for antisocial behavior and criminality, especially in the context of additional left-hemisphere hyperactivity.

However, this right-lateralized emotional deficiency does not automatically lead to disinhibition or overtly aggressive behaviors and might result in a variety of phenotypes dependent on other biological and environmental factors (Babiak and Hare, 2007; Lykken, 1995; Poythress and Hall, 2011; Skeem and Cooke, 2010a, 2010b). It has been argued and empirically supported that temperamental characteristics, such as fearlessness and stress-immunity, may
hold adaptive value in fast-paced and competitive environments, especially in the context of other protective factors such as a firm but authorative socialization, good executive functioning, and high intelligence (Babiak and Hare, 2007; Dutton, 2012; Gao and Raine, 2010; Lilienfeld et al., 2012; Lykken, 1995; Poythress and Hall, 2011; Stout, 2006). In accordance, a substantial subset of primary psychopaths are not disinhibited but rather well-controlled and calculating, and some are even highly successful in their professional careers (Babiak et al., 2010; Babiak and Hare, 2007; Board and Fritzon, 2005; Cleckley, 1941; Gao and Raine, 2010; Hare, 1993; Lilienfeld et al., 2012; Lykken, 1995).

In response to careful review of the types and levels of impulsivity in psychopathic subsamples, Poythress and Hall (2011) conclude that “the blunt assertion that “psychopaths are impulsive” is no longer defensible” (abstract). Instead, they argue that a significant portion of primary psychopaths exhibit adequate self-control, foresight, and planning ability, allowing them to refrain from serious antisocial behavior and to function relatively well in society, even attain success. Similarly, different researchers have opposed to the initial premise that criminality and overtly deviant behavior is central to the construct of psychopathy (Cooke and Michie, 2001; Cooke et al., 2004; Gao and Raine, 2010; Poythress and Hall, 2011; Skeem and Cooke, 2010a, 2010b). These scholars have argued that focusing on traits such as impulsivity and criminality to diagnose psychopathy may result in many false negatives, namely those who are equally psychopathic in personality but who manifest their lack of conscience through controlled and calculated schemes rather than through impulsive antisociality and impetuous risk-taking. In support of this hypothesis, different cluster-analytic studies in both community and incarcerated samples and in both juveniles and adults provide support a dual categorization of primary psychopathy into a deceitful, controlled, and low psychopathology group (controlled “successful” variants) and a more aggressive, impulsive, and criminal group (disinhibited “criminal” variants) (see Blackburn et al., 2008; Swogger and Kosson, 2007; Vincent et al., 2003).

Regarding neurobiological factors that may contribute to this heterogeneity, primary psychopathic individuals have been found to differ substantially regarding the functionality and structural integrity of neural regions involved in self-control, planning, organization, and instrumental learning.

First, it has been found that primary psychopathic individuals with
High levels of antisocial and impulsive behavior are characterized by both a lower stability and lower flexibility of PFC mediated executive processes during goal-directed behavior (Dolan, 2012; Gao et al., 2011; Ishikawa et al., 2001; Lapierre, et al., 1995; Mitchell et al., 2002; Moltó et al., 2007; Poythress and Hall, 2011). This PFC processing profile could underlie the automatic hyperfocus on immediate and strong reinforcements (insufficient stability to engage in longer term endeavors; easily bored) and the impaired behavioral adaptations to non-reward, punishment, or peripheral warning cues (impaired response modulation; inability to learn from experience) as observed in disinhibited and criminal subtypes of primary psychopathy (Blair et al., 2005; Newman and Lorenz, 2003).

Conversely, more controlled and well-adjusted primary psychopathic individuals show higher levels of PFC mediated cognitive stability and flexibility during goal-directed behaviors and thus engage more adaptively in long-term pursuits (higher persistence and conscientiousness) and adjust behavioral strategies more sensitively when confronted with error/punishment or when peripheral cues signal such a possibility (better response modulation) (Gao et al., 2011; Ishikawa et al., 2001; Mullins-Sweatt et al., 2010). Therefore, although controlled primary psychopaths may be equally likely to display a particular tendency to take risks and persist towards coveted rewards, their intact PFC processes and higher levels of cognitive flexibility may enable them to do so in a more strategic, deliberate, and calculated manner (deliberate gain-oriented risk-taking/functional impulsivity) (Gao and Raine, 2010; Poythress and Hall, 2011).

Second, violent, incarcerated, or convicted primary psychopaths show lower amygdala volumes bilaterally (right: 20%, left: 17% reduction), reduction of PFC grey matter (up to 22%), and hippocampal abnormalities such as an R>L asymmetry (both smaller left and greater right hippocampal volumes) when compared to controls or non-convicted/non-incarcerated psychopathic subjects (Gao and Raine, 2010; Laakso et al., 2001; Raine et al., 2004; Yang et al., 2005, 2009). Interestingly, a lower hippocampal volume and dysfunctional PFC-mediated regulation of goal-directed behavior have both been related to more pronounced and dysregulated mesolimbic dopamine-driven reward processes (Grace, 2010; Lisman et al., 2008; Lodge, 2011; Lodge and Grace, 2006, 2011). In accordance with the interhemispheric imbalances as associated with primary psychopathy (Hecht, 2011), dopamine-driven reward processes are predominantly lateralized to the left-hemisphere (see...
Tomer et al., 2014; Weiland et al., 2014). In other words, disinhibited and criminal variants of primary psychopathy may display a more hyperactive or dysregulated mesolimbic dopaminergic circuitry (Bjork et al., 2012; Buckholtz et al., 2010; Soderstrom et al., 2001, 2003), especially in the left hemisphere. Dopaminergic risk factors that might contribute to the heterogeneity observed in primary psychopathic samples will be discussed in more detail in chapter 4.

Biosociopsychological pathways to secondary psychopathy; disturbance

Secondary psychopathic individuals also display a genetic peculiarity that predisposes them to antisocial behavior (e.g., irritability, executive dysfunctionality, reward-sensitivity) but their socio-affective detachment is primarily an adaptation, and their aggression a ‘retaliation’, to traumatic, abusive, and painful social experiences that have instilled a paranoid outlook and hostile worldview (disturbed conscience) (Cook, 2010; Karpman, 1941; Lykken, 1995; Porter, 1996; Yildirim and Derksen, 2013). Instead of emotional deficiency, the core pathology associated with secondary psychopathy is the disturbed regulation, reduced awareness, undervaluation, and outward projection of one’s emotional processes, collectively termed here as emotional disturbance (Burns et al., 2015; Long et al., 2014; Yildirim & Derksen, 2013).

Therefore, despite a normal or high-responsive temperament, destructive social experiences, such as trauma and abuse, could disturb socio-emotional and neural development and result in phenotypically similar traits as found in primary psychopathy. Alternative pathways to antisocial behaviors as related to secondary psychopathy, may depend less on the amygdala but instead arise due to the neural dysfunctioning of cortical structures that mediate the cognitive appraisal and top-down regulation of socio-affective signals, and, of which the healthy maturation is dependent on sensitive and responsive social experiences early in life (Anderson et al., 1999; Blair, 2007, 2008; Blair et al., 2005; Blair and Cipolotti, 2000; Buckholtz and Meyer-Lindenberg, 2008; Burgess and Wood, 1990; Burns et al., 2015; Damasio et al., 1990; Decety and Chaminade, 2003; Eslinger, 1998; Kolb et al., 2012; Schore, 2001a, 2001b; Weber et al., 2008; Yildirim and Derksen, 2013).

One specific neurobiological mechanism through which the
relationship between social experience and secondary psychopathy could be mediated is through the maturation and functionality of the ventromedial prefrontal cortex, abbreviated as vmPFC. The vmPFC includes a medial division; the medial prefrontal cortex (abbreviated as mPFC and including the dorsal anterior cingulate; area 32, the subgenual cingulate; area 25, the ventral anterior cingulate; area 24, and the frontopolar prefrontal cortex; area 10), and a ventral part; the orbitofrontal cortex (abbreviated as OFC and including the medial OFC; area 11 and 12, and the lateral OFC; area 47) (see figure 2.2; areas correspond to Brodmann's numerical categorization of the cerebral cortex). The healthy maturation of in particular the right vmPFC is essential for affective skills such as self-regulation, emotional appraisal, and affective decision making, behavioral skills such as self-control, and interpersonal skills such as self-awareness, empathy, identification with others, and intersubjective processes more generally (Anderson et al., 1999; Damasio et al., 1990; Decety and Chaminade, 2003; Eslinger, 1998; Grattan et al., 1994; Fuster, 2008; Molnar-Szakacs et al., 2005; Schore, 2001a, 2001b).

vmPFC dysfunctioning has been related to both factors of the PCL-R and its healthy maturation is strongly dependent on the balanced interaction between biological factors such as genes, gender, and gonadal hormones, social experiences such as attachment, and other environmental factors such as substance abuse (Alia-Klein et al., 2011; Blair, 2008; Blair et al., 2005; Chugani et al., 2001; Dannlowski et al., 2012; De Brito et al., 2012; Edmiston et al., 2011; Franklin et al., 2002; Hanson et al., 2010; Kates et al., 2006; Koenigs, 2012; Lombardo et al., 2012b; Schore, 2001a, 2001b; Thomaes et al., 2010; Yang et al., 2005). It is especially the maturation of the right vmPFC that is influenced by the early attachment relationship and affects many affective and emotional capacities throughout life (Minagawa-Kawai et al., 2009; Schore, 2001a, 2001b). These results indicate that vmPFC dysfunctioning can arise out of an interaction between biology and destructive environmental influences and predispose to the whole range of psychopathic traits, making it the ideal candidate for the explanation of secondary psychopathy.

First, the autoregulatory tone of the medial prefrontal cortex (mPFC) on subcortical reactivity, facilitated by high levels of baseline serotonin functioning, provides an intuitive counterbalancing mechanisms to threat-related amygdalar and corresponding HPA-axis reactivity through feedforward inhibition, thereby attenuating emotional fluctuations and stabilizing the
homeostatic state (Akirav and Maroun, 2007; Banks et al., 2007; Fisher et al., 2009, 2011; Pezawas et al., 2005; Posner et al., 2007; Quirk et al., 2003). However, when confronted with salient events that violate our expectancies, and that require a shifting of attention to new future contingencies, catecholamine-driven processes temporarily override this autoregulatory tone and sensitize subcortical input into prefrontal modules (i.e., predictive allostatic regulation), thereby improving action monitoring, sensitizing emotional responsiveness, increasing awareness of emotional states, enhancing operant conditioning, and decreasing impulsive decision-making (Drabant et al., 2006; Pérez de la Mora et al., 2010; Laviolette et al., 2005; Pardey et al., 2013; Posner et al., 2007; Schultz, 1998; Shah et al., 2004; Stahl, 2008; Van Noordt and Segalowitz, 2012; Winstanley et al., 2006).

When this top-down serotonin-driven autoregulatory tone is compromised for whatever reason (e.g., prolonged stress), catecholaminergic activations have a more pronounced effect on physiology and behavior which can result in sensitized neural processing of, and impetuous behavioral responding to unexpected/salient affective events. In the context of rewards or cues signaling their potential presence, inhibiting mPFC-driven top-down autoregulation would induce a certain “reward hyperfocus” at the expense of peripheral warning cues or information regarding more optimal choices, thereby impairing response modulation and leading to impulsive decision-making (e.g., Harrison et al., 1997; Newman and Lorenz, 2003; Wallace and Newman, 2008; Winstanley et al., 2003, 2004, 2006). In the context of conflict, punishment, and social rejection/exclusion, this reduced top-down autoregulation may also amplify the salience of these events and induce an over-evaluative hypervigilance and paranoia (i.e., the induction of a hypervigilant state to stay prepared for dreaded future events) that can lead to anticipatory anxieties, aggression, worrying, nervousness, and fear (e.g., Stahl, 2008; Stein et al., 2006).

Second, for adaptive regulation of behavior according learned rules of reinforcement, the OFC comes online when an unexpected but salient future possibility is activated and serves in the online maintenance of its representation (Frank and Fossella, 2011; Grace et al., 2007; Lodge, 2011). During the online maintenance of these wanted or feared possibilities, the dorsolateral prefrontal cortex (dLPFC) constructs different action-plans that lead to the completion of the current goal (whether obtaining rewards or avoiding punishments) and the OFC continuously activates associational
networks of reinforcement schedules representing the relative outcome values of these various action-plans. In a Darwinian-like competition of neural signals, action-plans with the highest pay-off and least aversive neural traces or that signal the least chance of error of punishment, are least inhibited and the corresponding reverberation between the OFC and dLPFC increases the chance of them being carried out (Blair et al., 2005; Fuster, 2008; Gottfried et al., 2003; Padoa-Schioppa and Assad, 2006; Schoenbaum et al., 1998; Tremblay and Schultz, 1999).

Without the OFC serving as a relay station, temporarily holding representations about future outcomes active and deciding which signals to reverberate and which to inhibit, as is the case when lesioned, all internal motivations, emotions, and behavioral tendencies (the ‘Id’) that are normally inhibited by the OFC (the ‘Superego’), may become plausible and immediate possibilities and thus acted upon without adequate consideration of their consequence, adequateness, appropriateness, or relevance (Fuster, 2008). Serotonin functioning in the OFC is chiefly involved in this inhibitory function and its dysregulation thus strongly affects optimal OFC functioning (Fuster, 2008; Homberg, 2012; Walker et al., 2009).

In line with these vmPFC functions, individuals with vmPFC damage due to blunt force head trauma show acquired sociopathy after the incident such as an inability to use emotional information to guide behavior, impulsivity, reward-hyperfocus, emotional numbing, HPA-axis dysfunctioning, socio-emotional detachment, and reactive aggression (Anderson et al., 1999; Blair and Cipolotti, 2000; Buchanan et al., 2010; Burgess and Wood, 1990; Damasio et al., 1990; Eslinger, 1998; Grattan et al., 1994; Pennington and Bennett, 1993). Nonetheless, in contrast to primary psychopathy, individuals with vmPFC dysfunctioning still display heightened physiological responsivity after discovering that they made a bad decision, which is more characteristic of impulsivity and an inability to adequately appraise emotional information or regulate behavioral tendencies before decision-making rather than a properly dampened emotional response to the punishment of making a bad decision (Bechara et al., 1999, 2000a, 2000b; Blair, 2006a, 2006b). Therefore, patients with acquired lesions of the vmPFC show key differences in presentation compared to primary psychopathy (Blair et al., 2005).

Furthermore, vmPFC dysfunction is observed in many different clinical conditions marked by a dysregulation of emotions such as panic disorder, bipolar disorder, substance abuse, and major depressive disorder (Alia-Klein et
al., 2011; Althshuler et al., 2008; Lacerda et al., 2004; Roppongi et al., 2010; Tanabe et al., 2009). This type of neurophysiological dysfunction is thus not unique to secondary psychopathy but could be the neural substrate through which the comorbidity between these clinical conditions can be explained. Emotional dysregulation may specifically lead to antisociality and secondary psychopathy in response to neglectful experiences or rejection that result in socio-emotional detachment and frustrating/anger-inducing social experiences that engender hostile attributional biases (Dodge et al., 2001, 2003).

Similar to primary psychopathic samples, there is also a great deal of heterogeneity within the secondary psychopathic population and different variants may be crucially differentiated. For example, Porter’s “dissociative” secondary psychopath is described as affectionless, mentally alienated, insensitive to social cues, and its etiology is explained through the coping mechanism of dissociation in response to relational trauma and rejection (reduced emotional appraisal - OFC dysfunctioning), whereas Blackburn’s “borderline” or Karpman’s “symptomatic” secondary psychopath is described as fearful, harm avoidant, and stress sensitive and its development is explained through neurotic disturbances and the maldevelopment of self-control or -regulation mechanisms (reduced emotional regulation - mPFC dysfunctioning) (Blackburn, 1975; Karpman, 1941; Porter, 1996; Schore, 2001b; Yildirim and Derksen, 2013).

Accordingly, some relationally traumatized youth with normally functioning emotional systems might ‘acquire’ callousness and unemotionality through the mechanism of emotional detachment (dissociation of cognition and affect) resulting in an affectionless, interpersonally alienated, cognitively detached, and hedonistic-impulsive phenotype (i.e., reduced appraisal) (Kerig et al., 2012; Orsillo et al., 2007; Porter, 1996), whereas others who are more emotionally reactive, hyperactive, and irritable may additionally react with emotional dysregulation resulting in instability, interpersonal hostility, and reactive aggression (i.e., reduced regulation/control) (Putnam and Silk, 2005; Scott et al., 2014; Schore, 2001b; Sprague et al., 2012; Yildirim and Derksen, 2013). Just like two broad clusters of primary psychopathic individuals can be identified who diverge regarding behavioral self-control and (mal)adaptive behavioral patterns (Coid et al., 2012; Blackburn et al., 2008; Swogger and Kosson, 2007; Vincent et al., 2003), cluster-analytic studies have also identified different types of secondary psychopathic offenders (termed secondary, fearful, or inhibited psychopathy) who show equally pronounced PCL-R scores and
similar scoring patterns on the PPI but diverge crucially regarding measures of neuroticism, anxiety, extraversion, harm avoidance, impulsivity, and BPD traits (Blackburn et al., 2008; Cox et al., 2013; Docherty et al., 2015; Poythress et al., 2010).

Furthermore, the ASPD and BPD categories of the DSM have both been related to the entire spectrum of PCL-R traits, and it has been repeatedly argued that a continuum of severity might be observed within the ASPD and BPD population, with more severe variants gradually merging into a psychopathic phenotype (Cale and Lilienfeld, 2002; Coid and Ullrich, 2010; Skeem et al., 2003, 2007; Sprague et al., 2012; Verona et al., 2012; Yildirim and Derksen, 2013). Extrapolating potential subtypes of secondary psychopathy from the BPD and ASPD groups, it might be predicted that the “detached” ASPD types would more strongly express the deficits in affective appraisal, social alienation, attentional hyposensitivity, externalizing deviancy, and other-directed aggression found in secondary psychopaths, whereas the “unstable” BPD types would be more likely to show the affective instability, irritability, interpersonal hostility, attentional hypersensitivity, and both other- as well as self-directed aggression (Blonigen et al., 2005; Cale and Lilienfeld, 2002; Claes et al., 2009; Gratz et al., 2013; Krause-Utz et al. 2012; Paris et al., 2013; Sadeh et al., 2011; Schug et al., 2007; Verona and Vitale, 2006; Verona et al., 2012; von Ceumern-Lindenstjerna et al., 2010; Wynn et al., 2012).

2.5 Synthesis and Typology: The Primary and Secondary Psychopathic Continuum

*The primary psychopathic continuum*

Taken together, the etiology of primary psychopathic traits, such as fearlessness, callous insouciance, moral utilitarianism, and social potency, are strongly rooted in an emotionally deficient temperament. This emotional deficiency is largely engendered by a constitutionally defined hyporesponsivity of the right-hemisphere fronto-amygdalar complex to socio-affective stimuli or
peripheral cues. In the following chapters, I will argue that on the level of neurophysiology, such a neural information processing profile is likely to arise due to a higher testosterone activity/reactivity, hyperstability of baseline serotonergic functioning (little fluctuations), and a corresponding attenuation of HPA-axis reactivity to immediate stressors (dampened reactive allostasis).

Furthermore, this emotional deficiency is stable throughout life and common to all primary psychopaths regardless of adaptive or maladaptive life strategies. Whether adaptive or maladaptive patterns arise is dependent on other biological, social, and psychological factors that mediate and shape how this emotional deficiency manifests in behavior (controlled or disinhibited), cognition (aggressive/inflexible or assertive/flexible), and neurobiology (healthy or disturbed maturation and functioning of the PFC and hippocampus) (see chapter 4). Therefore, different variants of primary psychopathy may be crucially differentiated.

In response to the above review, three types of individuals may be hypothetically differentiated who express this emotional deficiency through different life-strategies and reside on a continuum that spans from controlled/well-adjusted to disinhibited/maladjusted;

(1) The first and most well-adjusted group is characterized by similar emotional deficiencies as their pathological counterparts but have nonetheless become properly socialized. These individuals can hardly be designated ‘psychopaths’ but do display core psychopathic features such as boldness (on the TriPM), fearless dominance (on the PPI), and interpersonal features (on PCL instruments) (e.g., Babiak et al., 2010; Guelker, 2012; Lilienfeld et al., 2012; Patrick et al., 2009; Smith et al., 2013). However, due to various protective factors, such as an authoritative socialization, loving maternal engagement, rewarding social network, and altruistic and prosocial role-models, they are not mean or disinhibited (TriPM), not coldhearted or impulsively antisocial (PPI), and do not display pathological levels of affective, lifestyle, and antisocial features (PCL instruments). On the contrary, despite their emotionally deficient, narcissistic, and socially insensitive nature, ‘socialized’ variants are adapted to society in a healthy and constructive manner (Dutton, 2012; Lilienfeld et al., 2012; Lykken, 1995; Smith et al., 2013). I have thus not included this group in figure 2.3 because this figure is intended to be
a schematization of pathological subtypes exclusively.

2) The second group is termed “controlled primary psychopathy” and consists of individuals who show the same core characteristics and emotional deficiency as the first group but who, due to less favorable childhood experiences such as maternal neglect/disengagement and social rejection, have become disaffiliated from their social surroundings. These primary psychopaths display high scores on both the boldness and meanness domains (TriPM), fearless dominance, Machiavellian egocentricity, and coldheartedness facets (PPI), and show significant interpersonal and affective features (PCL instruments). Thus, in addition to their emotional deficiency, this group is additionally characterized by a malignant narcissistic personality profile as Kernberg described it (i.e., need for control/power, aggression, callousness, and sometimes sadism) (Kernberg, 1992). Nonetheless, despite their malignant narcissistic style, controlled primary variants are not disinhibited (TriPM), impulsively antisocial (PPI), and do not display high scores on the lifestyle and antisocial features (PCL instruments). Furthermore, compared to their more disinhibited counterparts, controlled psychopaths are characterized by a more healthy maturation and functionality of brain regions involved in executive functioning, attentional processing, and behavioral stability/flexibility (most notably the hippocampus and PFC), enabling them to pursue long-term goals, sensitively adjust behavioral strategies in response to feedback, and successfully navigate society.

3) The third and behaviorally most disturbed variant is termed “disinhibited primary psychopathy”. Disinhibited primary psychopaths are characterized by high scores across all domains as defined by the TriPM, PPI-R, and the PCL instruments. In addition to their malignant narcissistic personality, disinhibited psychopaths are impulsively irresponsible, persistently antisocial, and overtly aggressive (Hare, 1993, 2003; McCord and McCord, 1964). However, the larger majority does not go on to commit severely violent acts such as rape, manslaughter, or murder and instead wanders in the periphery of society living a meaningless, parasitic, antisocial, and short-sighted lifestyle (Cleckley, 1941; Hare, 1993; Lykken, 1995).
Therefore, boldness (TriPM), fearless dominance (PPI-R), and interpersonal features (PCL instruments) potentially represent the core domains on which primary psychopaths show homogeneity (e.g., Babiak et al., 2010; Patrick et al., 2009; Lilienfeld et al., 2012). Conversely, the heterogeneity observed in the primary psychopathic population is likely to manifest on the other domains of these instruments.

*Figure 2.3* The different antisocial personalities hypothetically schematized according two axes of emotional functioning and self-control/cognitive functioning. The color gradient from green to orange and finally red represents the degree of pathology and maladjustment. The entire grid is continuous rather than categorical meaning that primary and secondary psychopathy, or that narcissistic personality and controlled psychopathy, reside on a continuum that spans from low (primary psychopathy) to normal (detached secondary psychopathy) to high emotionality (unstable secondary psychopathy). The corresponding emotional disturbances are named deficiency, hypoappraisal, and dysregulation respectively.

Therefore, boldness (TriPM), fearless dominance (PPI-R), and interpersonal features (PCL instruments) potentially represent the core domains on which primary psychopaths show homogeneity (e.g., Babiak et al., 2010; Patrick et al., 2009; Lilienfeld et al., 2012). Conversely, the heterogeneity observed in the primary psychopathic population is likely to manifest on the other domains of these instruments.
The secondary psychopathic continuum

In contrast, individuals who also score exceptionally high on nearly all psychopathy domains but who do not display the emotional deficiency that is so characteristic of primary psychopathy may belong more specifically to the secondary psychopathy group. Given the literature thus far, the etiology of secondary psychopathy, including traits such as aggression, impulsivity, social disaffiliation, callous hostility, and global antisociality, might be explained by the interaction between genetic liabilities, hormonal imbalances, and social experiences that can interactively impair the maturation of affective regulatory and appraisal systems situated in the vmPFC and lead to a disaffiliated and hostile worldview. More specifically, the emotional disturbance that is associated with secondary psychopathy is likely to result from dysfunctional top-down appraisal and regulation of emotions and control over behavioral urges rather than dampened bottom-up emotional input as observed in primary psychopathy.

In the following chapters, I will argue that on the level of neurophysiology, secondary psychopathy is likely characterized by higher levels of testosterone activity/reactivity, a deficient serotonergic regulation of affective and motivational processes, and a corresponding dysregulation of the HPA-axis (either over- or underactive; impaired predictive allostasis). Furthermore, both emotional hypoappraisal and dysregulation can predispose towards a large range of both internalizing and externalizing disorders but could specifically lead to secondary psychopathy in the context of hostile attributional biases and social disaffiliation due to relational traumas (abandonment) and severe levels of abuse, neglect, and/or rejection.

Because of their hostile and impulsive nature, secondary psychopaths may particularly display high levels of meanness and disinhibition (TriPM), impulsive antisociality and coldheartedness (PPI-R), and affective, lifestyle, and antisocial features (PCL instruments). However, since secondary subtypes do not possess the fearlessness and social potency that characterizes primary types more specifically, their scores on the boldness domain (TriPM), fearless dominance scale (PPI-R), and the interpersonal facet (PCL instruments) are likely to be lower (Cox et al., 2013; Poythress et al., 2010).

In response to the above analysis we might hypothetically differentiate between two secondary psychopathic subtypes who reside on a continuum that spans from normatively neurotic/affectively stable to highly neurotic/affectively
unstable;

1. The first group which is phenotypically most similar to primary psychopathy is termed “detached secondary psychopathy” and is characterized by a peculiar dissociation between emotion and cognition (emotional detachment). An important point of divergence between primary psychopathy and the individuals in this group regards their reaction to acute stressors or immediate threat—that is, primary psychopaths show a properly dampened fear and insouciance towards the outcomes of their actions afterwards, whereas the secondary psychopaths in this group mainly display an inability to appraise the potential consequences of their behavior beforehand but may react with strong affect such as frustration, anger, and anhedonia after discovering that they have made a bad decision (Yildirim and Derksen, 2013). Furthermore, in spite of their impulsivity and aggression, this group is not necessarily dysregulated in affect or neurotic and more closely resembles the ASPD category of the DSM-5 section III (Anderson et al., 2014; Kerig et al., 2012; Orsillo et al., 2007; Porter, 1996; Poythress et al., 2006; Schore, 2001b).

2. The second group is termed “unstable secondary psychopathy” and includes individuals who are primarily dysregulated in affect (emotional dysregulation) and therefore display high levels of anxiety, dysphoria, and hostility in addition to callousness, impulsivity, and aggression. Unstable psychopaths are highly fearful and anxious of the outside world and discharge intrapsychic conflicts in an aggressive and externalizing manner. In other words, these individuals are characterized by an underlying character neurosis that mediates their acting-out and violent behavior. This subtype can be seen as a hybrid condition of the BPD and ASPD categories of the DSM-5 section III (Davidson et al., 2000; Karpman, 1941; Putnam & Silk, 2005; Scott et al., 2014; Schore, 2001b; Sprague et al., 2012; Yildirim & Derksen, 2013). See figure 2.3 for a schematization of the different primary and secondary psychopathic subtypes.
CHAPTER 3
SEROTONERGIC RISKS TOWARDS EMOTIONAL PATHOLOGY

*Everything is About Balance*
ABSTRACT
Since its theoretical inception, psychopathy has been considered by philosophers, clinicians, theorists, and empirical researchers to be substantially and critically explained by genetic factors. In this systematic review and structural analysis, new hypotheses will be introduced regarding gene-gene and gene-environment interactions in the etiology of both primary and secondary psychopathy. Theory and research from neurobiological and behavioral sciences will be integrated in order to place this work in a broader conceptual framework and promote synergy across fields. It is examined how various serotonergic components and polymorphisms in corresponding genes (e.g., TPH, 5HTT, HTR1A, HTR2A, HTR2C, and HTR3) might contribute either individually or interactively to the development of these disorders and through which specific biological and behavioral endophenotypes this effect could be mediated. The main premise holds that serotonin mediates our internal homeostasis through moment-to-moment dynamic regulation of inhibition-excitation equilibria in fronto-amygdalar neural circuitry. A weak serotonergic functioning would therefore lead to instability and give rise to dysregulatory pathology as observed in secondary psychopathy while a non-optimally strong serotonergic regulation would lead to unemotionality and give rise to fearlessness and social insensitivity as observed in primary psychopathy. Finally, a short introduction is made into mediating variables such as GABAergic functioning which could potentially alter the decisive effect of serotonergic genotypes on behavior and physiology.

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Throughout the last decade, it has been repeatedly supported that a large variance of psychopathic traits is explained by genes. In light of these findings there is an increasing need to uncover the biological processes that mediate these causal effects. Elucidating the precise causal mechanisms involved could aid tremendously in designing new treatments and preemptive measures. There have been several attempts at reviewing the neurogenetic contributions to psychopathy, but none have sufficiently clarified the causal mechanisms involved. For example, Gunter et al. (2010) review the neurogenetic correlations of different antisocial spectrum disorders (suicide, substance abuse, aggression, antisocial personality disorder, and psychopathy), but do not provide in depth theoretical analyses on how the reviewed genes contribute to these conditions. Glenn (2011a) systematically reviews the potential genetic basis for endophenotypes uniquely observed in primary psychopathy (i.e., emotional deficiency), but focuses solely on the serotonin transporter gene and does not satisfyingly explain how serotonergic alterations increase risk for psychopathic development. In other words, while we are beginning to parse which genes can contribute to psychopathy, we are still far from a satisfying explanation of how these effects actually come about.

In this chapter, I will strive to clarify how alterations to the serotonergic
system (see figure 3.1), whether caused predominantly by genes, or by an
interaction between genes and environment, can profoundly alter emotional
processing and crucially contribute to primary or secondary psychopathy (see
also Yildirim and Derksen, 2013). In my view, these serotonergic alterations
form the basis from which the psychopathic condition crystallizes. The very
core pathology. Therefore, it is argued that psychopathy is by definition and
regardless of subtype associated with some or other form of altered serotonergic
functioning. Although such serotonergic risks may not be sufficient to trigger the
entire range of psychopathic traits, they might interact synergistically with other
risk-factors to incite the psychopathological process.

3.1 Homeostasis and Allostasis:
The Core Framework

An especially helpful framework to understand how serotonin contributes to
mental health and disease, is through the model of homeostasis and allostasis. First
introduced by Cannon (1929), *homeostasis is all about equilibrium*. The practical
meaning of the word homeostasis is somewhat similar to “balance”, as when we
refer to health as being “in balance”. Homeostasis and homeostatic control thus
refer to mechanisms by which physiological processes are stably maintained within
a certain operating range, or ‘set-point’, that promotes health and well-being
(Berntson and Cacioppo, 2007; Schulkin, 2003). When this homeostatic state
is suddenly disrupted, feed-back systems reflexively trigger dynamic equilibrium
adjustments in order to autoregulate towards the biologically relevant operating
range, or establish new homeostatic equilibria, such that growth promoting
processes can be re-initiated (Azmitia, 2007; Berntson and Cacioppo, 2007;
Schulkin, 2003). However, brief disruptions of the homeostatic state are highly
adaptive to survival since such destabilizations serve an important ‘surprise’ or
‘alarm’ function whenever our physiological system first detects an unexpected
but potentially relevant event. These disruptions force us to stop our ongoing
behavior and critically evaluate new possibilities. People who are more sensitive
to such homeostatic disruptions are more sensitively attuned to their (social)
environment and tend to react more emotionally to unexpected events.

In contrast to homeostasis, which signifies autoregulation towards
an internal balance with the environment, allostatic regulations shift these
operating ranges when the organism encounters, or when there is a possibility of encountering, new challenges, rewards, or threats that require an active and mobilizing coping response (Beauchaine et al., 2011; Berntson and Cacioppo, 2007; Schulkin, 2003). Thus, at the heart of allostasis is the depiction of change through sympathetic, catecholaminergic, and hypothalamic-pituitary-adrenal axis (HPA-axis) activation in order to maintain, or achieve, a preparatory state that is adaptive to salient circumstances (whether real or perceived and predicted or acute) (Schulkin, 2003). In effect, allostatic regulations naturally follow when the unexpected event that triggered the homeostatic disruption is also emotionally or cognitively appraised as needing of an active response. Allostatic regulations thus shift physiological operating ranges in order to mobilize energy and attentional resources to effort-requiring events, such as reinforcements, thereby initiating active coping and ensuring that health can be maintained in the long-term.

Furthermore, allostasis can be reactive or predictive in nature (see also figure 3.2) (Schulkin, 2003). Reactive allostasis refers to the potentiation of physiological processes (HPA-axis/catecholamines) in response to unexpected and immediately salient events such as the fight-or-flight response to imminent threat, arousal response to unexpected rewards, and the mobilization of energy resources in response to immediate challenges, and serves to mount an ad-hoc behavioral response to salient events in the here-and-now (e.g., fear) (Schulkin, 2003). Conversely, predictive allostasis refers to the sensitization of the psychophysiological system by inhibiting the autoregulatory tone and sensitizing attentional and emotional processing in order to prepare the organism when salient events are predicted, or likely to be expected (e.g., anxiety) (Berntson and Cacioppo, 2007; Clow et al., 2010; Schulkin, 2003). Both forms of allostasis are potent driving forces of our behavior and non-optimally weak allostatic regulations result in less pronounced activations/inhibitions of behavioral tendencies, non-adaptive coping behaviors, or weak modifications of ongoing behavioral responses.

Since serotonergic processes are first and foremost involved in regulating physiology, it is theorized that the serotonergic contribution to psychological disorders could be understood in the context of a dysfunctional homeostatic or allostatic regulation of specific neurophysiological processes, ultimately sensitizing or desensitizing the neural processing of salient emotional events. The gap between serotonergic genes and behavior could thus possibly be explained through intermediary neuro- and psychophysiological processes.
3.2 New Perspectives on the Role of Serotonin in Mental Health and Disorder: Understanding Socio-Emotional Disorders such as Psychopathy

A first remarkable and informative characteristic of the serotonergic system is that a relatively small number of serotonin synthesizing neurons originating in dorsal raphe nuclei innervate nearly the entire neuroaxis, attesting for a holistically general role of serotonin throughout the brain. Thus, although serotonin has a host of specialized functions through a variety of receptors in different brain structures, the adaptational significance and the essential role that these processes serve in mental health, adaptation, and coping behaviors can only be fully understood within the holistic role that serotonin subserves in neurophysiology. The serotonergic system is visualized in figure 3.1. Relevant structures regarding emotional processing and which will be discussed in this chapter are highlighted and corresponding Brodmann’s areas have been indicated. Based on the holistic role serotonin plays in physiology and ultimately behavior, a basic but crucial differentiation can be made between the serotonergic alterations associated with primary or secondary psychopathy.

To understand the overarching role of serotonin in mental health, one must first understand its evolutionary history. Since serotonin synthesis is strongly dependent on the presence of oxygen, and during the earliest geological times the Earth’s atmosphere had little oxygen, serotonin sprang first into being in unicellular systems capable of photosynthesis and the cellular production of oxygen (Azmitia, 2007, 2010). Azmitia (2010) summarizes that “the indole ring of tryptophan was the first and principal means of converting sunlight into biological energy. In these simplest cells, in the presence of sunlight, serotonin and related tryptophan derivatives function as a powerful antioxidant and serve to help organisms to maintain homeostasis, regulate differentiation, and promote cell division” (pp. 17). Interestingly, it has been recently confirmed that vitamin D, which is closely linked to sun exposure, also activates serotonin synthesis in humans by increasing tryptophan hydroxylase activity in the brain (Patrick and Ames, 2014). The role of serotonin in later evolving biological systems such as fungi, plants, crustaceans, amphibians, mammals . . . and eventually primates and humans is thus somehow consistent with its earliest functions in these
primordial unicellular systems (Azmitia, 2010). That is, while serotonin may interact with sunlight to facilitate homeostasis in more primitive life forms such as plants, in humans it may have additionally evolved to interact with attention, care, and security to facilitate mental and physical health (Dankoski et al., 2014). In more poetic words, loving and secure social attachments may nourish the human psyche such as sunlight nourishes the physiological health of plants, namely as a necessary source of growth and health. Interestingly, recent research has demonstrated that the hormone oxytocin, which is released in response to loving human interaction, touch, and trust, has the ability to improve serotonin functionality at its core, which in turn facilitates mental equilibrium and decreases stress and fear (Mottolese et al., 2014). People with a lower inherent serotonin functionality may thus need more of these regulatory inputs (sunlight, attention, security) to maintain mental equilibrium. In short, although subsequent evolving biological systems such as humans show increasing complexity and serotonin

Figure 3.1 The different structures that will be discussed in this chapter have been indicated. The numbers within the circles represent corresponding Brodmann’s Areas. I have only highlighted the areas important to this discussion. The serotonergic system additionally innervates other cortical structures within the parietal, occipital, and temporal lobes.
became involved in increasingly complex behavioral functions, its holistic role in maintaining health is remarkably consistent throughout evolution.

The theoretical contributions of this chapter are built upon the core proposition that the primary role of serotonin in the brain, and its relevance for psychology, is the active and dynamic adjustment of neurophysiological equilibria in order to maintain neural activity patterns within a homeostatic operating range necessary for proper brain development and a balanced mental health.

First, serotonin plays an important role during practically all phases of brain development including neurogenesis/neuroprotection, gliogenesis, apoptosis, migration, axonal elongation, synaptogenesis, and dendritic elaboration (see Whitaker-Azmitia, 2010 for the full discussion). For example, during critical brain maturation phases, serotonin stabilizes the microtubules which form the main framework of the cytoskeleton of neural cells and thereby regulates the morphology of adult neural networks (Azmitia, 2001, 2007), guides the migrational speed of pyramidal neurons and GABAergic interneurons during the assembly of these neural networks (Riccio et al., 2009, 2011), and homeostatically regulates brain arousal within optimal ranges for successful neurodevelopment and integration to occur (Lambe et al., 2011). In short, a healthy and stable serotonergic functioning homeostatically tunes the proper wiring of the brain, thereby influencing important cognitive and emotional functions throughout life.

Second, serotonin also plays an important role in maintaining mental equilibrium throughout life. During quiet waking states, serotonergic neurons show a spontaneous, regular, and slow firing pattern characteristic of the unmodulated operation of an endogenous pacemaker (Allers and Sharp, 2003). Indeed, during such comfortable waking states, pulse-like serotonin release maintains a smooth balance in active neural modules, mainly through its high-affinity 5HT2 and 5HT3 receptors, which ultimately stabilizes optimal levels of arousal and thereby promotes energy, alertness, and well-being (i.e., optimal activation of baseline catecholaminergic and HPA-axis output). When aroused or stressed, however, the firing activity of these neurons is strongly increased (Kawahara et al., 1993; Linthorst and Reul, 2010). This strong increase of serotonergic activity to psychological stressors (e.g., threat, social stress, worrying) and physiological demands (e.g., hunger, body temperature and blood pressure fluctuations) serves to counterbalance sudden neurophysiological disruptions and excitations by reflexively and dynamically adjusting internal equilibria (e.g., the balance between inhibition and excitation of neural structures) in order to
re-establish homeostasis after disruptions and preserve physiological equilibrium at different levels of allostatic load (Azmitia, 1999, 2007, 2010; Carnevali et al., 2012; Carver et al., 2008; Côté et al., 2004; Davidson et al., 2000; Donovan and Tecott, 2013; Hariri and Holmes, 2006; Holmes, 2008; Laporta et al., 2014; Petty et al., 1996; Pissios and Maratos-Flier, 2007; Poon, 2010).

Stronger stability of the homeostatic state, enabled by optimal levels of serotonergic stimulation of its regulatory receptors (mainly 5HT1A and 5HT2A postsynaptic receptors), attenuates the intensity and duration of disruptions (i.e., less resonance of physiological processes to salient events) or allostatic regulations (i.e., less excitation of physiological processes) and ultimately strengthens psychophysiological self-regulation (Beauchaine et al., 2011; Davidson et al., 2000; Hariri and Holmes, 2006; Holmes, 2008; Keele, 2005; Petty et al., 1996). In psychological terms, this process might be translated as a lower stress-sensitivity and dampened emotional resonance to salient cues and stimuli, and the concomitant ability to maintain in control of emotions and motivations during long-term stressful situations, the anticipation of salient events, and the confrontation with immediate threat/reward.

For example, enhanced serotonergic functionality is associated with lower levels of HPA-axis and amygdalar reactivity to stress and threat coupled with an improved PFC appraisal/regulation of emotion and behavior (low fear), whereas dampened serotonergic functionality has been implicated in dysregulated HPA-axis and amygdalar reactivity coupled with an impaired PFC-mediated appraisal/regulation of emotion and control over behavior (high fear) (Booij et al., 2010, 2012a; Davidson et al., 2000; Drevets, 2003; Fu et al., 2004; Harmer et al., 2006a; Homberg, 2012a; Kitaichi et al., 2014; Man et al., 2011; McCabe et al., 2010; Montoya et al., 2012; Nonkes et al., 2010; Roberts, 2011; Sheline et al., 2001; Siever et al., 1999; Soloff et al., 2000, 2003; Stahl, 2008; Zoratto et al., 2013). Furthermore, highly anxious monkeys who show an inability to regulate fear, indicating a more profound homeostatic disruption and prolonged allostatic regulation, characteristically show lower serotonin levels in the amygdala and smaller mPFC volumes (Mikheenko et al., 2015).

Since serotonin critically regulates vmPFC maturation and functionality, it plays a paramount role in the top-down appraisal and regulation of emotion and, ultimately, emotional behavior. Dysregulation of serotonergic functioning in these structures, especially during early life, would therefore disturb the automatic appraisal and regulation of emotion and behavior when confronted with salient reinforcements (e.g., threat, reward, conflict) (e.g., Den Ouden et al., 2015;
Montoya et al., 2012; O’Keane et al., 1992; Rood et al., 2014; Shamay-Tsoory et al., 2010). Nonetheless, because the maturation and functionality of the vmPFC structures is also strongly dependent on environmental influences such as levels of stress and sensitivity of parental care, this type of socio-emotional detachment is likely to be experience-dependent (Blair, 2007; Blair et al., 2005; Buckholtz and Meyer-Lindenberg, 2008; Karpman, 1941; Ohta et al., 2014; Skeem et al., 2003, 2007; Shore, 2001b; Weber et al., 2008). These results are in line with the hypothesis by Karpman (1941), stating that despite some genetic peculiarities in secondary psychopathic criminals (i.e., lower emotional resilience), the prime reason for disordered conduct may lie in a disturbed socialization.

One explanation is that the increased risk for aggression and impulsivity due to a disturbance in the regulatory functionality of serotonin combined with childhood maltreatment, rather than reflecting a proper neurobiological impairment, could actually reflect evolutionary physiological adaptations to a threatening and resource-scarce worldview. For example, Bilderbeck et al. (2014) found that acute serotonin depletion led to more aggressive, non-cooperative, and selfish strategies in a depletable resource sharing experiment. Thus, in a world where nobody cares and resources are scarce (childhood maltreatment, lower socioeconomic class), long-term adaptiveness and homeostatic stability likely come from selfishly satisfying needs whenever possible (competitive, impulsive, promiscuous, and opportunistic behavior), being on-guard for potential threat (threat hypersensitivity), and fiercely protecting acquired resources (reactive aggression), because of the risk that prosocial, conforming, and sharing behaviors will not be reciprocated and might be taken advantage of. Intriguingly, it has been recently demonstrated that the serotonergic system can undergo important epigenetic alterations over generations, suggesting that the detrimental effects of such childhood experiences may even resonate throughout many subsequent generations, even though the circumstances may have changed considerably (Nikolova et al., 2014).

In sum, the serotonergic system likely undergoes important experience-dependent changes during its maturational development such that in secure environments its activation leads to regulation of emotion due to a healthy regulatory balance of different serotonergic receptors, whereas in insecure environments, its receptor configuration may be tuned to boost emotional responses when activated by a surge of serotonin (see also figure 3.4 and 3.7). Both serve to maintain homeostasis but through different means.

However, in primary psychopathy, the risk for core psychopathic traits
could be increased through other, largely constitutionally based processes that operate more independently from socialization. For example, in the case of interactive genetic mechanisms that significantly increase serotonergic stability and regulatory functionality independent from environment, a more direct route to socio-emotional detachment could be observed through effects on empathy and the survival-based need for social attachments;

Human social attachments, which are prerequisite for empathy and conscience development, are in effect mutually rewarding bonds that serve to co-regulate physiological processes in order to maintain optimal ranges of functioning (Shore, 2001a, 2009; Schulkin, 2011). In the words of Shore (2009); “in a secure attachment relationship the regulatory processes of affect synchrony that co-create positive arousal and interactive repair of negative arousal allow for the emergence of efficient self-regulation. Thus, attachment represents biological regulation between and within organisms” (pp. 3). For example, increased stress responses to laboratory stressors has been related to increased prosocial behaviors and improved social cognition, likely enabling these stress-responsive individuals to seek out and befriend conspecifics, possibly in order to regulate their destabilized physiology (Smeets et al., 2009; Von Dawans et al., 2012). In agreement, the availability of social support and secure attachment is associated with improved serotonin functionality, more adaptive coping behaviors, lower levels of stress-induced psychopathology, and improved regulation of HPA-axis responses to laboratory stressors (Cohen and Wills, 1985; Ditzen et al., 2007; Heinrichs et al., 2003; Kim et al., 2010; Meuwly et al., 2012; Mottolese et al., 2014; Quirin et al., 2008). How serotonin modulates the need for regulatory social attachments can be clarified through an analogy with the interspecies differences in body temperature regulation. Just like homeothermic organisms (i.e., warm-blooded) differ from ectothermic organisms (i.e., cold-blooded) in that they can dynamically regulate body temperature in response to changing environments, making them rather independent from environmental sources of heat, individuals with a more stable serotonin functionality have a more effective and dynamic regulation of internal states in response to changing social environments, stressors, and salient events, making them less dependent on social attachments for stress-regulation, and thus by nature, more detached.

Second, emotional empathy is an important alarm response by resulting in a stop of ongoing behavior in order to re-appraise the situation (i.e., freeze response), which may then be followed by an allostatic regulation if the situation is appraised as emotionally relevant (e.g., the other is in serious distress) (Blair
Serotonergic risks towards emotional pathology

et al., 2005). Therefore, synergistic genetic effects or strong pharmacological interventions (e.g., SSRI treatment) that strengthen the regulatory functionality of serotonin and stabilize neurophysiological equilibria to a non-optimally strong state (i.e., beyond normal functioning), would be associated with higher socio-emotional detachment and a lower intuitive internal resonation to (social) reinforcements, thereby contributing to fear and empathy deficits. For example, 8-week long SSRI treatment (i.e., sertraline) is associated with an increase in core psychopathic traits but a decrease in impulsivity as measured by the Psychopathic Personality Inventory (PPI) (Dunlop et al., 2011). Also, long-term treatment with SSRI’s is consistently associated with a significant emotional blunting in reaction to adversity and an emotional indifference to the feelings of others (“just not caring”) (McCabe et al., 2010; Opbroek et al., 2002; Price et al., 2009; Price and Goodwin, 2009; Stahl, 2008).

However, in contrast to long-term SSRI treatment, acute increases in serotonergic neurotransmission, brought about by a single SSRI administration (i.e., citalopram), results in an increase in moral behaviors and a greater empathy response (Crockett et al., 2010). Similarly, administering tryptophan as a dietary supplement increases charitable donating (Steenbergen et al., 2014). However, acute SSRI administration also results in stronger conditioned fear expression (Burghardt et al., 2007), higher levels of amygdalar reactivity to threat (Bigos et al., 2008), and improved recognition of fearful facial expressions (Browning et al., 2007; Harmer et al., 2003). These results are particularly pronounced in anxious subjects (Pettersson et al., 2014). Therefore, acute and strong increases in brain serotonin levels may in fact disturb serotonin-driven homeostatic regulation because the brain has not yet adapted to a higher operating range. These acute increases may thus drive neural prediction errors through excitatory postsynaptic receptors and thus result in nervousness, hypervigilance, and anxiety. Since acutely heightened stress responses have been found to relate to prosocial behaviors (Von Dawans et al., 2012), it is likely that this temporary homeostatic disruption brought about by serotonin enhancing drugs is due to higher levels of stress-sensitivity. Indeed, acute treatment with citalopram enhanced acquisition, whereas long-term treatment (21 days) impaired the acquisition of fear-potentiated startle (Burghardt et al., 2004; Grillon et al., 2007, 2009; Homberg, 2012a). These results are also consistent with the high levels of restlessness, agitation, and anxiety reported by many patients during the first few days of SSRI treatment (Homberg, 2012a; Kent et al., 1998). It can be deduced from these combined results that serotonergic functioning must be
strengthened and stabilized for longer periods in order to desensitize and stabilize emotional processing and both acute drops and increases of serotonin activity can result in destabilization of emotion.

In sum, primary psychopathic traits are likely to be associated with a genetically determined and non-optimally strong serotonin regulatory functionality thereby providing healthy levels of baseline arousal while effectively dampening the psychophysiological response to threat, punishment, and social stimuli. In contrast, secondary psychopathy may be associated with the opposite serotonergic profile, namely a non-optimally weak stability and efficiency in serotonin-driven autoregulation of neurophysiology thereby leading to non-optimal levels of baseline arousal, boosting/sensitizing psychophysiological processes, and weakening self-regulation and -control. In agreement, core psychopathic traits, and the often comorbid instrumentally aggressive behavior in humans or offensive aggression in animals (goal-driven behavior), is associated with stronger serotonergic functionality, whereas secondary psychopathy and reactive types of aggression (impulse-driven behavior) are associated with a dampened serotonergic functionality (e.g., Davidson et al., 2000; De Boer and Koolhaas, 2005; Dolan and Anderson, 2003; Flory et al., 2007; Glenn, 2011a, 2011b; Homberg, 2012a; Montoya et al., 2012; O’Keane et al., 1992; Olivier, 2004; Soderstrom et al., 2001; Soloff et al., 2000, 2003; Van de Giessen et al., 2014). Furthermore, while reactive aggression was associated with a decreased 5HTT density in the mPFC, suggesting lower serotonergic functioning, callousness and associated proactive aggression showed a positive correlation (Rylands et al., 2012; Van de Giessen et al., 2014). Finally, severe conduct disorder and sexual aggression in adolescence has been related with near undetectable serotonin values (Kumar et al., 2014).

In simpler words; serotonin helps us to maintain balance in our minds and behavior, even when the environment is stressful, the situation threatening, or the task challenging, and thereby promotes health and growth. However, *even balance should be balanced* and either too much or too little balance can have a negative effect on emotional functioning; hyperstability of serotonergic regulation may disproportionately strengthen the homeostatic state and thereby severely dampen internal fluctuations to emotional or stressful events (e.g., socio-emotional detachment), whereas deficient serotonergic regulation would destabilize the homeostatic state, thereby causing a dysregulation of internal states (e.g., emotion and motivation) to salient events.
3.3 Allostasis in Primary and Secondary Psychopathy: HPA-axis functioning

The homeostatic stability differences between primary and secondary psychopathy are further reflected in corresponding physiological coping patterns to stressful events, such as indicated by specific abnormalities in their stress endocrinological profiles. In discussing these abnormalities, I will make the distinction between abnormalities reported in the more subtle hypothalamic-pituitary-adrenal axis (HPA-axis) tonic activity changes to potential contingencies and diurnal patterns (i.e., predictive allostasis) and the more intense phasic HPA-axis responses to immediate reinforcements (i.e., reactive allostasis) (see figure 3.2). Although a detailed review of the HPA-axis, and the genes that code for its enzymes and receptors, is beyond the scope of this chapter, this section serves mainly to explore which alterations are found regarding reactive and predictive allostasis in different psychopathic samples, and how these characteristic alterations relate to the neural pathologies observed in these groups (see chapter 2). For those who are interested, there have been reviews and empirical studies that investigate how polymorphisms in genes that affect HPA-axis endocrinology may affect stress-related psychopathology (see Derijk, 2009; Gillespie et al., 2009; Guillaume et al., 2013; Klok et al., 2011; Laryea et al., 2012; Mahon et al., 2013; Ridder et al., 2013; Sheikh et al., 2013; Tyrka et al., 2009).

First, basal HPA-axis output mediates optimal arousal levels according to expectations (i.e., predictive allostatic regulation). Fluctuations in this basal output can be modulated by diurnal patterns, to promote wakefulness in the morning, but also when confronted with potentially challenging, novel, or salient events to promote alertness, active coping, and energy mobilization. Thus, cortisol (abbreviated as C) levels are highest at waking or when anticipating potentially salient events and serve to prepare and energize the physiological system to cope with the upcoming challenges. Humans naturally behave in ways that will homeostatically regulate basal levels of C to pleasurable ranges of activity (Shabani et al., 2011; Zuckerman, 2007). Too high levels of basal HPA-axis activity could therefore result in the avoidance of further stimulating and arousal-inducing events, and motivate the individual to seek out predictability and safety from harm (e.g., harm avoidance and behavioral inhibition), whereas too low levels can contribute to the pursuit of stimulating activities and lead to sensation,
novelty, and reward seeking behaviors (Blair et al., 2004; Rademaker et al., 2009; Russ et al., 2012; Schulkin, 2003, 2011; Shabani et al., 2011; Tarullo et al., 2011; Tyrka et al., 2006).

Second, more acute but stronger HPA-axis responses to unexpected events in the here-and-now (phasic responses) mediate the strength with which energy resources are mobilized to such immediate reinforcements (i.e., reactive allostatic regulations) (Schulkin, 2003). Too strong HPA-axis reactions to immediate reinforcements may result in exaggerated physiological and behavioral activations and thereby lead to over-reacting and impulsivity, whereas too weak HPA-axis reactions may contribute to a non-adaptively dampened physiological and behavioral response to such salient events, and thus lead to fearlessness and detachment.

*Predictive allostasis:* In general, low basal C levels, indicative of lower basal HPA-axis output, have been related to increased BAS scores, impulsivity, aggression, and antisocial behaviors in both psychopathic and non-psychopathic samples, and most consistently in adolescent males (Alink et al., 2008; Cima et al., 2008; Feilhauer et al., 2013; Haltigan et al., 2011; Hawes et al., 2009; Kariyawasam et al., 2002; Kobak et al., 2009; Locke et al., 2009; Loney et al., 2006; McBurnett et al., 2000; Pajer et al., 2001; Platje et al., 2013; Oosterlaan et al., 2005; Poustka et al., 2010; Van Goozen et al., 1998; Vanyukov et al., 1993; Windle, 1994). However, some studies found non-significant results (Azar et al., 2004; Bergh et al., 2008; Krueger et al., 1989; Van Goozen et al., 2000), and one
found higher levels of basal C in conduct disordered adolescents (Van Bokhoven et al., 2005).

Interestingly, in line with these endocrinological findings, and the proposition that secondary psychopathy is related to abnormal vmPFC functioning, neonatal lesioning of the vmPFC in rhesus monkey’s results in lower levels of waking C and higher levels of hostility during adulthood, but shows no significant association with phasic HPA-axis reactivity to stressors (Raper et al., 2012). Accordingly, the intensity of HPA-axis reactivity to stressors is determined primarily by genetic factors and less by social experiences, whereas the more prolonged fluctuations in basal activity are mainly affected by fronto-limbic structures (e.g., hippocampus and vmPFC) and strongly determined by both genotype and social experiences (Hawes et al., 2009; Liu et al., 1997; Wüst et al., 2004). Since the life-long functioning of the vmPFC and HPA-axis is programmed and fine-tuned during the early years of life, traumatic and abusive experiences during childhood can permanently alter vmPFC cortex maturation and basal HPA-axis fluctuations throughout life, and both alterations are somehow linked (Shore, 2001b; Wilkinson and Goodyer, 2011).

One plausible hypothesis is that a normal to higher inborn amygdalar reactivity to threat coupled with the experience-dependent maldevelopment of the vmPFC early in life could impair self-regulation, thus increasing and prolonging HPA-axis activation during stressful experiences (Taylor et al., 2008). Prolonged hyperactivity of the HPA-axis may in due time lead to a compensatory downregulation of the HPA-axis stimulatory CRH receptors, or upregulation of the feedback-providing glucocorticoid receptors in the pituitary, which both serve to counterbalance chronic stressful states (De Bellis, 2002; Klaassens et al., 2012; Morris et al., 2012; Wilkinson and Goodyer, 2011). However, when traumatic circumstances subside and/or external stimulation levels drop below the threshold needed to activate the now desensitized HPA-axis, strong concomitant decreases in baseline energy, motivation, activation, arousal, and anticipation could heighten the risk for a host of psychopathological conditions (i.e., depression, dissociation, aggression, impulsivity, stimulation-seeking, substance abuse). For example, in maltreated children, HPA-axis activity is significantly higher at the time of the trauma and in the few months thereafter, but shows a significant downregulation several years after traumatic circumstances have subsided (De Bellis, 2002; Doom et al., 2013; Wilkinson and Goodyer, 2011). These results suggest that trauma victims may initially show increased levels of HPA-axis activity and only present with low basal C after a prolonged period of dealing
with the post-traumatic stress. Furthermore, meta-analysis of the literature indicated that individuals with post-traumatic stress disorder (PTSD), especially when due to sexual or physical abuse and without comorbid major depression, displayed lower levels of basal C (Meewisse et al., 2007; Morris et al., 2012), and a stronger C suppression in response to the dexamethasone suppression test (DST) suggesting non-optimally strong feedback control mechanisms (Klaassens et al., 2012).

However, increased basal C activity has also been reported in individuals exposed to early life adversity (Wilkinson and Goodyer, 2011). The heterogeneity of these results on the direction of basal C alterations might be explained by the type of stressor measured (repeated childhood abuse or major life events), whether the stressor was controllable/uncontrollable or acute/chronic, and the length of time between the stressor and data collection. Repeated, uncontrollable, and chronic physical/sexual abuse early in life, and the accompanying continuous anticipatory stress are more likely to result in lower levels of basal C several years after the traumatic circumstances have subsided and primarily due to the aforementioned stress-habituation mechanisms. Conversely, acute stressors or unexpected life events such as the loss of a parent and single abusive experiences may specifically condition and instill anticipatory anxieties and hypervigilance should another such dreaded experience occur again and can therefore result in higher levels of basal HPA-axis output later in life.

In sum, repeated or chronic abusive life experiences during critical phases when the life-long functionality of the vmPFC and HPA-axis is programmed, could desensitize basal HPA-axis output later in life, and individuals with less effective internal regulation could be more vulnerable to these effects.

Reactive allostasis: Reactive aggression, conduct disorder, and antisocial behavior have been related to increased laboratory induced HPA-axis reactivity (i.e., social stress task, social conflict situation, frustration induction, administration of exogenous C), especially in females (Böhnke et al., 2010; Kobak et al., 2009; Lopez-Duran et al., 2009; McBurnett et al., 2005; Susman et al., 2010). However, different studies also found lower HPA-axis reactivity in antisocial and aggressive subjects (Buydens-Branchey and Branchey, 2004; Fairchild et al., 2008; Snoek et al., 2004). Indeed, a large meta-analytic study reported that externalizing behavior is primarily related to basal C levels and shows no consistent relationship to HPA-axis reactivity (Alink et al., 2008), similar to the primates with vmPFC lesions (Raper et al., 2012). These results attest to a high
level of within-group variability of HPA-axis reactivity in secondary psychopathic individuals. That is, reduced levels of baseline HPA-axis activity and impaired vmPFC functionality brought about by long-term allostatic states, likely impair the physiological system in its ability to appreciate or anticipate the emotional significance of upcoming events, resulting in inappropriate physiological and psychological reactions. These inappropriate reactions could be manifested through either hypo- or hyperreactivity, dependent on idiosyncratic appraisals of the encountered stressor as either within or beyond coping capacity (Buchanan et al., 2010; Denson et al., 2009).

Both reduced and increased HPA-axis reactivity has been consistently reported in individuals exposed to early life stressors such as physical and sexual abuse, but a reduced reactivity seems to predominate, especially in response to early childhood maltreatment (Lovallo, 2013). Interestingly, gender-differentiated effects have been reported; males with mPFC lesions show a blunted HPA-axis reactivity, whereas females show increased HPA-axis reactivity possibly indicating differences due to cognitive appraisals (Buchanan et al., 2010), which may have been mediated partly by sex-specific gonadal hormones such as testosterone (Goel and Bale, 2010; Van Honk et al., 2004b). Men with vmPFC dysfunctioning may be more likely to underestimate potential threats or punishments in a given circumstance and overestimate their capacity to cope with it, resulting in dampened HPA-axis reactions and increased levels of overconfident and risky behaviors, whereas in women, opposite appraisals may increase HPA-axis reactivity and contribute to stress- and emotion-driven impulsive, compulsive, and aggressive behaviors.

In contrast to antisocial, aggressive, and impulsive behaviors convergent with factor 2 of the PCL-R and secondary psychopathy more specifically, factor 1 of the PCL-R and fearlessness as associated with primary psychopathy has been consistently related to attenuated phasic HPA-axis reactivity to experimentally induced social stress (i.e., public speaking task) or physical stress (i.e., cannulation) but shows no consistent associations with baseline C levels (Cima et al., 2008; Dolan et al., 2001; Feilhauer et al., 2013; Glenn, 2011b; Glenn et al., 2011; Loney et al., 2006; O’Leary et al., 2010; Poustka et al., 2010; Stadler et al., 2011). Since primary psychopathy is characterized by hypo responsiveness of the amygdala to salient stimuli, one mechanism underlying the reduced HPA-axis reactivity could directly relate to deficits in amygdalar reactivity (Taylor et al., 2008).

That is, activation of the central amygdala conveys emotionally relevant
information to the hypothalamus in order to elicit appropriate endocrinological processes during salient events (Flandreau et al., 2012; Gray et al., 1989; LeDoux et al., 1988; Lovallo, 2006; Sah et al., 2003). A significantly lower reactivity of the amygdala and stronger autoregulatory tone on emotional processes may thus concomitantly attenuate the reactivity of the HPA-axis to salient events as observed in primary psychopathic individuals. Lower HPA-axis output during stressors likely protects against stress-induced allostatic overload thereby promoting a stable level of basal HPA-axis activity during long-term allostatic states. Reduced levels of baseline C in as observed in disinhibited primary psychopathic individuals are therefore less likely to spring from destructive environmental effects on the feedback regulation of the HPA-axis but rather from additional biological risk factors such as catecholaminergic genotypes (Walder et al., 2010), and/or substance abuse (Lovallo, 2006), that impair hippocampal and PFC modulation of baseline HPA-axis output.

Synthesis: Taken together, in both primary and secondary psychopathic individuals, antisocial and impulsive behaviors are primarily associated with lower levels of baseline HPA-axis activity. Furthermore, only primary psychopathic individuals consistently show additional inborn deficits in HPA-axis reactivity to a variety of stressors, whereas secondary psychopaths are likely to display a high level of within-group variability in HPA-axis reactivity, partly mediated through the types of childhood adversity, gender-related biological factors, and cognitive appraisals of the stressful event (under- versus overestimation of threat). Secondary psychopaths may thus mainly present with an inability to regulate or modulate arousal levels corresponding circumstances or predicted/potential future events, thereby predisposing towards impulsivity and faulty assessment of potential risks (impaired predictive allostasis), whereas primary psychopathy is mainly related to lower levels of reactive allostatic regulations, which can dampen the internal resonation to salient events and thus result in fearlessness and emotional indifference. Nonetheless, in contrast to the more controlled variants of primary psychopathy, disinhibited primary psychopaths likely show additional decreases in predictive allostatic regulations and secondary psychopaths can show either dampened or increased reactive allostatic regulations, possibly dependent on within-group psychological (e.g., perceived coping capacity) and neurobiological variations.
3.4 Homeostatic Control of Brain Serotonin Levels (TPH, AAAD, and 5HTT): Relevance for Psychopathy

A stable serotonergic homeostasis is first and foremost reliant on its proper synthesis and recycling in the brain. Serotonin synthesis crucially depends on ingested amino acids (e.g., tryptophan), minerals (e.g., zinc, calcium, magnesium) and vitamins (e.g., D3, B1, B3, B6, B9). In the presence of these essential nutrients, and facilitated by high carbohydrate intake and sun exposure, the enzyme tryptophan hydroxylase (TPH) is enabled to convert L-tryptophan into 5HTP, which is then converted to 5HT, or serotonin, by the enzyme L-amino acid decarboxylase (AAAD) (see figure 3.3 and 3.4). Thus, both TPH and AAAD are essential and primary rate-limiting factors in serotonergic functioning.

TPH has a principal role in the homeostatic regulation of intrasynaptic serotonin levels by maintaining adequate levels of synthesis during baseline and dynamically reacting to heightened neurotransmission by refilling emptied vesicles (Boadle-Biber et al., 1986; Hasekawa and Nakamura, 2010; Herr et al., 1975; Linthorst and Reul, 2010). Specifically, higher efficiency of stress-induced transcription of genes controlling TPH expression results in a faster “vesicular refill” which stabilizes serotonergic homeostasis and facilitates mental health (see figure 3.3) (Hasekawa and Nakamura, 2010; Linthorst and Reul, 2010). For example, higher TPH expression has been related to strengthened emotional regulation and dampened HPA-axis reactivity (Chen and Miller, 2012; Waider et al., 2011). Also, highly stress sensitive compared to resilient macaque monkeys showed significantly lower TPH2 expression during both health and stress (Bethea et al., 2013).

In addition, higher basal TPH expression throughout neurodevelopment in utero and early childhood dampens the impact of stressful experiences on adult physiology and behavior (Chen and Miller, 2012). Conversely, blocking TPH synthesis during critical developmental phases has been demonstrated to result in pathological outcomes in animals when reaching adulthood such as attenuation of the prepulse inhibition, aggression, muricide in rats, anxiety, and behavioral disinhibition (Hasekawa and Nakamura, 2010). Therefore, a more efficient stress-induced TPH expression throughout critical phases of socio-
emotional development can effectively strengthen homeostatic regulation of emotion and mood (see figure 3.3).

A second step in the synthesis of serotonin, but which will not be discussed in full detail here, is the conversion of 5HTP into serotonin by the enzyme aromatic L-amino acid decarboxylase (AAAD). Unfortunately, research into the genetic variation of this enzyme, which is encoded by the DDC gene, and its effect on psychology, biology, and behavior is currently scarce. However, since AAAD is a major enzyme involved in the production of a number of neurotransmitters, alterations in its expression do not only affect serotonin and even cause serious physical problems (Helman et al., 2014, Lee et al., 2009b). Nonetheless, preliminary studies have implicated genetic variation in AAAD in psychological constructs such as attention, anxiety, autism, and substance abuse (Costas et al., 2010; Ma et al., 2005; Toma et al., 2013; Zhu et al., 2013).

In addition to TPH and AAAD, the serotonin transporter (5HTT) also plays an important role in maintaining serotonin homeostasis. While TPH and AAAD control intrasynaptic serotonin levels by dynamically adjusting synthesis in accord with demand (production mechanism), 5HTT homeostatically controls serotonin levels by rapidly transporting released serotonin back into the presynaptic terminal for re-packaging and re-use (recycling mechanism) (Stahl, 2008). Lower expression of 5HTT in the brain increases and prolongs synaptic serotonin levels after release, which can lead to compensatory mechanisms to suppress serotonin activity or alter its functional effect on postsynaptic neurons (see figure 3.4) (Daws and Gould, 2011; Hariri and Holmes, 2006; Van der Doelen et al., 2014). For example, genetically deleting the 5HTT in knockout mice increases 5HT1A autoreceptor feedback inhibition and skews postsynaptic receptor sites in the amygdala towards an excitatory drive, likely to counterbalance a synaptic deficiency (see Daws and Gould, 2011; Gobbi et al., 2001; Hariri and Holmes, 2006; Holmes et al., 2003; Li et al., 2003a; Soiza-Reilly et al., 2015). In addition, adequate inward transport of released serotonin rather than the much slower refilling of storage pools through TPH mediated synthesis, facilitates a homeostatic balance in neuronal serotonin levels since healthy levels of neurotransmission can be maintained over prolonged bouts of neurotransmission (Caron and Gainetdinov, 2009). Lower 5HTT expression has been related to increased fear conditioning and emotional reactivity in humans (Åhs et al., 2015). The effect of an efficient or non-efficient stress-induced TPH and 5HTT expression on brain serotonin stability and morphology is schematized and discussed in figure 3.3 and 3.4 on the following pages.
Serotonin Hyperstability (Reduced Plasticity)

Efficient adjustment of TPH and SHTT activity according demand thus adaptively maintaining a stable high operating range and a regulatory balance of postsynaptic receptor sites in the amygdala.

Active Wakefulness

- L-tryptophan
- Serotonergic Neuron
- TPH
- AAAD
- SHTP
- Reserve Pool
- SHT
- SHTT
- 5HT1A auto

Acutely Stressed State

- Short-term Stressor
- (TPH)
- AAAD
- Intersynaptic
- 5HT1A
- 5HT2A
- 5HT3

Chronically Stressed State

- When the Stressor Continues
- (TPH)
- AAAD
- Intersynaptic
- 5HT1A
- 5HT2A
- 5HT3
Figure 3.3 A step by step schematization of the effect of serotonin hyperstability (decreased plasticity) in the amygdalar complex on emotional processing and resilience (as associated uniquely with primary psychopathy). For example, this profile is more likely to characterize individuals who are homozygous for both the $L$-allele of the 5HTTLPR and G-allele of the G(-703)T SNP in the TPH2 gene.

(1) Beginning with the first step, the active wakefulness, which is the unstressed active state, we can see that compared to those with serotonergic hypostability (see next page), TPH mediated serotonin synthesis is higher and 5HTT driven re-uptake and recycling more efficient. Due to these first advantages, serotonin is more adequately confined to the synaptic cleft and less serotonin is diffused and lost (better recycling). In addition, because 5HT1A receptors have lower affinity (need more serotonin to be properly activated) and since there is a lower density of 5HT2C and 5HT3 receptors, serotonin mainly activates the high affinity 5HT2A receptors on GABAergic interneurons during tonic release rates thereby providing a strong inhibitory tone on amygdalar fluctuations.

(2) Then, during an acutely stressed state, TPH expression is increased and serotonin synthesis boosted to supply higher demand, but 5HTT is also efficiently upregulated to control for the suddenly increased synaptic serotonin levels. These mutually counterbalancing mechanisms ensure that the increase of synaptic serotonin is proportionate and controlled, that less serotonin escapes the synaptic cleft, and that more serotonin gets recycled, thereby negating the need to deplete reserve pools. Therefore, despite higher neurotransmission, reserve pools remain intact and a stable high operating range can be achieved. In addition, due to a higher ratio of 5HT1A/5HT2A-to-5HT2C/5HT3 postsynaptic receptor stimulation during heightened neurotransmission, serotonin inhibits rather than excites amygdalar reactivity; the stress is quickly contained and internal homeostasis restored.

(3) In due time, if the stressor continues into a more chronically stressed state, such as with inescapable stressors, 5HTT and TPH driven serotonin synthesis reach a sustainable equilibrium with synaptic serotonin demand and ensure that synaptic serotonin levels remain stable (not too high or too low). These regulatory mechanisms preclude over- or understimulation of 5HT1A, 5HT2A, 5HT2C, or 5HT3 postsynaptic receptors or 5HT1A presynaptic autoreceptors and, thus, preclude morphological changes to the receptor complex. Due to these adaptive adjustments, coping behavior is less avoidant or passive and more confronting, optimistic, and active, ultimately containing the stress experience and quickly regaining a sense of control (whether such control is perceived or real). In other words, primary psychopaths never lose their optimistic view on life, no matter how stressful the circumstances and how scarce the opportunities (incarcerated, hospitalized, in financial crises, chaotic environments, etc.).

As a side note; this schematization is specific to emotional deficiency. That is, because of a lower synaptic serotonin during baseline, the high-affinity 5HT2C and 5HT3 receptors should actually be higher compared to those with serotonin hypostability. However, this figure is meant to represent the hyperstability that characterizes primary psychopathy more specifically and as will be discussed later on in the chapter, in order for a high stable serotonin operating range to dampen emotion, there should be a regulatory balance of postsynaptic receptors (5HT1A and 5HT2A in equilibrium) and low levels of the excitatory 5HT2C and 5HT3 receptors. Primary psychopathy may thus be associated with low genetic expression of the 5HT2C and 5HT3 in addition to a higher and more stable expression of postsynaptic 5HT1A and 5HT2A receptors.
Serotonin Hyposstability (Increased Plasticity)

Insufficient upregulation of 5HTT and TPH activity according to demand thus quickly depleting reserve pools during heightened neurotransmission and leading to synaptic serotonin deficiency after prolonged stressors, which, in turn, skews receptor balance towards an excitatory drive in the amygdala.
Causal mechanisms: homeostatic control of brain serotonin

Figure 3.4 A step by step schematization of the effect of serotonergic hypostability (increased plasticity) in the amygdalar complex on emotional processing and resilience in response to stressors (as associated more generally with affective pathology but also with secondary psychopathy). For example, this profile is more likely to characterize individuals who are homozygous for both the s-allele of the 5HTTLPR and T-allele of the G(-703)T SNP in the TPH2 gene.

1) Already during the least demanding state, namely active wakefulness, these individuals show vulnerabilities; they have a lower expression of both TPH and 5HTT. A lower synthesis coupled with a greater diffusion and loss of released serotonin reduces the neurons ability to built up adequate reserves. The serotonergic system struggles to maintain balance and the smallest setbacks may lead to disproportionate disruptions to this vulnerable homeostasis. Because of the higher intersynaptic serotonin and an excitatory balance of postsynaptic receptors (lower 5HT1A and higher 5HT2A, 5HT2C, and 5HT3), amygdalar fluctuations are more labile and these individuals are more readily excitable, sensitive, and reactive, even during unstressed circumstances.

2) Then, when an acute stressor occurs, the higher demand for serotonin is not adequately met with an equally strong increase of TPH mediated synthesis or 5HTT driven re-uptake and recycling, which quickly necessitates the depletion of reserve pools. In addition, due to the higher ratio of excitatory to inhibitory receptor balance, acute stressors have a strong excitatory effect on emotion thereby prolonging the emotional reaction and impairing adequate regulation. Such individuals direly need a cool-down period so that their serotonergic systems can slowly re-adapt and refill its reserve pools and thereby re-establish equilibrium.

3) However, during more chronic stressed states, when the much needed rest to re-establish homeostasis is not granted, serotonin reserve pools are further and further depleted. Also, the greater diffusion of serotonin in the synaptic cleft and a lower re-uptake rate of released serotonin in due time provokes the 5HT1A autoreceptor to increase in density to counterbalance for uncontrolled serotonin release. An inefficient synthesis and re-uptake to compensate for the loss of reserve pools in conjunction with the now stronger 5HT1A autoreceptor mediated feedback autoinhibition ultimately engender a period of serotonergic deficiency. Finally, in response to this deficiency, postsynaptic excitatory receptors such as the 5HT2A, 5HT2C, and 5HT3 are upregulated and the receptor balance in the amygdala is even further skewed towards an excitatory balance thus further sensitizing threat and reward-reactivity.

This process may be evolutionary adaptive since harsh and stressful environments necessitate the sensitive detection of both threat and reward to survive. Thus, rather than regulating emotion, serotonin is shaped to boost emotion and behavioral vigor when activated (mainly through 5HT2C and 5HT3 mechanisms). Males from such abusive and stressful backgrounds often feel and believe that they need to watch their back constantly, opportunistically grab whatever they can, and proactively secure their reputation through aggressive dominance so that the ‘competition’ will be discouraged from challenging them or do them harm. Conversely, the trust that comes with secure and loving environments shapes the serotonin system to autoregulate the intensity of emotions when activated (mainly through 5HT1A and 5HT2A mechanisms). This regulatory functionality of serotonin is more adaptive in secure environments because in contrast to insecure environments where competition, aggression, and opportunism hold value, in secure environments it may be virtues such as cooperation, deliberation, and interdependency that are more adaptive to maintain homeostasis.
In humans there are two TPH isoforms; TPH1 and TPH2, that respectively located on chromosome 11 position p15.3-p14 and chromosome 12 position q21.1. Both are important in serotonin synthesis but have differential expression patterns, with TPH2 operating predominantly in the brain whereas TPH1 additionally regulates peripheral actions of serotonin in the body (Lin et al., 2007; Walther and Bader, 2003). In order to identify risk genotypes and understand the causal mechanisms involved, it is necessary to first examine the functional relevance of these genotypes. So the order of discussion when examining potential genetic contributions to psychopathy throughout this thesis is to (1) first clarify the how the studied genotype impacts on neuronal expression patterns and monoaminergic functionality, (2) establish its relationship with neurophysiological, psychophysiological, and behavioral patterns, and finally (3) discuss its potential relevance for the etiology of primary or secondary psychopathy.

*TPH1 genotype A(218)C:* One source of genetic variance in the expression of TPH1, is the A(218)C single nucleotide polymorphism (abbreviated as SNP; see for example figure 3.5) (rs1800532). Although the functional relevance of this SNP is unclear at this point, the C-allele has been associated with higher levels of serotonin metabolite (5-hydroxyindoleacetic acid: 5-HIAA) in cerebrospinal fluid (CSF), and stronger serotonergic responsivity to a fenfluramine challenge, especially in males (Jönsson et al., 1997; Manuck et al., 1999). Thus, the C-allele is associated with a higher serotonin synthesis and bioavailability.

In a large prison sample, the C-allele was disproportionately present in inmates with antisocial personality disorder (APD) (Cuartas Arias et al., 2011). In contrast, A-homozygosity (lower serotonin synthesis) has also been related to externalizing behaviors, but is additionally associated with harm avoidance and different mental disorders characterized by high emotional reactivity, such as violent suicide attempts, higher levels of anger related traits, bipolar disorder, and borderline personality disorder (BPD) (Abbar et al., 2001; Anghelescu et al., 2005; Bellivier et al., 1998; Buresi et al., 1997; Mann et al., 1997; Manuck et al., 1999; Nielsen et al., 1998; Rujescu et al., 2002; Tsai et al., 1999; Wilson et al., 2009).

Since both alleles have been related to antisocial behavior, clarification regarding their specific effect on psychology may be achieved by specifying
associated endophenotypes. For example, suicide attempters with A-homozygosity showed lower levels of anger control, made more impulsive decisions, and learned less from repeated punishments in the IOWA gambling task, thus demonstrating lower levels of emotional regulation and higher levels of impulsive responding (Baud et al., 2009; Jollant et al., 2007). However, C-allele inpatients without psychotic disorders have also been found to score higher on a measure of impulsive behavioral tendencies (Staner et al., 2005). Nonetheless, individuals with major depressive disorder who are homozygous for the C-allele show lower amygdalar reactivity to sad vs. neutral faces compared to other allelic configurations, also after including duration of illness and medication as covariates in the analysis (Lee et al., 2009a).

These results demonstrate that both the A-allele and C-allele may be associated with psychopathic traits through increased impulsivity, but that the A-allele may be more strongly related to these behaviors through emotional dysregulation, higher harm avoidance, and higher levels of anger (more closely associated with secondary psychopathy), whereas in C-allele carriers other endophenotypes may be involved, possibly an insensitivity to punishment (more closely associated with primary psychopathy).

**TPH2 genotypes G(-703)T**: Interindividual variation in the expression of TPH2 in the human brain is regulated by at least 22 different SNP’s. Among these, the G(-703)T SNP is the most widely studied (rs4570625) (see figure 3.5) (Lim et al., 2007). Using a luciferase reporter assay, Chen et al. (2008) reported that the haplotype containing the T-allele of the G(-703)T and T-allele of the T(-473)A SNP (rs11178997), showed the lowest levels of genetic expression but only when the A-allele for the A(90)G SNP in 5’UTR region (rs11178998) was also present (i.e., TTA-haplotype), indicating a potent inhibitory effect by the A(90) allele on the post-transcriptional process of mRNA, regardless of the upstream sequence or cell line (see Chen et al., 2008 for technical details). Other studies have also found that the A(90)G SNP crucially modifies gene expression regardless of other genotypes (Henkhaus et al., 2010), suggesting that this SNP has an overruling effect on the expression of TPH2. Unfortunately, this SNP has not been studied with regard to psychology and more research into this potentially crucial SNP is paramount.

Contrastingly, however, Scheuch et al. (2007) reported that the TAG haplotype of these three SNP’s showed the lowest expression patterns, and identified the T→A nucleotide change in the T(-473)A SNP as responsible for
this effect. The inconsistencies between the Chen (TTA = low expression) and the Scheuch study (TAG = low expression) could be due to methodological differences (see Chen et al., 2008 for technical discussion of these differences), although it is interesting to note that the sole similarity between the differentially identified low-expressing haplotypes is that both contain the T-allele for the G(-703)T SNP.

However, to complicate matters even more, Lin et al. (2007) reported that it was the GA haplotype of the G(-703)T and T(-473)A SNP’s which was related to lowest gene expression through a reduced binding to Pou domain class 3 transcription factor 2 (POU3F2). Finally, Lim et al. (2007) reported no significant effects of the G(-703)T SNP on mRNA expression patterns.

These highly inconsistent and opposite results preclude powerful predictive hypotheses on the functional relevance of the different SNP’s on
TPH2 mRNA expression and more research is needed. Nevertheless, given that the effect of the G(-703)T SNP on biology and behavior is amply studied, some hypotheses may still be deduced regarding the functional relevance of this specific SNP in mental health.

Examining neurophysiological responses to threat, it has been consistently reported that the T-allele for the G(-703)T SNP is associated with significantly increased amygdalar reactivity to affective stimuli and social threat (Canli et al., 2005, 2008; Furmark et al., 2009; Hermann et al., 2012; Herrmann et al., 2007). TPH2 genotypes might modulate amygdalar reactivity by influencing the efficiency with which the vmPFC is able to regulate limbic responses during emotional events (Osinsky et al., 2009). For example, TPH2 gene expression patterns are highest in the raphe nucleus and vmPFC and significantly lower in other limbic structures (Booij et al., 2012b; Zill et al., 2004, 2007). As discussed, serotonergic activity in the vmPFC is paramount in proper emotional and behavioral regulation (e.g., Siever et al., 1999; Soloff et al., 2000, 2003). Indeed, Yoon et al. (2012) found that G-homozygosity was related to higher control over anger and this effect was specifically mediated by OFC gray matter volume, suggesting higher top-down control of emotional reactions.

TPH2 genotypes also influence psychophysiological processes in response to threat. Herrmann et al. (2007) examined the effect of the G(-703)T SNP on the early-posterior negativity (EPN) during a passive emotional picture task. Comparing individual polymorphism, G-allele carriers had a trend toward lower values than T-allele carriers, indicating reduced attention-driven sensitization of emotional responses to salient stimuli. In line with the deductions above, such dampened attentional responses in G-allele carriers may be explained by a higher serotonin-driven regulatory tone on these processes. In agreement, infants with at least one T-allele showed increased difficulty in disengaging attention from threatening stimuli (Forssman et al., 2014). Another interesting finding is that individuals with G-homozygosity have larger improvements in symptoms of anxiety and the greatest reductions in left amygdalar reactivity to a social stressor after several weeks of placebo treatment (Furmark et al., 2008).

Taken together, these results attests to a more cognitively mediated and attention-driven anxiety in the higher serotonin synthesizing G-homozygotes. Since anxiety in G-homozygotes likely originates more strongly from cognitive appraisals, it may be more amenable to treatment by redirecting attention from feared disability to potential improvement (placebo effect), whereas T-allele carriers benefit less from these re-appraisals because their core difficulties are
more strongly related to an inability to regulate or control unconscious emotional reactions, especially fear and anger.

However, it has been asserted that serotonin-genotype effects on emotional processing are partly dependent on cultural identity and social values (Chiao and Blizinsky, 2010). As such, contrasting findings have been mainly reported in Asian populations and in females. In both Asian and female subjects, G-homozygosity has been related to higher amygdala reactivity to sad facial expressions and stronger startle potentiation to aversive stimuli (Armbruster et al., 2010; Lee and Ham, 2008). Furthermore, in a Korean sample studied by Lee and Ham (2008), other serotonergic alleles consistently associated with lower amygdala reactivity in Caucasian populations (e.g., $L$-allele of 5HTTLPR), were also associated with higher amygdala reactivity. Recent work has demonstrated a robust cross-national correlation between the relative frequency of variants in serotonergic genotypes and the relative degree of individualism–collectivism in each population, suggesting that collectivism could have developed and persisted in populations with a high proportion of putative social sensitivity alleles because it was more compatible with such groups (Way and Lieberman, 2010). These differences point to a cultural or gender-related differentiation in the effect of these specific serotonergic genotypes on emotional processing.

Thus, not genotype status per se, but rather the compatibility with environmental demands may strongly influence emotional processing by decreasing or increasing sympathetic resonance of internal states to specific social requests (i.e., norms and values). In other words, gender and/or culture can mediate the ultimate effects of serotonergic genotypes on observed phenotypes, attesting for a strong epigenetic regulation. Since both collectivism and female gender roles emphasize intragroup cohesiveness, cooperation, and harmony, these individuals may be less affected by serotonergic genotypes that increase emotional sensitivity to the social environment. In fact, such plasticity genes may enable them to adapt more appropriately to other-centered norms and values, thereby increasing adaptation and decreasing stress (Homberg and Lesch, 2011). Especially during healthy states, the T-allele may be related to lower emotionality in Asian subjects and in females due to their improved ability to emotionally tune into their social environment, whereas the G-allele may decrease sensitive adaptation to socio-emotional norms and values, thereby evoking rejection and criticism, and ultimately increasing the risk for psychopathology.

Nevertheless, these results pertain particularly to healthy samples. That is, in patient samples, the T-allele is more frequently found in personality
patterns marked by increased emotionality such as cluster B and C personality disorders, regardless of gender (Gutknecht et al., 2006). A relevant finding in a predominantly female population (61%) is that at lower levels of stressful life events, T-allele carriers show lower cluster C personality disorders than G-homozygotes, but while this risk increases considerably in the context of higher life events in T-allele carriers, this environmental modulation is not found in G-homozygotes who show equal levels of risk despite a higher number of life events (Jacob et al., 2010). These behavioral results are also reflected by gene-environment interactions on physiological processes. Hermann et al. (2012) reported an interesting interactional effect between the G(-703)T SNP and traumatic life events in the modulation of amygdalar and vmPFC reactivity and levels of fear-conditioning measured by the skin conductance response, in both males and females. Specifically, under the condition of a higher number of traumatic life experiences, T-allele carriers showed a higher amygdalar reactivity during the acquisition phase, and higher vmPFC response accompanied by stronger interval electro-dermal responses during the extinction phase of a fear-conditioned response. Indeed, female T-homozygotes had significantly greater reactivity to stressful life events exhibiting a higher level of depressive symptoms (Mandelli et al., 2012). Finally, T-allele carriers showed significantly higher reward dependence (Inoue et al., 2010), indicating a stronger dependence on social attachments for the regulation of internal states (Cloninger, 1986).

These findings indicate that in response to stressful life events, T-allele carriers, independent of gender, show higher levels of internalizing disorders, sensitized neural reactivity to threat, stronger fear-conditioning, and reduced efficiency of the vmPFC in regulating emotional responses. These results underscore the importance of considering gene-environment interactions and confirm that genotypes presumably linked to lower levels of serotonergic functioning (i.e., less efficient refill) interact with environmental factors to increase the risk for psychopathology through emotional dysregulation. This destructive effect of long-term allostatic states is less dependent on gender since the above findings are reported in both males and females. Thus, although female T-allele carriers show lower levels of emotionality during healthy states and may be more resilient because of a higher physiological compatibility with social norms and values, stressors that do disrupt the homeostatic balance could ultimately have equally adverse effects in T-allele carriers across gender and culture because of a generally less efficient homeostatic regulation of these disruptions. In other words, the T-allele is likely an plasticity allele, increasing adaptation and
decreasing emotionality and stress when necessary environmental conditions are met (i.e., social cohesiveness, security, and harmony), but also contributing to psychopathology when exposed to stressful life events.

Taken together, TPH genotypes related to increased expression (e.g., presumably the C-allele of the A(218)C SNP in the TPH1 gene and G-allele of the G(-703)T SNP in TPH2) likely result in higher stability of intrasynaptic serotonin homeostasis thereby dampening the impact of allostatic states on physiology and neurodevelopment. Concomitantly, the composite alleles (A- and T-allele) are related to a weaker serotonergic autoregulation thereby showing higher plasticity of emotional processes and could interact with childhood adversity and stressful life events in the etiology of mental disorders linked to emotional dysregulation. In this context, the C/G haplotype may be particularly prevalent in primary psychopathic groups while the A/T haplotype may be more strongly related to secondary psychopathy.

**Serotonin transporter genetics; synaptic serotonin homeostasis**

5HTT expression in the brain is regulated by the gene called the solute family carrier 6, member 4 (SCL6A4) and is located on chromosome 17 position q11.1-q12. The 5HTTLPR (serotonin-transporter-linked polymorphic region) is a repeat polymorphic region within SCL6A4 that encodes for 5HTT expression. Carrying the long allele (longer repeat sequence) is associated with higher levels of 5HTT expression in the brain, and accordingly, a stronger serotonergic functioning compared to the short allele (shorter repeat sequence) (Bah et al., 2008; Manuck et al., 2004; Reist et al., 2001). Nonetheless, similar to the cultural or gender-dependent findings with TPH discussed above, some studies in healthy participants have found sex-differences in the relationship between 5HTTLPR genotypes and 5-HIAA levels, with men showing lower levels in the presence of the s-allele and women in the presence of the l-allele (Williams et al., 2003). Nonetheless, similar to the cultural or gender-dependent findings with TPH discussed above, some studies in healthy participants have found sex-differences in the relationship between 5HTTLPR genotypes and 5-HIAA levels, with men showing lower levels in the presence of the s-allele and women in the presence of the l-allele (Williams et al., 2003). Furthermore, there has been discovered an additional A to G SNP within the long allele which is associated with differential transcriptional activity. The lG- and s-allele show largely similar expression patterns and only the lA-allele shows a significantly higher gene expression (Hu et al., 2005; Zalsman et al., 2006).

Beginning with the impact on endocrine responsivity, a meta-analysis across eleven studies revealed that s-homozygotes consistently showed stronger responsivity of the HPA-axis to laboratory induced social stressors (Miller et
al., 2013). Even in 3-day-old newborns, $l_h$-homozygotes showed much weaker HPA-axis reactivity to a painful heel prick which was not mediated by birth weight, mode of delivery, or prenatal stress levels in the mother, indicating a true genetic effect on stress responsivity (Mueller et al., 2010). In pre-school children the effect of the $s$-allele on HPA-axis responsivity to maternal separation and a frustrating task was strongly mediated by a polymorphism regulating brain-derived neurotrophic factor (BDNF), whereas in $l$-homozygotes this modulation was not seen (i.e., low responsivity regardless of BDNF alleles), attesting for a greater plasticity of the HPA-axis response in $s$-allele carriers (Dougherty et al., 2010). Higher levels of baseline cortisol and HPA-axis reactivity to stressors in $s$-allele carriers has been consistently replicated in adolescents and adults (Chen et al., 2009; Goodyer et al., 2009; Gotlib et al., 2008; Jabbi et al., 2007; Wankerl et al., 2010; Way and Taylor, 2010). More specifically, in the context of a high number of stressful life events, $s$-homozygotes showed the highest cortisol response to a social stressor (i.e., public speaking) compared to all other groups, whereas in $l_h$-homozygotes, a higher number of life-events was actually related to attenuated HPA-axis responsivity but did not influence baseline cortisol levels (Alexander et al., 2009; Mueller et al., 2011; Vinberg et al., 2010). These results in $l$-homozygotes are remarkably similar to findings in primary psychopaths as discussed above (i.e., normal basal activity but dampened reactivity of the HPA-axis).

These endocrinological findings are further supported by consistent reports of a higher amygdalar reactivity to threat in $s$-allele carriers, especially in the right hemisphere (see for review Hariri and Holmes, 2006; Hariri and Weinberger, 2003; Hariri et al., 2006). Beginning with the least salient stimuli exposure, $s$-homozygotes across all ages show stronger amygdala responses to masked emotional facial expressions (i.e., subliminal presentation) and to unconditioned socio-emotional stimuli (Dannlowski et al., 2008, 2010; Fortier et al., 2010; Furmark et al., 2009; Lau et al., 2009; Lonsdorf et al., 2011; Von dem Hagen, 2011). Additionally, $l_h$-homozygotes have also been found to display attenuated amygdalar reactivity to more salient and consciously analyzed emotional stimuli (i.e., unpleasant pictures and scenes from the International Affective Picture System) (Herrmann et al., 2007). Further increasing the saliency of the emotional stimulus, $s$-homozygotes have been shown to display earlier peak and higher levels of amygdala reactivity during the real-life induction and regulation of a sad mood (Furman et al., 2011; Gillihan et al., 2010), and a greater amygdalar reactivity to a real-life social stress induction (Furmark
et al., 2004, 2008). Finally, during the anticipation of electric shocks in fear-conditioning paradigms, s-homozygotes demonstrated higher levels of limbic reactivity (amygdala and insula) and a stronger fear-conditioning response (Drabant et al., 2012; Hermann et al., 2012). Also, during extinction, s-allele carriers have been found to show reduced amygdalar activation, likely reflecting weaker consolidation of extinction related memories resulting in lower levels of fear-extinction (Hermann et al., 2012).

In sum, lₐ-allele carriers consistently show lower levels of amygdalar reactivity to aversive stimuli or events throughout all levels of stimuli salience (masked, unmasked, real-life mood induction, and real-life threat anticipation), which attests to a lower level of bottom-up emotional processing as found specifically in primary psychopathy (see also Glenn, 2011a). Nevertheless, some scholars have recently criticized the 5HTTLPR-amygdala connection and argued that due to publication bias the putative relationship has been exaggerated (Bastiaansen et al., 2014).

Nonetheless, psychophysiological findings also attest to a lower emotional processing in lₐ-homozygotes. First, s-allele carriers show a stronger attentional bias for anxious stimuli compared to l-homozygotes in both psychiatric inpatients and healthy women (Beevers et al., 2007; Osinsky et al., 2008). Furthermore, s-homozygotes experienced greater difficulty to disengage from emotional stimuli (Beevers et al., 2009). When positive and negative emotional pictures were presented simultaneously, l-homozygotes viewed the different stimuli in an evenhanded fashion, whereas s-homozygotes disproportionately focused on the positive images, which might indicate attempts to regulate greater reactivity to negative stimuli by purposefully turning their attention towards positive stimuli (Beevers et al., 2010, 2011). Fear-conditioning paradigms have also demonstrated differences between the allelic configurations. Specifically, s-homozygotes show greater potentiation of startle responses and skin conductance reactivity in response to conditioned cues of threat (Crișan et al., 2009; Garpenstrand et al., 2001; Klumpers et al., 2012; Lonsdorf et al., 2009). In fact, in some studies, l-homozygotes completely failed to show startle potentiation during conditioning (Lonsdorf et al., 2009).

There have also been some non-significant results between 5HTTLPR genotype and skin conductance during conditioning (Hermann et al., 2012) or during social stress tasks (Gilissen et al., 2008). However, Gilissen et al. (2008) found no main effect of genotype but reported that in children with secure attachments, l-homozygotes showed lower levels of skin conductance reactivity
during a social stress task, demonstrating the importance of accounting for gene x environment interactions. Regarding cardiovascular functioning, \(L\)-homozygotes show lower resting heart rate and a stronger vagal tone and higher heart rate variability in response to stressors, indicating improved regulation of autonomic reactivity (Brummett et al., 2011b; Crişan et al., 2009; McCaffery et al., 2003). Taken together, \(L\)-homozygosity, especially in males, is related to dampened potentiation of psychophysiological responses to stressors and threat, parallel to the findings in primary psychopathy (Glenn, 2011a). A higher consistency of this finding in male samples attests that gender-dominant biological factors such as gonadal hormones might strongly modulate the direction and size of the effect of the different allelic configurations on physiology and behavior (see chapter 5).

Studies into the direct association between 5HTTLPR and psychopathy have been inconsistent. Fowler et al. (2009) found that it was \(s\)-homozygosity rather than \(L\)-homozygosity which was related to a higher score on callous/unemotional items. However, this effect was found in a disturbed adolescent population with ADHD. Reports of impaired top-down regulation and threat hyperreactivity in ADHD youth with comorbid conduct disorder (Arnsten and Rubia, 2012; Herpertz et al., 2008), and the fact that it was the \(s\)-allele of 5HTTLPR that was related to callous/unemotional traits, suggest that the psychopathic traits in these youngsters may have reflected the presence of secondary rather than primary psychopathy. Three other studies reported that \(L\)-homozygosity was the risk gene for psychopathy in both adolescents and adults (Sadeh et al., 2010, 2013; Herman et al., 2011). In agreement with the assertion that callous/unemotional traits in the Fowler study could have reflected secondary psychopathy, recent studies into the role of 5HTTLPR in moral decision-making, empathetic responding, and shame-induced embarrassment supports the findings of the Sadeh and Herman studies. Marsh et al. (2011) found that \(L\)-homozygotes rated perpetrating unintentional harm as more acceptable than did heterozygotes or \(s\)-homozygotes, with strong effect sizes, thereby indicating that \(L\)-homozygotes were more likely to make utilitarian moral judgments, which relates specifically to dampened bottom-up modulation of moral decision-making (Glenn et al., 2009). In addition, Gyurak et al. (2012) found that \(L\)-homozygotes showed lower levels of self-reported emotional empathy backed up by lower physiological responses when watching other’s in serious distress. Accordingly, \(L\)-homozygote mothers are less sensitive to distressful signals of their child (Cents et al., 2014). Also, \(L\)-homozygotes showed less emotionally expressive behaviors and reported less amusement, shame, or anger when watching themselves in embarrassing
situations (Gyurak et al., 2012). Finally, even as young as 12-months, lower levels of anxiety towards novel stimuli and strangers have been reported in infants carrying at least one $l$-allele (Lakatos et al., 2003). These results combined point to lower empathy, lower shame, lower levels of temperamental anxiety towards novelty, and higher utilitarianism in $l_A$-homozygotes, thus suggesting that this genotype may be more specifically related to primary psychopathy.

In contrast, whereas $l_A$-homozygosity for 5HTTLPR is likely related to primary psychopathy, the $s$-allele has been linked to impulsive, externalizing, aggressive, and antisocial behaviors and could thus be an important risk factor for secondary psychopathy (Aluja et al., 2009; Cadoret et al., 2003; Garcia et al., 2010; Gerra et al., 2005; Haberstick et al., 2006; Hohmann et al., 2009; Lyons-Ruth et al., 2007; Sakai et al., 2006). In agreement, the $s$-allele has been related to impaired top-down modulation of decision-making and behavior in laboratory contexts. For example, $s$-homozygotes made more disadvantageous decisions on gamble tasks and learned less from repeated mistakes, demonstrating higher cognitive impulsivity (Jollant et al., 2007; Must et al., 2007). Also, $s$-allele carriers exhibited higher levels of motor impulsivity on response inhibition tasks (Walderhaug et al., 2010). The relationship between $s$-allele status and antisocial behaviors is strongly modulated by childhood maltreatment (Cicchetti et al., 2012; Reif et al., 2007). That is, $s$-allele carriers are significantly more likely to develop insecure attachment, impulsivity, disinhibition, distrust, low self-control, conduct problems, or neuroticism, but only when exposed to insensitive treatment, victimization, and childhood adversity (Barry et al., 2008; Cheon et al., 2014; Fox et al., 2005; Ivorra et al., 2010; Kochanska et al., 2009; Nederhof et al., 2010; Schmidt et al., 2007; Paaver et al., 2008; Pauli-Pott et al., 2009; Retz and Rösler, 2009; Sonuga-Barke et al., 2009; Williams et al., 2009). Indeed, in response to chronic stress during adolescence, $s$-allele carriers show greater increments in aggression at the transition into adulthood (Conway et al., 2012). These results resonate with the previously discussed findings of higher levels of both internalizing and externalizing psychopathology in the context of chronic stress and childhood trauma and imply that presence of at least one $s$-allele may especially characterize secondary psychopathic individuals.

Nonetheless, large nation-wide and ethnically representative studies report that in males with adverse childhood events, antisocial personality disorder and criminal behavior is just as frequent in carriers of the $l_A$- or $s$-allele (Douglas et al., 2011; Li and Lee, 2010; Vaske et al., 2012). Thus, in the case of childhood maltreatment, the different alleles might lead to antisocial behaviors equally likely

Serotonergic risks towards emotional pathology
but probably through different endophenotypic pathways. Since the s-allele is associated with insecure attachment, impulsivity, threat hyperresponsivity, low self-control, and neuroticism, it may specifically contribute to reactive antisocial behaviors (i.e., impulse-driven), whereas \( l_A \)-homozygotes is associated with fearlessness/emotional hyporesponsivity, attenuated shame/guilt, utilitarian decision making, and low empathy and could thus contribute primarily to instrumental antisocial behavior (i.e., goal-driven).

In addition to childhood experiences with caregivers and stressful life events, broader societal processes also impact strongly on the pathway from serotonergic genotypes to psychopathic and antisocial phenotypes. Inherent in our competitive and capitalistic society is what can be described as “structural classism”. Structural classism is the system-inherent discrimination of the lower socioeconomic classes due to lower financial resources and thus less access to life-quality enhancing services (i.e., health care, education). This unavoidable social discrimination in capitalistic societies can have a destabilizing effect on the psychology of vulnerable individuals who live in the lower socioeconomic classes (Wadsworth and Achenbach, 2005), especially in countries with higher levels of income inequality (Elgar and Aitken, 2011). These adverse living conditions can affect the developing personality of young children through interactions with stressed caregivers and unfair conditions, ultimately engendering feelings of hostility, envy, and injustice and justifying motivations towards retribution (see Millon et al., 2004 “covetous antisocial personality”).

For example, different studies have found that lower socioeconomic status was related to a higher incidence of hostile attributional biases in children (Weiss et al., 1992; Schultz and Shaw, 2003). Adolescent \( l \)-homozygotes who live in low SES environments exhibit higher levels of callous/unemotional traits than do youth carrying the same polymorphism but raised in high SES environments (Sadeh et al., 2010). Furthermore, adolescents with both \( l_A \)-homozygosity of 5HTTLPR and the 7R-allele of the dopamine receptor D4 (DRD4) variable number tandem repeat (VNTR) showed the highest levels of rule-breaking behavior but only when raised in low SES environments (Nobile et al., 2007). Therefore, although adversity might not have a significant effect on emotional functioning in \( l_A \)-homozygotes, they may still learn through “cold” psychological conditioning that the world is a harsh and threatening place, which could pose an early developmental risk factor for absent conscience development and the etiology of predatory behaviors devoid of strong emotional reactions.
Gene-gene interactions; tryptophan hydroxylase x serotonin transporter

As schematized in figure 3.3 and 3.4, genes that control for serotonin components can either counterbalance or boost each other’s impact on emotional processing (e.g., when both 5HTT and TPH expression is low or high). Beginning with presynaptic mechanisms, additive effects on emotional responsivity have been repeatedly observed for the TPH2 and 5HTTLPR polymorphisms. Herrmann et al. (2007) examined the interactional effect between the G(-703)T SNP in TPH2 with 5HTTLPR on the early-posterior negativity (EPN) during a passive emotional picture task. Interactional effects explained a larger variance of negativity scores than main effects, with the group characterized by both l- and G-homozygosity showing the lowest negativity values, the l/l-T/T and s/s-G/G group showing intermediate negativity values, and subjects with both s- and T-homozygosity having the highest values.

Canli et al. (2008) replicated these findings and showed that amygdala reactivity to emotional facial expression, especially fearful faces, is interactively modulated by these two polymorphisms. The dampening effect of either l- or G-homozygosity on amygdalar reactivity was augmented when both genotypes were present in the same individual, especially regarding the amygdalar response to fearful faces. Other studies have also found interactive effects of these polymorphisms on amygdalar reactivity to angry faces versus neutral faces with the highest responses reported in s/s-T/T carriers (Furmark et al., 2009). Another interesting finding is that individuals with the l/l-G/G profile have the largest improvements in symptoms of anxiety and the greatest reductions in left amygdalar reactivity to a social stressor after several weeks of placebo treatment compared to other groups that have at least one s- or T-allele (Furmark et al., 2008). Individuals carrying multiple serotonin regulating genotypes may thus have an especially strong capacity to regulate their fears with the help of cognitive beliefs and effortful control, which attests to a more cognitively induced anxiety that can be alleviated by shifting attention (i.e., believing that one has received a medicine for his anxiety) rather than a reflexive and uncontrollable emotional response to threat (Grillon, 2008). In agreement, combined presence of the s- and T-allele is associated with an additively greater response in the mPFC during extinction of traumatic life events which might indicate more difficulty in extinguishing fear-related memories (Hermann et al., 2012).
3.5 Serotonergic Receptor Profiles (5HT1A, 5HT2A, 5HT2C, and 5HT3): Relevance for Psychopathy

Serotonergic receptors; tuning homeostatic control

Serotonergic receptors can be broadly subdivided into two categories; the inhibitory and the excitatory. The 5HT1-type inhibitory receptors, consisting of the 5HT1A, 5HT1B, 5HT1D, 5HT1E, and 5HT1F subtype, are the primary means through which serotonin is enabled to directly dampen neuronal activation. In this chapter I will focus mainly on the 5HT1A receptor because it is the most widely distributed and abundantly expressed serotonin receptor in fronto-limbic areas. Also, other 5HT1 receptors have been scarcely studied with regard to genetics, emotion, or behavior. 5HT1A receptors have two main functions; (1) as somatodentritic autoreceptors in raphe nuclei, where they provide the negative feedback regulation of serotonergic activation (see figure 3.6, nr. 1), and, (2) as postsynaptic heteroreceptors in cortico-limbic structures, where they mediate serotonin-driven regulatory effects (see figure 3.6, nr. 2-5) (Albert et al., 2011; Stahl, 2008; Savitz et al., 2009).

The second class of serotonergic receptors that are paramount in emotional regulation are the excitatory 5HT2-type receptors, which generally oppose the inhibitory actions mediated by 5HT1 receptors (Marek, 2010; Millan, 2006a, 2006b). The opponent interaction between the 5HT1 inhibitory and 5HT2 excitatory receptors could provide the neurophysiological means through which serotonin is enabled to fine-tune the excitatory-inhibitory balance of neurophysiological processes, thereby dynamically adjusting neurobiological equilibria on a moment-to-moment basis. 5HT2 receptors consist of three subtypes, namely the 5HT2A (see figure 3.6, nr. 6-9), 5HT2B, and 5HT2C, which are distributed both in overlapping as well as different brain structures (for review see Mengod et al., 2010). I will focus mainly on the 5HT2A and 5HT2C subtypes since there is a paucity of information regarding the distribution and role of the 5HT2B subtype (Marek, 2010; Mengod et al., 2010). Also, I will spend attention on the 5HT3 receptor which works in tandem with the 5HT2 group to influence emotion and behavior.
Inhibitory 5HT1A somatodentritic autoreceptors in the raphe nucleus; The 5HT1A somatodentritic autoreceptors, which regulate serotonergic output through a feedback auto-inhibitory loop (see figure 3.6, nr.1), are highly important in emotional processing simply because they directly influence the strength of serotonergic activity in the brain (Donaldson et al., 2014; Richardson-Jones et al., 2011). The anxiolytic and antidepressant effects of SSRIs and 5HT1A agonists are strongly mediated by the time-course dependent decrease of 5HT1A autoreceptors, thereby boosting serotonin activity (Blier and Abbott, 2001; Blier and Ward, 2003; Newman et al., 2004). In healthy individuals, however, 5HT1A autoreceptor density shows a negative association with amygdalar reactivity, accounting for up to 33-40% in the variance of amygdalar reactivity (Fisher et al., 2006; Selvaraj et al., 2014). These apparently contradictory results can be reconciled when considering that both non-optimally low (in healthy individuals) and non-optimally high levels (in depressed individuals) of 5HT1A autoreceptors can have deregulating effects on emotional responsivity. That is, too low autoreceptor levels impair autoregulatory feedback and thus induce increased levels of brain serotonin when activated, which in turn may negatively affect the functionality of the serotonergic system and lead to increased emotionality (Donaldson et al., 2014). Conversely, too high autoreceptor densities result in too strong autoregulations of serotonin release, which directly impairs serotonergic regulatory functionality by substantially lowering its output. From these combined results it might be inferred that serotonergic autoregulation of physiology and behavior is enhanced at homeostatically optimal levels of somatodentritic 5HT1A autoreceptors (i.e., within median values).

Inhibitory 5HT1A postsynaptic heteroreceptors in PFC-limbic circuits; Interestingly, just as 5HT1A somatodentritic autoreceptors regulate efferent projections from raphe nuclei, and thereby provide an inhibitory influence over serotonergic output, 5HT1A postsynaptic heteroreceptors have been found to exert similar effects on efferent projections from PFC and amygdalar structures (see figure 3.6, nr. 2, 3, 4, and 5). For example, 5HT1A postsynaptic receptors are primarily expressed on pyramidal neurons in the PFC and limbic structures, and show a less dense expression on GABAergic interneurons (De Almeida and Mengod, 2008; Palchaudhuri and Flügge, 2005). Apart from regulating cortical arousal and cortico-cortical information flow through their modulatory effects on intra-cortical connections (Goodfellow et al. 2009), 5HT1A receptors also have
regulatory effects on PFC and amygdalar output neurons. Specifically, 5HT1A receptors, located in mPFC projections to the amygdala, and on central amygdalar output neurons, have been demonstrated to directly gate the excitatory output of these structures (see figure 3.6, nr.2 and 3) (Fisher et al., 2011; Rainnie, 1999). Lower functional output of the mPFC and amygdala due to heightened 5HT1A receptor activation may have varying effects on emotional reactivity; decreasing mPFC mediated top-down regulation of subcortical processes could increase threat reactivity and result in anxiogenic effects (Fisher et al., 2011; Solati et al., 2011), whereas attenuating central amygdalar output may result in
anxiolytic effects (Li et al., 2012), attesting to a rather complicated role of these postsynaptic receptors in emotional reactivity and regulation:

Inhibitory 5HT1A postsynaptic heteroreceptors in the amygdalal/hippocampus: First, subjects with higher levels of anxiety and depression show reduced postsynaptic 5HT1A densities in hippocampal and amygdalar areas (figure 3.6, nr. 2), and psychotropic medications such as buspirone, which regulate anxiety, mainly work by activating 5HT1A postsynaptic receptors in these limbic structures (Gordon and Hen, 2004; Hahn et al., 2011; Lanzenberger et al., 2006, 2010; Lesch et al., 1992; Mineur et al., 2014; Nash et al., 2008; Neumeister et al., 2004). Higher levels of 5HT1A binding in the amygdala and hippocampus are strongly related to attenuated cortisol levels in patients with social phobia (Lanzenberger et al., 2010). Finally, significantly reduced levels of 5HT1A receptors have been found in limbic areas of patients with temporal lobe epilepsy, and in individuals high in reactive aggression (i.e., hypersensitized limbic reactivity), thus demonstrating a strong inhibitory influence of limbic 5HT1A receptors on amygdalar kindling (Parsey et al., 2002; Savic et al., 2004). In sum, higher levels of 5HT1A binding in limbic structures, in particular in the hippocampus and amygdala, are related to lower emotional responsivity to salient events, likely by modulating the functional output of these structures.

Inhibitory 5HT1A postsynaptic heteroreceptors in the mPFC: Second, since mPFC activation during emotional regulation has been specifically related to top-down regulation of amygdalar reactivity (Banks et al., 2007; Akirav and Maroun, 2007; Pezawas et al., 2005; Quirk et al., 2003), a higher serotonin-driven fronto-limbic coupling of especially the mPFC with the amygdala is directly associated with lower limbic responsivity to threat (Pezawas et al., 2005). Indeed, the callousness dimension of psychopathy has been associated with an increased coupling of the mPFC and amygdala (Yoder et al., 2014). Therefore, a lower influence of 5HT1A compared to 5HT2A receptors on mPFC pyramidal neurons that project onto GABAergic interneurons in amygdalar structures, might strengthen the serotonin-driven autoregulatory tone on emotional responsivity (see figure 3.6, nr. 3). In agreement, higher excitatory 5HT2A receptor binding potentials in the mPFC predict increased fronto-limbic functional coupling and lower threat related amygdala reactivity in healthy individuals, but only in the context of lower 5HT1A signaling (Fisher et al., 2009, 2011). In other words, 5HT1A receptors in the mPFC effectively gate the capacity for 5HT2A receptors to drive
PFC pyramidal neuron excitability related to the regulation of threat-related amygdalar reactivity (Fisher et al., 2011). In accordance, 5HT1A binding in the mPFC is positively associated with harm avoidance (Bailer et al., 2005). Additionally, infusions of 5HT1A agonists versus antagonists directly into the mPFC respectively lead to anxiogenic and anxiolytic effects in rats (Solati et al., 2011). Finally, 5HT1A receptors in the mPFC function partly as autoreceptors, inhibiting serotonergic output from the raphe nucleus (Casanovas et al., 1999; Celada et al., 2001; Hajós et al., 1999; Soiza-Reilly et al., 2015). That is, higher 5HT1A binding in the mPFC is associated with lower levels of serotonin synthesis and an associated increase in stress responsivity (Frey et al., 2008; Soiza-Reilly et al., 2015).

Inhibitory 5HT1A postsynaptic heteroreceptors in the OFC: Third, a similar relationship between 5HT1A receptors and behavioral control may exists in the OFC as found for emotional regulation in the mPFC, namely that lower 5HT1A receptor activation boosts OFC driven inhibitory control over subcortically generated action-tendencies (behavioral inhibition), whereas higher levels decrease OFC driven regulation by suppressing top-down regulatory signals (impulsivity) (see figure 3.6, nr. 4) (Witte et al., 2009). For example, Witte et al. (2009) reported higher total aggression and impulsivity scores in healthy male and female subjects exhibiting a higher density or affinity of postsynaptic 5-HT1A receptors in the dlPFC and vmPFC. These results contradict an earlier study who found significant negative results between lifetime aggression scores and 5HT1A binding in the OFC, but in females only (Parsey et al., 2002). However, in addition to the relatively smaller number of subjects, the age range of the Parsey study was quite large and statistical results were considerably weaker and found only in females. Furthermore, Parsey and Witte used different questionnaires that measured lifetime aggression and current trait-aggression respectively. Similar limitations could also explain the negative findings of Rabiner et al. (2002), who failed to find any significant associations between 5-HT1A receptor distribution and several personality traits. In line with the Witte study, SSRI type antidepressants, which mainly decrease impulsive and aggressive behaviors, have been found to specifically decrease 5HT1A receptors in the OFC of rodents (El Mansari and Blier, 2005). Furthermore, higher levels of 5HT1A receptors in closely adjacent structures, such as the ventrolateral PFC, have been found in suicide attempters (Arango et al., 1995).

However, since the OFC can also re-activate conditioned emotional traces
and behavioral action-tendencies in response to expected outcomes (Bechara et al., 2000a), heightened OFC output due to decreased 5HT1A receptors could also increase anticipatory anxieties and avoidance behaviors (conditioned fear) (see figure 3.6, nr. 5) (Ferreira and Nobre, 2014). That is, heightened OFC activation, and reduced 5HT1A mediated gating of its influence over subcortical structures, may boost the salience of reinforcing representations in response to certain cues (e.g., awareness of bodily sensations, dreaded future events, social situations) and thus increase the impact of these representations on the subcortical initiation of corresponding physiological and behavioral responses. If those representations of predicted future outcomes are negative, which is more likely in individuals with adverse life events or a stressful childhood (Ayoub et al., 2006; Fischer et al., 1997), the resultant effect may be a strong increase in conditioned and anticipatory anxieties. For example, patients with panic disorder and social phobia display lower 5HT1A receptors in the OFC, which are normalized by SSRI treatment (Hahn et al., 2011; Nash et al., 2008). In addition, subjects with obsessive-compulsive disorder or social phobia have been found to display heightened OFC activity (Graybiel and Rauch, 2000; Veit et al., 2002). Therefore, both increased and decreased OFC output could contribute to psychopathological states and 5HT1A binding in the OFC might thus display an inverted U-shaped association with adaptive behavioral regulation. Non-optimally high levels may then result in too weak top-down regulatory control (emotional dysregulation, impulsivity), while non-optimally low levels likely result in too strong OFC mediated regulation of behavior and physiology (anxiety, behavioral inhibition).

In sum, optimally balanced 5HT1A somatodentritic autoreceptors in the raphe nucleus and 5HT1A postsynaptic receptors in the mPFC secure both short- and long-term stability of synaptic serotonin homeostasis. Additionally, a higher ratio of 5HT1A postsynaptic receptors in the amygdala compared to 5HT1A postsynaptic receptors in the mPFC increases emotional resilience and reduces threat-reactivity. Finally, optimally balanced 5HT1A postsynaptic receptors in the OFC secure a healthy balance between behavioral inhibition/anxiety and disinhibition/impulsivity.

Excitatory 5HT2A postsynaptic receptors in PFC-limbic circuits; 5HT2A receptor binding sites show a close overlap with immunoreactivity and mRNA attesting to a predominantly postsynaptic location (López-Giménez et al., 1997, 2001). High levels of 5HT2A receptor sites have been primarily identified in different
structures of the PFC and in the caudate, nucleus accumbens, amygdala, hypothalamus, entorhinal cortex, and hippocampus (Jiang et al., 2009; López-Giménez et al., 1997, 2001; Pazos et al., 1987).

Opposite to the 5HT1A receptors, which provide a direct inhibitory influence on pyramidal cells in the PFC, the 5HT2A receptors provide the major excitatory drive onto pyramidal cells, especially those in layer V, which are the principal output cells of the PFC (see figure 3.6, nr. 6 and 7) (Amargós-Bosch et al., 2004; Holmes, 2008; Marek, 2010). These results suggest that 5HT2A receptors are ideally situated to modulate fronto-limbic information coupling and top-down modulation/regulation of emotional signals.

First, as discussed, activation of 5HT2A receptors on glutamatergic projections from the mPFC to GABAergic interneurons within the amygdala serves to counterbalance amygdalar reactivity (see figure 3.6, nr. 6) (Fisher et al., 2009, 2011; Holmes, 2008; Quirk et al., 2003). In humans, 5HT2A receptors in the mPFC were positively related to amygdala habituation to fear-related expressions, a phenomenon likely dependent on top-down PFC regulation of limbic activity (Fisher et al., 2009; Phelps et al., 2004). In addition, lower levels of 5HT2A binding in the inferior frontal cortex and mPFC predict higher harm avoidance scores and characterizes patients with depression, or individuals who have committed suicide (Dean et al., 2014; Moresco et al., 2002).

Besides the modulation of fronto-limbic coupling related to emotional regulation, 5HT2A-driven excitation of GABAergic interneurons within the amygdala also provides a more direct inhibitory tone on amygdalar output (see figure 3.6, nr. 8) (Jiang et al., 2009, 2011; Rainnie, 1999). In fact, the 5HT2A receptor is the primary receptor responsible for the serotonergic facilitation of GABA release in the amygdala (Jiang et al., 2009; but see Jiang et al., 2011 for review). Rats treated with p-chlorophenylalanine to reduce serotonergic neurotransmission show higher levels of fear-potentiated startle, which can be normalized by administration of agents with 5HT2A agonistic properties (Hughes et al., 2012). Furthermore, the strong reduction of 5HT2A receptors in the amygdala, hypothalamus, and hippocampus in response to inescapable stress, is associated with learned helplessness in rodents (Dwivedi et al., 2005). Finally, chronic or traumatic stressors readily impair 5HT2A signaling in the amygdala and increase fear-related behaviors (see Jiang et al., 2011).

Excitatory 5HT2A postsynaptic receptors as regulators of catecholamine activations: Second, the 5HT2A receptors in the vmPFC may provide part of
the neurobiological basis through which serotonin homeostatically regulates catecholamine outflow in fronto-limbic projections (see figure 3.6, nr. 7 and 9). During quiet waking states, tonic catecholamine levels in fronto-limbic structures are associated with background levels of arousal and alertness (Aston-Jones et al., 2007a, 2007b; Beauchaine et al., 2010; Berridge and Waterhouse, 2003). Should we be suddenly confronted with events that violate our expectancies and require a shifting of attention to new future contingencies (such as when confronted with unexpected punishment, threat, pain, reward, or social rejection/exclusion, or unexpected cues signaling their potential presence), a strong phasic burst of catecholaminergic signaling to mPFC and its reciprocal connections with limbic structures, such as the amygdala and hippocampus, promotes executive attention to these events, sensitizes their emotional salience and reinforcing value, and facilitates emotional conditioning of relevant cues preceding them (Drabant et al., 2006; Finlay et al., 1995; Floresco and Tse, 2007; Grace et al., 2007; Kienast et al., 2008; Kröner et al., 2005; Laviolette et al., 2005; Loos et al., 2010; Li et al., 2003b; Pardey et al., 2012; Pezze and Feldon, 2004; Rosenkranz and Grace, 2001, 2002a, 2002b; Shah et al., 2004; Ventura et al., 2008; Wanat et al., 2009).

Several lines of evidence support the proposition that 5HT2A receptors drive the homeostatic regulation of these catecholaminergic processes. For example, it has been reported that during quiet waking states, or in the absence of agents that boost catecholamine levels, 5HT2A receptors in the PFC have an excitatory tone on catecholaminergic and glutamatergic signaling (figure 3.6, nr. 9), whereas during salient events, or the administration of agents that boost catecholamines (e.g., amphetamine, raclopride), the activation versus inactivation of serotonin, and specifically the 5HT2A receptors in the PFC, has been respectively found to inhibit and excite catecholaminergic neurotransmission in the PFC (figure 3.6, nr. 7) (Andersson et al., 1995; Bortolozzi et al., 2005; Frånberg et al., 2012; Gobert and Millan, 1999; Kuroki et al., 1999; Minabe et al., 2001; Mocci et al., 2014; Nomikos et al., 1994; Pehek, 1996; Pehek and Bi, 1997; Stahl, 2008). Therefore, 5HT2A receptors likely excite PFC catecholaminergic pathways when their activity drops below a certain threshold, such as during non-aroused and quiet waking states, but inhibits them when their activity is raised beyond a certain threshold, such as during emotionally and motivationally salient events, and thus serves to maintain optimal levels of arousal and vigilance within a biologically optimal operating range.

In other words, stronger 5HT2A functioning may decrease catecholaminergic oscillations and stabilize and narrow their operating range,
whereas weaker functioning could lead to more extreme fluctuations (both drops and increases) and thus widen these operating ranges; First, in the context of non-salient events or during quiet waking states, the absence of 5HT2A mediated upregulation of catecholamine activity may result in a background hypoarousal of emotional and motivational faculties, which can be experienced psychologically as anhedonia, demotivation, frustration, and lethargy, whereas higher activity at 5HT2A receptors may result in a more optimal arousal state, associated with the motivation to explore/exploit, waking alertness, and well-being. Second, when serotonin is not sufficiently able to regulate sudden increased PFC catecholamine outflow because of a lower ratio of 5HT2A receptors compared to 5HT1A receptors in the PFC, unexpected and salient events could lead to sensitized neural processing without sufficient dynamic inhibitory regulation. In the context of reward or cues signaling their potential presence, lowering 5HT2A functionality in the PFC would then amplify their immediate salience and induce a certain “hyperfocus” on these rewards and cues at the expense of peripheral warning cues or information regarding more optimal choices, thereby impairing response modulation and increasing impulsive responding (e.g., Harrison et al., 1997; Newman and Lorenz, 2003; Wallace and Newman, 2008; Winstanley et al., 2003, 2004, 2006). In the context of conflict, punishment, and social rejection/exclusion, lower activity at 5HT2A receptors may also amplify the catecholaminergic driven salience of these events and induce an over-evaluative and self-conscious hypervigilance that can lead to anticipatory anxieties, worrying, nervousness, and fear (i.e., the induction of a hypervigilant state to stay prepared for dreaded future events) (e.g., Stahl, 2008; Stein et al., 2006). Lower serotonin activity at 5HT2A in the PFC may thus increase the risk for both externalizing and internalizing pathology and disinhibit behavior in response to threat or reward (Den Ouden et al., 2015).

Excitatory 5HT2A postsynaptic receptors in the OFC: Finally, continuing with higher order prefrontal structures, catecholaminergic signaling in the OFC, especially dopamine, is important for adequate and weighed neural representations of expected future outcomes, particularly during periods when those reinforcing events are not concretely available to the senses. When dopamine is phasically activated by reinforcing cues, the mesocorticolimbic pathway is activated and when this activation is not inhibited and/or crosses a certain threshold, it can create a prolonged duration of increased tonic signaling in the OFC and lateral PFC, which then inhibits subsequent phasic activations that are irrelevant to the
now-activated goal (Frank and Fossella, 2011; Grace et al., 2007; Lodge, 2011). However, dopamine induced representations of delayed reinforcements only lead to successful task performance if, during that intermediate period of actual effort or waiting, irrelevant and unexpected emotional and motivational action-tendencies are sufficiently inhibited so that one can stay focused on the goals and not be thwarted by irrelevant action-tendencies. Serotonin functioning in the OFC is strongly involved in this inhibitory function, namely automatically inhibiting action-tendencies that are either irrelevant or that thwart current objectives, thereby enabling patience and long-term goal persistence (Fuster, 2008; Homberg, 2012b; Miyazaki et al., 2014; Rygula et al., 2014; Walker et al., 2009; Worbe et al., 2014). Furthermore, when some actions lose their reinforcing value, serotonin serves in the subsequent inhibition of those behaviors so that new, more adaptive behaviors can be attained, and in so doing facilitates reversal learning (Clarke et al., 2007; Homberg, 2012b; Rygula et al., 2014; Walker et al., 2009). These behavior regulating functions of serotonin are likely mediated through its actions at 5HT2A receptors in the PFC (see figure 3.6, nr.7) (Furr et al., 2012). Therefore, in the absence of this serotonin-driven inhibitory function of the OFC as would be the case in emotional dysregulation, the individual reacts impulsively to immediate rewards, threats, and behavioral tendencies without consideration of their relevance, and of alternative, more adequate ways of achieving the same goals (Anderson et al., 1999; Burgess and Wood, 1990; Grattan et al., 1994). Since the relationship between PFC functioning and behavioral flexibility shows an inverted-U pattern whereby optimal functioning is increased at median levels, I suggest that behavioral regulation is optimal at median levels of 5HT2A activation. Too high activation of 5HT2A receptors in the OFC may result in excessive behavioral inhibition and reduced behavioral flexibility (e.g., obsessiveness, neuroticism, harm-avoidance), whereas too low activation may result in behavioral dysregulation and reduced stability of goal-directed behavior (i.e., impulsivity).

However, regarding 5HT2A functionality in OFC, behavioral findings in patient samples mostly demonstrate a positive rather than inverse correlation with behavioral dysregulation. For example, physically aggressive personality disordered patients show higher levels of 5HT2A receptor binding in the OFC compared to healthy controls (Rosell et al., 2010). Additionally, borderline personality disorder, which is related to reactive aggression, has also been associated with higher levels of 5HT2A binding in the hippocampus, medial temporal cortex, occipital cortex, and a trend significant result in the OFC.
(Soloff et al., 2007). These positive associations are mainly found in the OFC and show much weaker associations in the mPFC (Rosell et al., 2010; Soloff et al., 2007). Nevertheless, because it has been found that 5HT2A density is strongly and inversely correlated with brain serotonin levels (Roth et al., 1987; Stockmeier and Kellar, 1986; Todd et al., 1995), these higher binding potentials in patient samples could reflect a general sensitization of these receptors in response to long-term serotonin depletion in the OFC, which has by itself also been related to impulsivity, aggression, and borderline personality (e.g., Soloff et al., 2000, 2003). Since regulation of behavior is lacking in these patients, the physiological system might try to compensate by sensitizing the expression of 5HT2A receptors in the OFC (see also figure 3.4). Alternatively, since 5HT2A receptors in the OFC also facilitate the expression of conditioned fear, such increases in density may indicate a higher tendency towards strong conditioned anticipatory responses to potential threat and reward, which makes sense in the context of a harsh and threatening worldview.

Other lines of research examining within-group designs (comparing healthy individuals or comparing violent individuals) and the effects of 5HT2A active ligands may provide clarification. In healthy subjects, higher levels of 5HT2A receptor binding in OFC, medial inferior frontal cortex, superior frontal cortex, entorhinal cortex, has also been associated with personality risk factors for anxiety such as neuroticism and emotional vulnerability (Frokjaer et al., 2008). In contrast, individuals higher in aggression and impulsivity showed lower levels of 5HT2A binding in the OFC and ventral prefrontal cortex (Meyer et al., 2008; Nomura and Nomura, 2006). Furthermore, in healthy male participants, aggression was found to be negatively related whereas suspiciousness was positively correlated to 5HT2A binding in the OFC and mPFC (Soloff et al., 2010). In agreement, acute blockade of 5HT2A receptors does not affect amygdala reactivity but attenuates the neuronal response in the OFC to emotive facial expressions of anger and fear indicating reduced cortical appraisal of the value of emotional stimuli (Hornboll et al., 2009), which has been directly related to aggression and impulsivity (Blair, 2010; Coccaro et al., 2007; Soloff et al., 2000, 2003).

5HT1A genetics; regulating emotional resilience

The gene regulating 5HT1A expression, namely HTR1A, is located on
chromosome 5 location q11.2 to q13. The C(-1019)G SNP in the promoter region of HTR1A (rs6295) has been demonstrated to affect 5HT1A protein and binding (Czesak et al., 2006; Lemonde et al., 2003; Parsey et al., 2006). Czesak et al. (2006) report that the G-allele fails to bind identified repressors Deaf-1 and Hes5 during prolonged serotonergic release, leading to upregulation of 5HT1A autoreceptors and consequently attenuating serotonergic functionality. This effect has also been demonstrated in genetically mutated mice that lack Deaf-1 (Deaf-1-/-) (Czesak et al., 2012; Hahm et al., 2004). When compared to wild-type controls, Deaf-1-/- mice displayed increased levels of 5HT1A mRNA in the dorsal raphe nucleus although serotonin cell number and TPH2 expression were unchanged. In line with human studies, these results indicate that failure to bind to Deaf-1 may lead to a region-specific (i.e., raphe nuclei) dysregulation of 5HT1A autoreceptor expression (Lemonde et al., 2003; Parsey et al., 2006). G-allele carriers could thus be more vulnerable to prolonged stressors and more likely to react with a sensitization of 5HT1A receptivity, which can lead to deficient serotonin functionality and increased emotionality (Albert et al., 2011; Lemonde et al., 2003; Marek, 2010).

Furthermore, while Deaf1 represses 5HT1A expression in the raphe nucleus, it enhances 5-HT1A expression in projection areas, thereby homeostatically regulating serotonergic functionality during long-term allostatic states (Czesak et al., 2006). Based on this dual activity of Deaf1, G-homozygosity, when exposed to long-term stressors, is expected to lead to increased levels of presynaptic 5HT1A autoreceptors but decreased levels of postsynaptic 5HT1A receptors, thereby synergistically altering serotonin regulatory functionality (Albert et al., 2011). Another possibility supported by empirical research is that an increase in autoreceptors leads to a parallel increase in postsynaptic receptors in fronto-limbic structures, which could serve to compensate for the lower serotonergic output to these structures (Hahn et al., 2011). It is therefore yet unclear how 5HT1A postsynaptic receptors adapt to a sensitization of 5HT1A autoreceptors and how genetic factors such as the C(-1019)G SNP influence this adaptation.

Regarding neurobiology, different studies in patient samples (panic disorder and major depression), showed that the G-allele was associated with higher amygdalar and lower OFC and mPFC reactivity to emotive facial expressions (Dannlowski et al., 2007; Domschke et al., 2006; Straube et al., 2014). Also, the G-allele was associated with right frontal electrical asymmetry during resting states (Bismark et al., 2010), which is parallel to the high reactive
temperamental subtype as identified by Kagan and Snidman (2004). Regarding psychophysiology, G-allele carriers show higher levels of skin conductance reactivity when anticipating reinforcing outcomes (either positive or aversive) (Schmitz et al., 2009). Behavioral findings support these physiological results; the G-allele is related to neuroticism and harm avoidance (Straube et al., 2014; Strobel et al., 2003), major depression and suicide (Lemonde et al., 2003), schizophrenia (Huang et al., 2004), substance use disorders (Huang et al., 2004), panic attacks and panic disorder with agoraphobia (Huang et al., 2004; Rothe et al., 2004), cluster B personality disorders (Jacob et al., 2010), and a poorer pharmacological and cognitive-behavioral treatment response in depression and panic disorder (Lemonde et al., 2004; Straube et al., 2014; Yevtushenko et al., 2010; Yu et al., 2006).

Interestingly, opposite findings have also been reported in healthy individuals. Fakra et al. (2009) examined the allelic configuration in community samples and found that C-homozygotes showed increased bilateral amygdalar reactivity to social threatening stimuli compared to G-homozygotes. Analyses in Mplus 4.0 revealed significant direct paths from HTR1A genotype on amygdalar reactivity to trait anxiety scores, predicting 9.2% of the variance in these scores. These higher amygdala reactions are also reflected by stronger context and cue-evoked fear-conditioning in healthy C-homozygotes (Baas and Heitland, 2014). In addition, Armbruster et al. (2011) found that healthy G-homozygotes showed a markedly lower cortisol response to the Trier social stress test, although both groups did not differ in baseline cortisol responses indicating a particular effect on reactive allostatic regulations. Therefore, the G-allele may be especially related to emotional dysregulation in patient samples, whereas it may be related to lower emotional responsivity in healthy participants, indicating that it could be a plasticity allele.

For example, in the case of childhood maltreatment, G-allele carriers show significantly higher levels of negative affectivity (depression and anxiety), whereas this modulation is not found in C-homozygotes in both Asian and Western populations (Kim et al., 2011; Perea et al., 2012). A transmission disequilibrium test reported a higher transmission of G-alleles in suicide attempters with more prior life events, hinting that G-allele carriers could be more likely to attempt suicide in response to adverse life events, whereas in C-allele carriers these behaviors may have other antecedents (Wasserman et al., 2006). In addition, G-homozygotes report less stressful events preceding hospitalization for bipolar depression, also attesting to a lower stress-resilience (Benedetti et al., 2011).
In contrast, a large nation-wide study including individuals of different age groupings (20-24, 40-44, 60-64 years of age) and equal numbers of males and females, concluded that there were no significant associations between HTR1A genotypes with symptoms of anxiety or depression (Chipman et al., 2010). Significant gene x environment interactions unadjusted for multiple testing were found in females in the 20–24 and 60–64-year-old cohorts, especially for the interaction between the polymorphism and recent stressful life events on depression, but the authors did not specify which alleles mediated this association (Chipman et al., 2010). In addition, Koller et al. (2006) found no significant associations between the C(-1019)G SNP and harm avoidance, neuroticism, and suicide attempts. However, this study exclusively examined alcohol dependent patients and did not include a healthy control group, which may have decreased variability and thus the power to detect significant differences. Strong epigenetic regulation of alcohol dependence upon 5HT1A receptor expression (Thompson et al., 2012), may have overshadowed more subtle effect brought about by single genotype status. Indeed, as pointed out by the authors themselves, participants were drug free only for 1.5 to 2 weeks before the study while the 5-HT1A autoreceptor takes 2–3 weeks to desensitize (Koller et al., 2006). Reinvestigation of the participants after a longer drug free interval could bring forth different results. For example, in type B alcoholics, G-homozygotes indeed showed higher levels of harm avoidance and neuroticism compared to C-homozygotes, but these results did not reach significance levels. Therefore, when the effect of alcohol dependence on 5HT1A receptor expression wanes, these differences could become more pronounced.

Regarding mediating endophenotypes to antisocial behavior, Chipman et al. (2010), reported higher levels of psychoticism in male C-homozygotes, which is indicative of coldhearted, egotistical, stimulation-seeking, and antisocial behaviors. Mekli et al. (2011) further reported that homozygotes for the G-allele showed faster reactivity to negative facial emotions but a worse recognition of sadness suggesting increased intensity of reflexive responses but reduced PFC appraisal of these reflexive signals. In addition, G-allele carriers showed a faster reaction time when anticipating punishment, which was directly related to negative emotionality (Schmitz et al., 2009). This increased emotional responding to aversive stimuli without adequate top-down appraisal of behavioral tendencies in G-allele carriers is also reflected by their higher levels of total, motor, and cognitive impulsivity on the Barratt Impulsiveness Scale (BIS-11) and the Impulsiveness subscale of the Eysenck Impulsiveness, Venturesomeness
and Empathy scale (IVE) (Benko et al., 2010).

These results on behavior and personality scales also indicate that the C-allele may contribute to antisocial behavior by increasing callousness, selfishness, and sensation seeking (i.e., psychoticism), which may be associated with both primary and secondary psychopathy, whereas the G-allele may contribute by negatively affecting impulse control and emotional resilience, especially in response to prolonged allostatic states, which is mainly associated with secondary psychopathy.

**5HT2A genetics; balancing internal homeostasis**

Different common polymorphisms have been identified that regulate the expression of 5HT2A receptors in the brain. The gene regulating 5HT2A expression, namely HTR2A, is located on chromosome 13 and contains three exons and two introns spanning 20 kb (Chen et al., 1992; Sparkes et al., 1991). Several common polymorphisms occur in the regulatory region of HTR2A with the most widely studied being the T(102)C and the A(-1438)G SNP. These two SNP’s have been found to be in complete linkage disequilibrium; the A-allele is always linked with the T-allele (Bray et al., 2004; Kusumi et al., 2002; Spurlock et al., 1998). Different studies have indicated that the T-/A-haplotype result in significantly higher 5HT2A receptor densities and promoter activity in both healthy and patient samples (Khait et al., 2005; Parsons et al., 2004; Polesskaya and Sokolov, 2002; Turecki et al., 1999). However, other studies did not find an association between genotype and 5HT2A receptor densities or promoter activity in patient samples (Du et al., 1999; Kouzmenko et al., 1997, 1999; Spurlock et al., 1998) or found a higher expression in heterozygotes (Myers et al., 2007). Thus, although it is generally accepted that the T-/A-haplotype is related to a higher expression, these inconsistent results attest to a more complicated effect on gene expression and receptor density than has yet been elucidated. As with the HTR1A polymorphisms, the effect of HTR2A genotype expression patterns are likely region-specific and dependent on different variables such as stress.

Different studies have examined the association between these common SNP’s in HTR2A and physiological and behavioral measures. Regarding the A(-1438)G SNP in healthy individuals, it was found that the G-allele was related to higher levels of neuroticism and a higher HPA-axis responsivity to a psychosocial
stressor (Fiocco et al., 2007). G-allele carriers also show non-suppression of cortisol after dexamethasone treatment indicating impaired ability to autoregulate HPA-axis activity (Rosmond et al., 2002). Both studies thus demonstrate impaired ability to regulate allostatic states in carriers of the C-/G-haplotype. In line with these physiological findings, G-allele carriers show higher levels of depressive symptomatology, social introversion, neuroticism, emotional vulnerability, and harm avoidance (Barskiĭ et al., 2010; Chee et al., 2001; Choi et al., 2004; Golinbet et al., 2004; Lo et al., 2010; Rybakowski et al., 2006; Tochigi et al., 2005). Expectedly, the linked C-allele has also been associated with depressive symptomatology and harm avoidance (Jokela et al., 2007a, 2007b). A 21-year prospective longitudinal study reported that C-homozygotes were less responsive to the protective effect of nurturing mothering or high parental SES, and showed higher levels of depressive symptomatology and harm avoidance despite these favorable circumstances (Jokela et al., 2007a). However, the C-allele has also been associated with higher levels of externalizing, aggressive, and antisocial behaviors (Bjork et al., 2002; Giegling et al., 2006; Hwu and Chen, 2000; Jakubczyk et al., 2012; Zalsman et al., 2011). Thus the C-/G-haplotype has been consistently associated with emotion driven psychopathology, both internalizing and externalizing psychodynamics, independent from social experiences.

In contrast, the A-allele has been associated with impulsivity, substance abuse, and criminality in both healthy and patient samples (Berggård et al., 2003; Nomura et al., 2006; Nomura and Nomura, 2006; Sáiz et al., 2008). Higher impulsivity and criminality associated with the A-allele for A(-1438)G is in contrast with reports of higher levels of impulsivity, reactive aggression, and behavioral problems associated with C- rather than its linked T-allele at the T(102)C SNP (Bjork et al., 2002; Giegling et al., 2006; Hwu and Chen, 2000; Jakubczyk et al., 2012; Zalsman et al., 2011). Nonetheless, these externalizing traits in C-homozygotes where found in the comorbid presence of substance abuse, suicidal ideation and attempt, and depression (Bjork et al., 2002; Du et al., 2000; Giegling et al., 2006; Hill et al., 2002; Hwu and Chen, 2000; Jakubczyk et al., 2012). The C-allele is also consistently associated with suicide (Du et al., 2000; Giegling et al., 2006; Wrzosek et al., 2011), which is a severe mixture of both internalizing and externalizing behaviors (i.e., severe violence directed at self). Indeed, C-allele carriers show a stronger neural response to aversive stimuli in the right-hemisphere (Guo et al., 2014). Thus, higher impulsivity and antisocial behavior in C-homozygotes displays a particular comorbidity with internalizing dynamics and substance abuse.
In contrast, the T-allele is related to higher levels of novelty seeking, cynicism, and hostility (Keltikangas-Järvinen et al., 2008; Salo et al., 2010; Serretti et al., 2007). Interestingly, higher hostility in T-homozygotes was comorbid with paranoia and cynicism but not with anger. Thus, the hostility in T-/A-haplotype carriers might have sprung from hostile attributional biases (i.e., cognitive appraisal) rather than dysregulation of strong emotional drives (i.e., frustration-driven) (Keltikangas-Järvinen et al., 2008). For example, T-allele carriers are more responsive to childhood maternal nurturance in secure attachment formation, but also show increased levels of avoidant attachments and lower reward dependency in the context of childhood adversity (Salo et al., 2011). Avoidant attachment reflects attempts to minimize attachment needs and alienate from interpersonal relationships and has been associated with lower emotional empathy, hostile attributional biases, lower fear related measures, and higher levels of instrumental aggression, externalizing traits, and antisocial behavior (Bakermans-Kranenburg and Van Ijzendoorn, 2009; Burgess et al., 2003; McElwain et al., 2003; Mikulincer, 1998; Rosenstein and Horowitz, 1996; Simpson et al., 2011; Sonnby-Borgström and Jönsson, 2004; Suess et al., 1992). These results indicate that the T-allele may be a plasticity gene, increasing adaptive behaviors when necessary environmental conditions are met but also increasing the risk for externalizing and antisocial behaviors in the context of adversity.

Summarizing, the T-/A-haplotype is associated with increased top-down control over emotional processing, lower harm avoidance, and higher novelty seeking when specific environmental conditions of sensitivity and security are met. Because of the stronger autoregulatory tone on limbic processing, T-/A-haplotype carriers are less likely to be affected by adversity in levels of emotional or behavioral regulation. Nonetheless, in the context of early childhood abuse or stress, the T-/A-haplotype configuration may specifically heighten the risk of impulsivity and criminality through avoidant attachment disorders, heightened novelty seeking, paranoia, cynicism, hostility, lower empathy, socio-emotional detachment, and lower reward dependence. Conversely, in the context of abuse or stress, C-/G-haplotype carriers could be more detrimentally affected in top-down emotional and motivational regulation thus resulting in a mixture of both externalizing and internalizing pathology. The T-/A- as compared to the C-/G-haplotype could therefore respectively contribute to the development of primary and secondary psychopathy.
Compared to 5HT2A receptors, the 5HT2C receptors show a much lower binding in cortical structures (Marek, 2010; Mengod et al., 2010). Autoradiographic studies have identified this receptor in the choroid plexus, cortex, nucleus accumbens, hippocampus, vmPFC, and amygdala (e.g., Abramowski et al., 1995; Clemett et al., 2000; Li et al., 2003a, 2012; Mengod et al., 2010). In contrast to the 5HT2A receptors, the 5HT2C receptors have been identified as regulating the negative feedback loop by activating GABAergic interneurons in the raphe nucleus and thereby suppressing serotonergic cell firing (Mengod et al., 2010). Furthermore, the 5HT2C receptor has been found to mediate the pro-anxiety effects of serotonin at the level of the amygdala (Christianson et al., 2010; Holmes, 2008; Li et al., 2012) and the effect of SSRI’s on serotonergic functioning is augmented by additional 5HT2C antagonism (Cremers et al., 2007). The 5HT2C receptor is asserted to exert counterbalancing effects on the 5HT1A postsynaptic receptor functions (Millan, 2006a, 2006b). Thus, decreased activation of 5HT2C in limbic structures improves 5HT1A-mediated inhibition of limbic processes. Systemic treatment with 5HT2C antagonists blocks anxiety-like behavior in rodents and this effect is directly associated with a reduction in amygdalar reactivity (e.g., Griebel, 1995; Griebel et al., 1997; Hackler et al., 2007; Harada et al., 2006, 2007; Millan, 2003). In addition, the HPA-axis stimulating effects of serotonin seem also to be primarily mediated through 5HT2C receptors in the paraventricular nucleus of the hypothalamus (Calogero et al., 1990, 1993; Heisler et al., 2007; Jorgensen et al., 1998, 2002). That is, blockade of these receptors ablates this excitatory effect of serotonin on HPA-axis reactivity (Heisler et al., 2007). Indeed, Brummett et al. (2011a) found that men with the less active G-allele of the G(23)C SNP in HTR2C (rs6318) had similar baseline cortisol levels as the men with the more active C-allele. However, during emotion induction (i.e., public speaking, anger induction, and sadness induction) men with the G-allele had significantly less increases in cortisol, anger, and depressive mood than men with the C-allele. Lower expressing genotypes of the HTR2C gene may thus be associated with dampened HPA-axis and amygdalar reactivity but data is still preliminary and further research is needed to replicate and elaborate on results.

Finally, the third class of serotonin receptors, the 5HT3 receptors show many similar functions as the 5HT2C receptors. The opponent interaction between 5HT1A and 5HT3 receptors mediates the inhibitory versus excitatory
Figure 3.7 Region-specific densities and the balance in inhibitory/excitatory serotonergic receptors associated with different emotional processing profiles.
balance in limbic structures (Marek, 2010). Higher activation of 5HT1A receptors has thus been found to suppress the excitatory effects of 5HT3 receptors in amygdalar neurons (Koyama et al., 2002). For example, administration of 5HT3 antagonists has been related to an anxiolytic effects in rodents (Costall and Naylor, 2004; Griebel, 1995; Millan, 2003) and 5HT3A knockout mouse show lower levels of anxiety on a variety of tasks (Kelley et al., 2003). In humans, it has been found that the clinical effectiveness of SSRI’s and other antidepressants is partly mediated by their antagonistic properties at 5HT3 receptors (Eisensamer et al., 2003, 2005). Furthermore, antagonizing 5HT3 receptors with odansetron abolishes the acquisition of fear-potentiated startle (Harmer et al., 2006b). Other lines of evidence also suggest an anxiogenic effect of the 5HT3 receptor in fronto-limbic structures (see Costall and Naylor, 2004, and Holmes, 2008 for an extensive review). Lower expressing HTR3 genotypes such as the T-allele of the c.-42C>T SNP and the C-allele for the C(178)T SNP results in lower amygdala and PFC reactivity when confronted with social stimuli (Iidaka et al., 2005; Kilpatrick et al., 2011), and the latter SNP is also associated with lower harm avoidance (Melke et al., 2003). These preliminary results provoke speculations that lower expressing HTR3 genotypes could be associated with lower levels of emotional processing and may thus contribute to the etiology of primary psychopathy but further research is needed to confirm these preliminary hypotheses. Receptor profiles that may be associated with both sensitized and desensitized emotional processing are schematized in figure 3.7.

Gene-gene interactions; 5HTT, 5HT1A, and 5HT2A

Since both the C-allele of the C(-1019)G SNP in HTR1A and l-homozygosity of the 5HTTLPR are associated with higher levels of postsynaptic 5HT1A densities in fronto-limbic structures (Czesak et al., 2006; David et al., 2005; Lemonde et al., 2003; Parsey et al., 2006), they are likely to have interactive effects on emotional processing. Indeed, Dannlowski et al. (2007) reported an interaction between 5HTTLPR and the C(-1019)G SNP in HTR1A on amygdalar reactivity to social threat. Both the lA-homozygotes and C-homozygotes independently showed dampened amygdalar reactivity as compared to other allelic configurations of the corresponding polymorphism. However, interactions between both polymorphisms demonstrated that amygdalar reactivity decreased linear as a function of the number of “risk” genes (0-2) and “risk” alleles (0-
4) (Dannkowski et al., 2007). Gene-gene interactions between the 5HTTLPR and serotonin receptor genes have also been observed in behavioral measures. For example, no main effects were observed for either 5HTT or 5HT2A genotypes on impulsivity but when analyzed together, strong interactive effects appeared. Scores on the Barratt Impulsivity Scale were significantly elevated in $l_A$-homozygotes for 5HTTLPR but only in the presence of C-homozygosity for the T(102)C SNP in HTR2A and not in the presence of the T-allele (Stoltenberg et al., 2012) supporting the hypothesis that although intersynaptic homeostasis of serotonin levels may be stable, without adequate functioning of the 5HT2A system, its regulatory role over subcortical drives and emotions could still be compromised.

Furthermore, the opponent interaction of 5HT1 and 5HT2 receptors is also reflected by gene-gene interactions on top-down sensorimotor gating (Bräuer et al., 2009). For example, the presence of the T-allele in T(102)C SNP of HTR2A leads to an attenuated prepulse inhibition of the startle response (i.e., top-down regulation of emotional processes), but only when the G-allele for the C(-1019)G SNP in HTR1A is not present. In contrast, in carriers of the G-allele prepulse inhibition was not modulated by HTR2A genotype status. Since the G-allele has been specifically related to heightened 5HT1A autoreceptor control, this finding demonstrates that both higher serotonergic output and putatively higher activity at 5HT2A receptors is positively related to top-down prepulse inhibition. Taken together, these results indicate that genotypes of various serotonergic components interact additively or synergistically to modulate physiology and behavior.

### 3.6 The Important Role of GABA in the Regulatory Functions of Serotonin

The final effector mechanisms of serotonin on neural processes, and ultimately mental health, are in many cases dependent on proper glutamatergic and GABAergic functionality within these neural substrates (e.g., Ciranna, 2006; De Oliveira-Sergio et al., 2011; Park and Williams, 2012; Waider et al., 2013). Serotonin has dense synaptic connections with GABAergic, in particular parvalbumin containing interneurons, and glutamatergic pyramidal neurons in fronto-limbic structures via a multitude of serotonergic receptors (see also figure
Serotonergic risks towards emotional pathology

3.6) (Aznar et al., 2003; Holmes, 2008; Mascagni and McDonald, 2007; Muller et al., 2005, 2007; Puig and Gulledge, 2011). Moreover, both in vivo and in vitro studies show that serotonin has direct effects on the migration, differentiation, and survival of GABA expressing neurons during brain development (Bonnin et al. 2007; Di Pino et al. 2004; Gaspar et al. 2003; Waider et al., 2013). For example, serotonin influences GABAergic and pyramidal cell migration via 5HT6 receptors during late embryonic states, which might indicate a facilitatory role of serotonin in the integration of GABAergic interneurons in neural networks (Riccio et al., 2009, 2011). Therefore, genetic variations that mediate the functionality of various components of the GABAergic system could strongly modulate the decisive effect of the various serotonergic genotypes on neural processes and render some genetic alterations in serotonergic components less destructive or less protective.

Information flow within the mPFC-amygdala complex is regulated by serotonin through its effects on GABAergic and glutamatergic mechanisms in both afferent and efferent pathways. Information from the environment reaches the basolateral amygdala via thalamic and cortical afferents where it is processed based on its immediate salience and conditioned value, and subsequently relayed to the central unit, which in turn projects to the hypothalamus and striatum to initiate the appropriate endocrinological and behavioral responses, respectively (Amaral et al., 1992; Davis and Whalen, 2001; Flandreau et al., 2012; Gray et al., 1989; LeDoux et al., 1988; McDonald et al., 1996; McDonald, 1998; Romanski and LeDoux, 1993; Sah et al., 2003). The flow of information into and within the amygdala is strongly modulated by GABAergic interneurons located within the intercalated paracapsular islands that are partly controlled by afferent glutamatergic projections (see for references; Pérez de la Mora et al., 2010).

First, the lateral intercalated paracapsular island forms GABAergic connections with the basolateral nuclei and its autoregulatory tone on amygdalar excitability is achieved by descending glutamatergic pyramidal neurons from the mPFC (see also figure 3.6) (Marowsky et al., 2005; Pérez de la Mora et al., 2008; Quirk et al., 2003). As discussed, high affinity 5HT2A receptors which excite efferent pyramidal neurons in the mPFC, enable serotonergic control over amygdalar reactivity to threat (Amargós-Bosch et al., 2004; Fisher et al., 2009, 2011; Holmes, 2008; Marek, 2010). In other words, descending glutamatergic neurons from the mPFC are modulated by serotonin to regulate the excitability of basolateral amygdalar neurons by synapsing onto GABAergic interneurons.
within the lateral intercalated paracapsular islands (see also Waider et al., 2013).

Second, within the amygdalar complex, the main intercalated and medial intercalated paracapsular islands receive glutamatergic inputs from basolateral nuclei and send GABAergic axons to central nuclei, thereby autoregulating the flow of information between amygdalar nuclei and keeping central amygdalar neurons tonically inhibited (Paré et al., 2004; Pérez de la Mora, 2010). Immunocytochemical techniques to chart serotonin transporter (5HTT) labeled fibers in the amygdala have reported high concentrations of these fibers in the central nucleus and intercalated islands that tightly control the flow of information within the amygdala (O’Rourke and Fudge, 2006). Rainnie (1999) reported that serotonin release primarily and dose-dependently excited GABAergic interneurons through its actions at 5HT2A receptors. This excitation resulted in a concomitant indirect inhibition of projection neurons via an increased release of GABA and subsequent activation of postsynaptic GABA-A receptors. In fact, it has been recently reported that 5HT2A receptors are the dominant serotonergic receptors that facilitate the release of GABA in the amygdala (Jiang et al., 2009, 2011). In a minority of efferent projection neurons (12%), serotonin also had a direct inhibitory action via an activation of postsynaptic 5-HT1A-receptors (Rainnie, 1999). Serotonergic activity at both 5HT2A and 5HT1A receptors in the amygdala may thus gate signals from the basolateral to central nuclei and its final output neurons via excitation of GABAergic and inhibition of glutamatergic mechanisms, respectively, and in so doing, regulate the strength and duration of amygdalar excitation (O’Rourke and Fudge, 2006; Rainnie, 1999). In short, serotonin-driven GABAergic mechanisms may provide the underlying neurobiological basis through which serotonin exerts regulatory influences over amygdalar reactivity.

GABA exerts its effects through a variety of postsynaptic receptor classes, including mainly the GABA-A, GABA-B, and GABA-C receptors (Stahl, 2008). GABA-A receptors are pentameric proteins that are highly important in the anxiolytic effects mediated by serotonin-driven GABA release (Rainnie, 1999). GABA-A receptors contain specific configurations of 19 different subunits that can vary from receptor to receptor and determine its specific affinity, chance of opening, conductance, and other properties. Whereas the alpha1 (GABRA1) and alpha5 subunits (GABRA5) have been associated with the sedative and memory/learning-impairing effects, alpha2 (GABRA2) and gamma1 subunits (GABRG1) have been primarily associated with anxiolytic effects through inhibition of basolateral and central nuclei within the amygdala (Esmaeili et al.,
For example, reduced GABRA2 expression in the temporal and prefrontal cortex has been related to higher levels of anxiety in rodents (Raud et al., 2009), and drugs that decrease anxiety have been found to increase GABRA2 expression (Wisłowska-Stanek et al., 2012). Also, it has been reported that low and high-anxious rodents differed with regard to alpha2 subunit densities in the amygdala and hippocampus (Lehner et al., 2010), and that juvenile stress impacted on limbic densities of alpha1 and alpha2 subunits (Jacobson-Pick and Richter-Levin, 2012). Regarding antisocial behaviors in humans, Lane and Gowin (2009) reported that administration of GABA enhancing drugs decreases cooperation on the prisoner’s dilemma indicating that enhanced GABAergic neurotransmission may alter cooperative and prosocial behavior and increase the risk for antisocial behavior. Indeed, a variety of polymorphisms that regulate GABRA2 expression have been related to conduct disorder and externalizing behaviors in childhood and adolescence (Dick et al., 2006, 2009; Sakai et al., 2010), and substance dependence and impulsivity in adulthood (Dick et al., 2006; Enoch et al., 2006; Villafruente et al., 2012). Taken together, alpha2 subunits on GABA-A receptors influence emotional processes and genes (GABRA2) controlling levels of expression have been associated with antisocial and impulsive behaviors. It would be interesting to examine whether different functional polymorphisms that control GABA-A receptor functioning (especially expression of alpha2 and gamma1 subunits on GABA-A receptors in limbic structures) interact with or modulate the associations between certain serotonergic genotypes and emotional processing profiles, and further clarify through which endophenotypes this potential modulation may take place. For example, studies have confirmed an additive role of serotonergic and GABAergic psychotropics in anxiolytic actions (e.g., De Bortoli et al., 2008; Donatti and Leite-Panissi, 2009), and this might also hold true for gene-gene interactions.
CHAPTER 4
DOPAMINERGIC RISKS TOWARDS AN ANTISOCIAL LIFESTYLE
When Wanting Overrules Having
ABSTRACT

Despite similar emotional deficiencies, primary psychopathic individuals can be situated on a continuum that spans from controlled to disinhibited. The constructs on which primary psychopaths are found to diverge, such as self-control, cognitive flexibility, and executive functioning, are crucially regulated by dopamine (DA). As such, the goal of this review is to examine which specific alterations in the meso-cortico-limbic DA system and corresponding genes (e.g., TH, DAT, COMT, DRD2, DRD4) might bias development towards a more controlled or disinhibited expression of primary psychopathy. Based on empirical data, it is argued that primary psychopathy is generally related to a higher tonic and population activity of striatal DA neurons and lower levels of D2-type DA receptors in meso-cortico-limbic projections, which may boost motivational drive towards incentive-laden goals, dampen punishment sensitivity, and increase future reward-expectancy. However, increasingly higher levels of DA activity in the striatum (moderate versus pathological elevations), lower levels of DA functionality in the prefrontal cortex, and higher D1-to-D2-type receptor ratios in meso-cortico-limbic projections may lead to increasingly disinhibited and impetuous phenotypes of primary psychopathy. Finally, in order to provide a more coherent view on etiological mechanisms, we discuss interactions between DA and serotonin that are relevant for primary psychopathy.

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Based on serotonergic functioning in cortico-limbic structures, I have attempted to delineate the neurophysiological basis to the emotional deficiency that uniquely characterizes primary psychopaths, and which sets them apart from phenotypically comparable disorders such as secondary psychopathy (also termed “sociopathy”). Despite a rapidly growing interest in such differentiations on the level of monoamine neurobiology, there have been no attempts in the scientific literature to clarify possible mechanisms that might contribute to the within-group variability observed among primary or secondary psychopaths more specifically. In this regard, dopamine (DA) and the genes that code for dopaminergic components have been consistently related to constructs on which primary psychopaths have been found to diverge, including self-control, error/punishment learning, aggression, disinhibition, impulsivity, executive functionality, and social cognition. Moreover, serotonin and DA exert their effects on emotion, impulsivity, and empathy in a mutually regulating and reciprocally interconnected manner (e.g., Boureau and Dayan, 2011; Deakin, 2003; Kim et al., 2014; Nikolaus et al., 2010; Seo et al., 2008; Stahl, 2008; Tops et al., 2009; Weitemier and Murphy, 2009). Studying interactions and interdependent equilibria, rather than alterations in singular monoaminergic systems, will bring forth a more complete and coherent view of neurobiological

“The hyperdopaminergic society is above all, an extremely goal-driven society in which achievement is highly rewarded in a highly competitive and uncertain environment….it is typified more by conquest, competition, and aggression than by nurturance and communality…it is fast-paced and even manic, given that dopamine is known to increase activity levels, speed up our internal clock and create a preference for novel over unchanging environments” (Fred Previc).
profiles that contribute to heterogeneous psychiatric conditions such as primary psychopathy.

The goal of this chapter is to construct new theories on the possible relationship between DA functioning and the etiology of primary psychopathy more generally and to further detail which specific dopaminergic alterations could increase or decrease the risk for impetuous risk-taking, shortsightedness, instrumental aggression, and persistent criminality in this group, thereby contributing to within-group heterogeneity. Based upon a comprehensive overview of current literature, I will argue that alterations in the mesocorticolimbic DA system and corresponding genes can steer development towards either a more controlled or a more disinhibited variant of primary psychopathy. The causal explanations of these risk or protective DA profiles are guided by well-established theories on the relationship between DA functioning and behavior and detailed through structural analysis of the actions of DA at its receptors in the striatum, amygdala, and prefrontal cortex (PFC) more specifically. Where possible, I will review direct empirical research into DA functioning in primary psychopathy. Importantly, the insights gained specifically from this chapter may facilitate the development of pharmacological treatment aimed at decreasing disinhibition and impulsivity in primary psychopathy. A short notice on terminology; in the remainder of this paper, the terms “psychopathy” and “psychopathic” consistently refer to primary psychopathy. Secondary psychopathy is not described unless specifically mentioned.

4.1 New Perspectives on the Role of Mesolimbic Dopamine in the Etiology of Primary Psychopathy

Mesocorticolimbic DA projections that arise from the ventral tegmental area (VTA) have a strong modulatory effect on neural information processing within fronto-limbic circuitry (mesolimbic for limbic projections and mesocortical for PFC projections) (see figure 4.1). Other dopaminergic pathways such as the nigrostriatal (NS) and tuberoinfundibular dopaminergic pathways (see also figure 4.1) have also been identified and will be discussed when necessary but will not be a focus of this chapter.

Different electrophysiological studies have demonstrated that VTA DA
neurons can exist in one of at least three different states of excitation; (1) firing single action potentials at a regular or irregular tonic frequency during active waking states, (2) firing action-potentials in synchronized phasic bursts when confronted with unexpected positive feedback or reward-predictive cues, and, (3) showing a phasic inhibition of tonic activity following the absence of expected reinforcements (see also figure 4.4) (Grace, 1991; Heien and Wightman, 2006; Knutson and Gibbs, 2007; Schott et al., 2008; Schultz, 1998, 2002, 2007; Zhang et al., 2009). The dynamic operating ranges and interdependence between these three states of DA neuron firing and their effects on the various DA receptors

Figure 4.1 The different dopaminergic pathways and relevant structures that will be discussed in this chapter. Blue = mesocorticolimbic pathway; 1: VTA, ventral tegmental area, 2: nucleus accumbens/ventral striatum (behind caudate), 3: ventromedial caudate, 4: amygdala, 5: hippocampus, 6: medial (pre)frontal cortex, 7: orbitofrontal cortex, 8: ventrolateral prefrontal cortex, 9: dorsolateral prefrontal cortex. Green = nigrostriatal pathway; 10: substantia nigra, 11: dorsolateral caudate, 12: putamen. Purple = tuberoinfundibular pathway; 13: from hypothalamus to pituitary gland.
elegantly mediate the myriad DA-driven behavioral and psychological functions. In addition to these three states of excitation, another factor which crucially mediates DA functionality in the brain, is how many neurons are tonically active at any given time rather than the firing rate of those neurons, termed here as *population activity* (see figure 4.2)(Floresco, 2007; Grace et al., 2007).

*A short notice on terminology;* I will use the term “D2-type receptors” to refer to the group of D2, D3, and D4-receptors as a family, and the term “D2-receptors” to refer to both the D2S-autoreceptor and D2L-receptor combined. The various functions of DA in mesolimbic projections are mediated through higher affinity D2-type receptors during tonic states (D2L, D3, and D4) and lower affinity D1-type receptors during phasic bursts (D1 and D5) (Dreyer et al., 2010; Grace, 1991; Jackson and Westlind-Danielsson, 1994; Richfield et al., 1989). Also, the definition of “*reward*” has been highly inconsistent in the literature, and it is thus appropriate to clarify my usage of the term (Salamone and Correa, 2012). In this manuscript, reward refers to stimuli that have a positive motivational significance for the subject and trigger the exertion of effort to reach them, regardless of whether this significance is due to situational demands (e.g., food when hungry, safety when in threat) or because it facilitates long-term goals (e.g., finding a mate, becoming rich, increasing social status).

*Tonic and population dopamine activity in primary psychopathy; increased drive toward reward- and novelty seeking*

A key neural component of the mesolimbic DA pathway is the striatum. The primary function of the striatum as a unified system is the integration of neural information from sensory, limbic, and executive modalities in order to regulate energy expenditure, alertness, motivation, and adaptively direct behavior towards relevant goals (Floresco, 2015; Salamone and Correa, 2012). Thus, the striatum is consistently activated in response to behaviorally relevant cues which trigger mobilization towards reward (incentive motivation) or in response to cues of impending punishment which trigger mobilization towards safety (active avoidance) and it is deactivated when predicted reinforcements are not forthcoming or when withholding automated response tendencies (Abler et al., 2005; Levita et al., 2012; Salamone and Correa, 2012; Schott et al., 2008; Schultz, 2002, 2007; Yin et al., 2008). The striatum can be topographically organized into a ventral region, which includes the much studied nucleus accumbens, and
a dorsal region, which largely includes the caudate-putamen complex (see figure 4.1) (Voorn et al., 2004).

**Tonic firing rate of mesolimbic DA neurons (lethargic and inattentive vs. energized and alert);** During non-stressed waking-states, the basal firing rate of striatal DA neurons fluctuates around 3-5 Hz and arises from a pacemaker-like activity of NS and VTA projections. This basal firing rate is called *tonic DA activity* and serves to enable voluntary movement, wakefulness, and general arousal/motivation (see figure 4.2) (Stahl, 2008). Tonic DA activity shows an inverted U relationship with arousal levels, with too low firing rates leading to distractibility, demotivation, and lethargy but too high firing rates leading to anxiety, hyperactivity, and paranoia (Stahl, 2008).

However, tonic DA activity is not fixed and can be dynamically modulated according situational demands (i.e., predictive allostasis). Glutamatergic afferents from fronto-limbic brain regions such as the PFC, hippocampus, and amygdala dynamically regulate tonic striatal DA activity (Ballard et al., 2011; Floresco, 2007; Grace, 1991; Grace et al., 2007; Karreman and Moghaddam, 1996; Murase et al., 1993). Such dynamic increases of mesolimbic DA output serve to stabilize effort and sensitize alertness and emotion when anticipating reinforcements, when coping with stressful events, during effortful goal-pursuit, or during novel but potentially salient circumstances (Ballard et al., 2011; Howe et al., 2013; Pérez de la Mora et al., 2010; Schultz, 1994, 2002, 2007; Wittmann
et al., 2007). After the salient event has subsided or the goal attained, tonic DA release rates drop back down to their basal level (see also figure 4.4).

Population activity of mesolimbic DA neurons (conserve and exploit vs. expend and explore); Apart from tonic firing rates, another important factor that determines the overall output and behavioral impact of the mesolimbic DA system is the number of neurons that show activity, and which are thus available for excitatory modulation (see figure 4.2) (Grace et al., 2007). This ‘population’ activity of DA neurons mediates longer-term fluctuations of DA output in the striatum (i.e.,
synaptic DA levels). The population activity of the VTA DA system is mainly controlled by two opposing neural influences (Floresco et al., 2001, 2003; Lodge and Grace, 2006). The ventral pallidum serves as a global inhibitory module for VTA DA neurons through a continuous GABAergic inhibition of the VTA, thereby hyperpolarizing nearly half of all VTA DA neurons (Floresco et al., 2001; Grace, 2010; Grace et al., 2007). These ventral pallidal GABAergic projections to the VTA can be excited by glutamatergic input from basolateral amygdala which consequently dampens DA population activity (see figure 4.3) (Belujon and Grace, 2015). Conversely, ventral hippocampal glutamatergic afferents into the striatum can excite inhibitory efferents to the ventral pallidum thereby dampening pallidal GABAergic projections and thus releasing VTA DA neurons from constant inhibition, ultimately boosting the population activity of striatal DA neurons (see figure 4.3) (Floresco et al., 2001, 2003; Grace, 2010; Grace et al., 2007; Lisman et al., 2008; Lodge and Grace, 2006, 2011). The hippocampus and amygdala thereby interactively control the population activity of VTA DA neurons by providing an excitatory versus inhibitory influence respectively (Belujon and Grace, 2015).

Such longer-term increases or decreases in striatal DA neuron population activity as controlled by the hippocampus and PFC reflect the perceived availability of environmental resources and punishments more generally (Beeler et al., 2012; Belujon and Grace, 2015; Tomas et al., 2015). By regulating the exertion of effort, and thereby controlling energy expenditure strategies in accord with perceived resource availability, these longer-term fluctuations in DA output serve to facilitate a sustainable equilibrium between internal need and external supply (Beeler et al., 2012). For example, environmental enrichment and novelty boosts striatal DA output and induces exploration, active coping, and energy expenditure (actualization/acquisition mode = maximizing reward through any means possible), whereas environmental deprivation and perceived resource scarcity has been consistently reported to downregulate striatal DA activity and induce exploitation, passive coping, and energy conservation (survival mode = minimal effort to reach maximal payout) (Beauchaine et al., 2011; Cabib and Puglisi-Allegra, 2012; Costa et al., 2014; Mehta et al., 2010; Segovia et al., 2010; Tomas et al., 2015). In other words, if the organism perceives the environment as interesting, safe, and containing important rewards, the costs of not acting/exploring is greater than the costs of expending energy and executive regions such as the hippocampus and PFC boost striatal DA activity to promote exploration, reward-seeking, and vigorous responding (Beeler et al., 2012; Niv et al., 2007)
In accordance, subjects with higher levels of striatal DA activity show an increased reward-expectation, readiness to seek novel rewards, and a drive towards exploration (activity, curiosity, enthusiasm, thrill-seeking), which then secondarily enhances the rewarding properties of stimuli while concomitantly diminishing the sensitivity to response costs (effort-tolerant, optimistic) (Alcaro et al., 2007; Beeler et al., 2012; Berridge, 2007; Costa et al., 2014; Gan et al., 2010; Humphries et al., 2012; Lawrence and Brooks, 2014; Niv et al., 2007; Phillips et al., 2007; Salamone, 2011; Salamone and Correa, 2012; Sharot et al., 2009, 2012). Heightened striatal DA activity thus reduces the reliance on existing and guaranteed sources of reward while increasing the willingness to explore novel, and possibly better alternatives, thereby effectively decoupling reinforcement history from future behavioral choices (opportunistic, progressive, risk-taking) (see Beeler et al., 2012; Breitenstein et al., 2006; Clarke et al., 2014; Costa et al., 2014; Niv et al., 2007). However, pathologically increased levels of DA activity can result in a switch to dyscontrol, leading to traits such as recklessness, irresponsibility, disinhibition, overconfidence, compulsive reward-seeking, and impetuous risk-taking (Evans et al., 2006; Fulford et al., 2010; Lawrence and Brooks, 2014; Silston and Mobbs, 2014).

Conversely, if the environment is perceived as stressful and deprived of important sources of reward, the activity of the striatal DA system is downregulated in order to conserve energy. While a subset of DA neurons fire in response to acute stressors or cues of impending punishment, such DA responses are only observed if there is a possibility of avoiding the stressor or punishment, and it is thus argued that DA actually reacts to the possibility of achieving relief or safety (which are also forms of reward), thereby facilitating active avoidance behaviors (Oleson et al., 2012; Wenzel et al., 2015). Indeed, acute deprivational states (e.g., hunger), immediate stressors, or cued punishments initially increase striatal DA output which boosts vigor and incites active avoidance responses but chronic and/or unavoidable stressors dampen DA output (Beauchaine et al., 2011; Cabib and Puglisi-Allegra, 2012; Oleson et al., 2012). This may be evolutionary adaptive as it is wasteful to expend much needed energy resources in deprived, inescapable, and uncontrollable conditions (Seligman, 1975). Chronically dampened DA activity thus induces a “survival mode” by shutting down growth and exploration, increasing energy consumption and conservation, and biasing behavior towards immediate, effortless, and guaranteed rewards (Beeler et al. 2012; Cardinal, 2006; Salamone and Correa, 2012). Such decreases of DA population activity and striatal DA output are observed in conditions marked
by lethargy, disinterest, short-sightedness, and demotivation such as depression, ADD, and substance dependence (e.g., Belujon and Grace, 2014; Bowden et al., 1997; Chang and Grace, 2014; Dunlop et al., 2007; Kunugi et al., 2015; Wanat et al., 2009).

These experience-dependent dynamic changes in striatal DA output are predominantly coordinated by limbic regions such as the hippocampus and amygdala during childhood and adolescence, but increasingly more by later maturing PFC regions when reaching adulthood. The hippocampus upregulates striatal DA population activity in response to novelty or acute stressors and triggers an active coping response, and the amygdala downregulates this population activity in response to stress withdrawal and promotes further harm avoidance and stress recovery (see figure 4.3) (Belujon and Grace, 2015; Floresco, 2007). In contrast to these shorter term dynamic regulation by limbic regions, the PFC stabilizes striatal DA processes towards long-term goals and modulates its activity in response to feedback (Luciana et al., 2012: Naneix et al., 2012).

Cohen et al. (2009) report that fiber tracts between a subcortical network, including the hippocampus, amygdala, and the ventral striatum predicted individual differences in novelty seeking, whereas tracts between PFC and the striatum predicted individual differences in reward dependence. As such, the transition to PFC control of hippocampal-driven striatal DA output when maturing into adulthood likely corresponds to the gradual transition from a novelty-seeking and risk-taking mode to a more socially sensitive, deliberate, conservative, and foresighted mode of behavior (Cohen et al., 2009; Luciana et al., 2012: O’Donnell, 2010; Smith et al., 2013; Steinberg, 2008). For example, activation of the infralimbic PFC in rats directly dampened the hippocampal-driven increase of striatal DA activity, whereas inactivation of the PFC DA system in marmoset monkey’s boosted striatal DA levels (Clarke et al., 2014; Patton et al., 2013). Also, Galiñanes et al. (2009) found a gradual decrease in spontaneous striatal activity and an increase in the temporal tuning of striatal neurons to cortical rhythms from pre- to post-adolescence, which corresponded to a less disinhibited behavioral pattern.

However, individuals who have pathologically high levels of striatal DA activity or who have an impairment or delay in the development of PFC driven control of hippocampal-striatal connections, would be expected to have more problems regulating striatal DA output when maturing through adolescence, which can impede adaptive long-term goal pursuit and prolong the exploratory phase, ultimately also increasing the risk for dysregulatory psychopathology.
geared towards obtaining short-term and/or novel rewards (Chambers et al., 2003; Ernst et al., 2006; Fareri et al., 2008; Luciana et al., 2012; Naneix et al., 2013; Shannon et al., 2009). In accordance, exposure to amphetamine or pharmacological stimulation of D2-receptors during adolescence has been found to impair PFC DA development and lead to higher behavioral disinhibition to drug-paired cues and lower levels of behavioral flexibility in adulthood (Naneix et al., 2013; Reynolds et al., 2014). It is especially a lower volume and dysfunctionality of hippocampal and PFC modules (probably due to delayed or impaired maturation) that has been related to more deregulated levels of striatal DA neuron activity and an increase in risk-taking, novelty-seeking, and short-term reward-seeking behaviors (Burns et al., 1996; Crunelle et al., 2014; Lodge and Grace, 2006; Luciana et al., 2012; Sun and Rebec, 2003).

Tonic/population mesolimbic DA activity in primary psychopathy; Summarizing the foregoing discussion, the following propositions may be constructed. Moderately elevated levels of tonic/population activity of striatal DA neurons would likely induce a hypomanic state without hindering and possibly even stimulating healthy development of PFC mediated self-control (e.g., Mastwal et al., 2014). More pathologically elevated levels, however, may impair healthy PFC maturation and lead to a divergent trait profile dependent on the level of emotional stability and trait-anxiety (discussed in more detail in section 6). In the context of emotional resilience and fearlessness, pathologically elevated tonic/population activity of striatal DA neurons may result in traits such as impetuous risk-taking, irresponsibility, reward hyperfocus, dominance/aggression, overconfident decision-making, and response perseveration (Fulford et al., 2010; Lawrence and Brooks, 2014; Naneix et al., 2013; Silston and Mobbs, 2014), whereas in emotionally unstable and fearful individuals, it may equally manifest as anxiety, mania, paranoia, and harm-avoidance (Kienast et al., 2008; Mizuki et al., 1997; Nikolaus et al., 2010; Reynolds, 1983; Stahl, 2008). Parallel to their human counterparts, rodents with higher levels of DA turnover, extracellular DA, DA reactivity, and D2-receptor subsensitivity in mesolimbic projections also display higher levels of exploratory behaviors, aggression, reward seeking, active coping behaviors, and lower levels of anxiety and stress sensitivity (De Miguel et al., 2011; Mällo et al., 2007; Tournier et al., 2013), and these associations are especially pronounced in strains that are selectively bred for being low in emotional reactivity and fear (Beiderbeck et al., 2013; Lehner et al., 2014).

From these propositions, two hypotheses may be formulated regarding
striatal DA activity in psychopathic subtypes. (1) Since core psychopathic traits have been generally related to measures of positive affectivity and reward sensitivity, including traits such as boldness, extraversion, risk-taking, motivational drive, behavioral activation (BAS scores), and novelty seeking (see Anderson et al., 2014b; Del Gaizo and Falkenbach, 2008; Patrick et al., 2009; Ross et al., 2007, 2009; Seibert et al., 2011; Yildirim and Derksen, 2015), it is hypothesized that primary psychopathy would associate with a higher tonic and population striatal DA activity regardless of subtype. (2) However, since anatomical alterations of the PFC and hippocampus or severe levels of risk-taking and dysfunctional impulsivity characterize disinhibited psychopaths more specifically (Gao and Raine, 2010; Laakso et al., 2001; Poythress et al., 2010; Raine et al., 2004; Yang et al., 2005, 2009, 2010), they might show a more extreme dysregulation of striatal DA activity. In contrast, controlled subtypes, who evince a more healthy development of the PFC, normal hippocampal anatomy, and a more calculated and foresighted approach to life, might show elevations of DA activity that are within the confines of normal variation. A chronically and non-optimally increased striatal DA activity as related to disinhibited variants may partly explain their intolerance for boredom and routine (destabilization of identity in favor of exploration and novelty-seeking) and their tendency towards an short-sighted, impulsive, reckless, irresponsible, and antisocial lifestyle (Cleckley, 1941; Hare, 1993). As if the external world is too exciting and potentially rewarding to pursue any particular life-path or routine other than continuously seeking for new and possibly more exciting ways to gratify hedonistic needs.

When reviewing the empirical evidence, both hypotheses can be partially supported. First, two studies have directly assessed DA turnover in psychopathy through cerebrospinal fluid homovanillic acid (HVA) levels (which is closely and positively related to mesolimbic DA turnover and output; Amin et al., 1992; Sourkes, 1973). These studies have indeed supported higher DA activity in increasingly disinhibited and violent psychopaths. First, Soderstrom et al. (2001) compared HVA levels with psychopathy scores in 22 violent offenders referred to forensic psychiatric assessment. HVA levels were predominantly related to an antisocial lifestyle (total sample: $r = 0.65$) but also showed substantial but non-significant correlation to the core features of psychopathy (total sample: $r = 0.41$, NS). Interestingly, when authors divided the total sample into further subgroups, psychopathic offenders who were most likely of the primary subtype (i.e., who never attempted suicide, were not prescribed psychotropic medication, or did not show any Axis 1 diagnosis) showed high to very high positive
correlations between cerebrospinal fluid HVA and core psychopathy features (r = 0.57 to 0.65) and antisocial lifestyle scores (r = 0.69 to 0.86). A subsequent study by the same research group reported similar correlations in a separate sample of 28 psychopathic subjects who were selected from a larger group of 121 forensic psychiatric inpatients (Soderstrom et al., 2003). They found that HVA concentrations were specifically related to antisocial lifestyle scores (r = 0.39), but not to the core features of psychopathy (r = 0.02). Nonetheless, when the three factor solution was applied (see Cooke and Michie, 2001), cerebrospinal fluid HVA showed a trend correlation with arrogant and deceitful interpersonal style (r = 0.33), and impulsive/irresponsible behavioral style (r = 0.33), but not with deficient affective experience (r = -0.03). Indeed, as discussed in the previous chapter, the emotional deficiency in primary psychopathy may be more strongly related to serotonergic mechanisms (Glenn, 2011; Yildirim and Derksen, 2013).

Contrary to primary psychopathic subjects, traits such as hostility, aggression, suicidal behavior, and impulsivity in both healthy controls and groups of neurotic, violent, and/or suicidal personality disordered patients have been mainly related to lower HVA levels (r = -0.32) (Coccaro and Lee, 2010; Engström et al., 1999; Limson et al., 1991; Sher et al., 2006; Vaz-Leal et al., 2011), or to higher HVA levels in the context of serotonergic deficiency (Nilsson et al., 2010). Therefore, higher DA functioning could specifically relate to antisocial traits in primary psychopathic individuals, whereas in non-psychopathic (or secondary psychopathic) individuals characterized by emotional dysregulation and serotonergic deficiency, it may be a deregulation of DA activity (both lower and higher HVA levels) which is associated with aggression and impulsivity.

Second, a higher striatal DA activity and the related downregulation of D2-receptors has been related to a variety of both adaptive and maladaptive attributes associated with primary psychopathy more generally such as heightened dominance, extravagance, optimism-bias, internal locus of control, irresponsibility, selfishness, self-confidence (i.e., higher grandiosity, superiority illusion, and self-perceived social desirability), behavioral activation, motivational drive, extraversion, venturesomeness, trait positive affectivity, and creativity (Andreou et al., 2014; Ashby et al., 1999; Berridge, 2003; Cabib and Puglisi-Allegra, 2012; Cervenka et al., 2010; Declerck et al., 2006; Depue, 2006; Depue and Collins, 1999; Egerton et al., 2010; Flaherty, 2005; Forbes and Dahl, 2005; Lawrence et al., 2013; Lawrence and Brooks, 2014; Pedroni et al., 2014; Previc, 2009; Sharot et al., 2009, 2012; Tomer et al., 2014; Yamada et al., 2013).

Third, all the different psychopathy dimensions have been related to an
increased volume of the striatum, which has been associated with higher levels of striatal DA activity (Churchwell et al., 2012; Glenn et al., 2010; Glenn and Yang, 2012; Shiffer et al., 2011). Finally, psychopathic traits, especially the antisocial and impulsive domains, are positively correlated with amphetamine induced DA release, which has been related to higher levels of presynaptic DA activity and turnover (Boileau et al., 2013; Buckholtz et al., 2010; Lehner et al., 2014; Matthews et al., 2013).

Taken together, while higher levels of tonic and population activity of mesolimbic DA neurons relate to core psychopathic traits more generally, especially in emotionally stable and fearless individuals, pathologically elevated levels may increase the risk for an antisocial, reckless, and disinhibited lifestyle in such groups.

Phasic mesolimbic dopamine reactivity in primary psychopathy; reward hyperfocus

The phasic DA signal serves two core functions: (1) as a prediction-error signal when confronted with unexpected reinforcement (mainly rewards) or unconditioned but salient sensory stimuli, and (2) as an incentive-motivation signal when confronted with cues that are probabilistically associated with rewards (see figure 4). The phasic DA response as a function of the prediction-error serves to alert the organism that adjustment of ongoing behavior may be needed (surprise signal). Conversely, the phasic DA response to reward-predictive cues mediates a switch from exploration to exploitation of the potentially rewarding contingency (mobilization signal) and is characteristically followed by a more transient rise of tonic DA activity, which reflects the uncertainty of actual reward delivery and the accompanying rise of task-relevant focus (alert anticipation) (Fiorillo et al., 2003; Harley, 2004; Heien and Wightman, 2006; Redgrave et al., 1999; Schultz, 2002, 2007). Both mechanisms and their potential relevance to primary psychopathy will be discussed below.

Tonic activity/phasic DA as a prediction-error (behavioral adjustment): Glutamatergic afferents from a multitude of sensory, executive, and arousal modules converge in the pedunculopontine tegmental nucleus, which in turn drives phasic burst firing of VTA and NS DA projections in response to unexpected reward-feedback, unconditioned reward, and unexpected but salient sensory stimuli (prediction-error) (see figure 4.4 first trial) (Floresco et al., 2003; Grace et al., 2007; Hong
Dopaminergic risks towards an antisocial lifestyle

Figure 4.4 VTA neuron firing during reinforcement trials (see also Schultz, 2002; Harley, 2004; Schultz, 2007). In the first trial, when associations still need to be learned, VTA DA neurons respond phasically to the unexpected reward (phasic prediction-error; experienced as surprise) which acts as a teaching signal and informs the organism that some of the preceding cues or behaviors should be remembered as they might lead to reinforcement. After initial learning, the phasic DA response transfers from the moment of reward to the first cue in the temporal order of events that might lead up to that reward (phasic incentive-motivation; experienced as enthusiasm and motivation). However, because the cue-reward association is not yet fully certain, this phasic DA response is characteristically followed by a slow ramping of tonic DA activity which sensitizes alertness and responding (experienced as nervousness, arousal). Finally, when the expected reward is not forthcoming, there is a phasic inhibition of DA neuron activity (experienced as anhedonia, frustration, disappointment) which acts as a sort of ‘reset button’ and facilitates the extinction of learned material so that new behaviors can be learned. Important to note: phasic DA activation to predictive cues is only observed if the expected reward is still somewhat uncertain. If the required action has become automated and the reward certainly forthcoming, then DA neurons do not show much activity.
and Hikosaka, 2014; Kobayashi and Okada, 2007; Martinez-Gonzales et al., 2011; Redgrave et al., 1999). These initial phasic DA responses serve as alerting signals to attend appropriately to environmental stimuli, and as teaching signals to learn new behavioral strategies. Especially the dorsal component of the striatum (in particular the caudate nucleus), which receives a major dopaminergic input from both the substantia nigra (NS pathway) and the VTA, has been critically implicated in alerting attention to salient stimuli and action-contingent learning (Anderson et al., 2014a; Dang et al., 2014; Glenn and Yang, 2012). When confronted with unexpected reward-feedback for a certain performed action or after a certain cue, the ensuing prediction-error in the dorsal striatum ensures that the action will be repeated or the cue attended to when similar contingencies arise (Balleine et al., 2007; Glenn and Yang, 2012; Grahn et al., 2008).

However, because these DA-driven prediction-errors need to overcome the background noise to be neurally registered as salient and worthy of proper attention, higher levels of background tonic DA activity naturally reduce the signal-to-noise ratio and thus decrease the impact of unpredicted reward-feedback and environmental stimuli on behavioral or attentional adjustments (Breitenstein et al., 2006; Clarke et al., 2014). Indeed, a specific deficit in action-contingent learning has been ascribed to a lower amplitudal difference of dorsal striatal activation in response to rewarded versus non-rewarded trials (Glenn and Yang, 2012). In contrast, a lower tonic DA would boost phasic DA prediction-errors due to a higher signal-to-noise ratio and incite an impulsive reorientation and behavioral disinhibition to all sorts of salient environmental stimuli (e.g. ADHD) (Sikström and Söderlund, 2007).

Population activity/phasic DA responses to reinforcement-predictive cues (behavioral mobilization); Once associations are learned, the PFC and amygdala drive VTA and striatal DA neurons to respond to the first cue in the temporal order of events that has been probabilistically associated with the reinforcement (mainly to reward-predictive or to escapable punishment-predictive cues) (see figure 4.4, second trial) (Schultz, 2002). The phasic DA burst to reinforcement-predictive cues immediately activates D1-receptors in the striatum and D2-receptors in the PFC, which engages goal-directed behavior, cognition, and decision-making, and the subsequent ramping of tonic DA activity observed between cue exposure and goal attainment, mainly stimulates D2-type receptors in limbic and D1-receptors in PFC structures, which stabilize goal-directed effort and sensitize attention and emotion towards task-relevant stimuli (Assadi et al., 2009; Howe
Dopaminergic risks towards an antisocial lifestyle

et al., 2013; Knutson and Gibbs, 2007; Pérez de la Mora et al., 2010; Salamone and Correa, 2012; Schott et al., 2008; Seamans and Yang, 2004; Wanat et al., 2009).

Phasic DA responses to reinforcement-predictive cues are thus crucially mediated through amygdalar, hippocampal, and PFC glutamatergic afferents which directly innervate the VTA and the ventral striatum and modulate DA neuron activity and efflux in response to conditioned cues, to novel but potentially salient contexts, or to task-relevant stimuli (Ambroggi et al., 2008; Blaha et al., 1997; Bossert et al., 2012; Floresco, 2007; Grace, 1991; Gruber and McDonald, 2012; Ishikawa et al., 2008; Johnson et al., 1994; Overton and Clark, 1997; Phillips et al., 2003; Shinonaga et al., 1994). The mesoamygdaloid DA pathway is involved in the retrieval and propagation of the salience/relevance of perceived reinforcement contingencies, especially in response to conditioned stimuli, and thus selects which reinforcements to pay attention to, thereby regulating striatal-driven energy mobilization to these contingencies (Nader and LeDoux, 1999; Phillips et al., 2003; Balleine and Killcross, 2006; Murray, 2007; Ambroggi et al., 2008; Gruber and McDonald, 2012; Ousdal et al., 2012).

For example, cue-evoked amygdalar signals actually precede and crucially modulate the subsequent striatal DA response either directly (short-route; intuitive/reflexive) or indirectly through activation of the mPFC (long-route; evaluative), thereby boosting the behavioral mobilization and cognitive engagement to reinforcement-predictive cues and relevant stimuli (Ambroggi et al., 2008; Di Ciano and Everitt, 2004; Floresco et al., 1998, 2003; Gariano and Groves, 1988; Ishikawa et al., 2008; Jackson and Moghaddam, 2001; Johnson et al., 1994; Jones et al., 2010; Phillips et al., 2003; Setlow et al., 2002; Stuber et al., 2011; Sugase-Miyamoto and Richmond, 2005; Taber and Fibiger, 1995). Nevertheless, although glutamatergic afferents can induce phasic burst firing of VTA and striatal DA neurons, these afferent projections can only induce these phasic bursts in DA neurons that already display spontaneous activity (Floresco et al., 2003; Grace et al., 2007; Komendantov and Canavier, 2002; Overton and Clark, 1997). In this context, a greater hippocampal drive on striatal GABA neurons to the ventral pallidum may boost DA neuron population activity and substantially increase the number of action- and outcome-possibilities that can mobilize behavior or attract attention, ultimately inciting reward-exploration and novelty-seeking (see figure 4.3).

When we translate these biological findings into psychological terms, we might better understand the common sense underlying their functional
relevance. That is, when we are motivated, energetic, optimistic, and lively (higher DA population activity), we are more likely to see potential reward in a wider variety of situations, less likely to be inhibited towards novelty, risk, or potential punishment, less lethargic towards delayed or effortful reinforcements, and more readily aroused and enjoyed by pleasurable contingencies (sensitized phasic DA reactivity to reward-predictive cues). Conversely, when we are hopeless, lethargic, disinterested, and cynical towards the future (lower DA population activity), we are less likely to see possibilities when they do arise and more likely to stay focused on only those rewards that we can control ourselves and which have a certainty of working out (desensitized phasic DA reactivity to reward-predictive cues).

Interestingly, lower (left-hemisphere) hippocampal volumes (as found in disinhibited psychopathy) might specifically arise due to maldevelopment or loss of perineuronal nets and GABAergic interneurons within this region (see figure 4.3) (Boley et al., 2014; Le Magueresse and Monyer, 2013; Martisova et al., 2012; Ohira et al., 2013; Raine et al., 2004). The loss of these feedforward inhibitory mechanisms within the hippocampus may disinhibits its glutamatergic efferents to striatal GABA projections, thereby dampening the effect of pallidal inhibition and releasing DA neurons from their ongoing autoregulatory tone (Boley et al., 2014; Floresco et al., 2001; Shah and Lodge, 2013). For example, activating glutamatergic neurons in the ventral subiculum of the hippocampus has been found to increase DA population activity, facilitate phasic burst firing, and boost extrasynaptic DA levels, without altering tonic firing rates (Blaha et al., 1997; Floresco, 2007; Floresco et al., 2003; Lodge and Grace, 2006), and this increase of synaptic DA has been found to promote novelty seeking and reward exploration (Costa et al., 2014; Sun and Rebec, 2003).

Furthermore, hyperactivity of mesolimbic DA projections and the ensuing oversaturation of D2-receptors increases the functional coupling between the amygdala, hippocampus, and striatum which sensitizes sensory processing and behavioral mobilization towards goal-relevant stimuli, while at the same time attenuating PFC input implicated in executive functioning, risk-assessment, performance monitoring, and behavioral flexibility (Grace et al., 2007; Grace and Rosenkranz, 2002; Goto and Grace, 2005; Kohno et al., 2014; Kröner et al., 2005; O’Donnel and Grace, 1994; Rosenkranz and Grace, 1999, 2001, 2002a, 2002b; Xu et al., 2009). For example, inactivation of the PFC, and/or administration of D2-agonists, boosts reward expectancy, lowers punishment sensitivity, impairs behavioral flexibility, and increases risk-taking.
(Goto and Grace, 2005; Kuryloa and Sarah Tanguay, 2003; Norbury et al., 2013). Therefore, when taken to extremes, tonic DA hyperactivity in limbic structures can dampen the influence of PFC-driven feedback on ongoing behavior and thereby result in a hyperfocus towards rewards, impetuous risk-taking, and impaired response modulation, which is characteristic of disinhibited forms of psychopathy (Baskin-Sommers et al., 2010; Newman and Lorenz, 2003).

Phasic mesolimbic DA reactivity in primary psychopathy; Taken together, we can differentiate between four tonic/population activity profiles of mesolimbic DA neurons with varying associations to phasic DA activity and behavior; (1) Low tonic/low population DA activity (with upregulated D2-receptors) may boost prediction-errors to unexpected feedback, decrease the number of contingencies that can drive phasic DA responses, and dampen the mobilization of behavior to reinforcement-predictive cues in general (lethargy, disinterest, inattention, and motor retardation, as found in ADD, depression, and substance dependence). (2) Low tonic/high population DA activity (with upregulated D2-receptors) may boost prediction-errors to reinforcement feedback and induce orienting and mobilization responses towards a large range of environmental stimuli (impulse-driven disinhibition, hyperactivity, and distractedness, as found in ADHD, generalized anxiety, substance abuse, and psychosis) (Grace, 1991; Grace et al., 2007; Ilgin et al., 2001; Sikström and Söderlund, 2007). (3) High tonic/low population DA activity (with downregulated D2-receptors) may impair prediction-errors and decrease the number of action- and outcome-contingencies that can drive behavior but specifically boost phasic DA responses and attentional hyperfocus to cues predictive of immediate, guaranteed, and effortless rewards (delay discounting, reward-sensitivity, and perseverance, as found in ADHD, L-DOPA medicated Parkinson patients, pathological gambling, substance abuse, and antisocial behavior) (Dodd et al., 2005; Nombela et al., 2014 Voon et al., 2010). (4) High tonic/high population DA activity (with downregulated D2-receptors) may impair prediction-errors but increase the number of action- and outcome-contingencies that can drive behavior and boost phasic DA responses and attentional hyperfocus to cues predictive of reward more generally, especially novel, uncertain, and risky rewards (reward-hyperfocus, novelty-seeking, risk-taking, goal-driven disinhibition, and perseveration as found in primary psychopathy, mania, and stimulant intoxication) (Cooper et al., 2006; Fulford et al., 2010; Naneix et al., 2013; Silston and Mobbs, 2014).

From these propositions, three hypotheses may be stated regarding
phasic DA functioning in primary psychopathic subtypes. First, (1) because of a non-optimally heightened tonic and population activity of striatal DA neurons in disinhibited primary psychopaths, they might show a concomitant increase of phasic striatal DA responses to cues predictive of novel and risky but potentially larger rewards, thereby engendering impetuous risk-taking, behavioral disinhibition, persistent novelty exploration, and aggressive behaviors towards incentive-laden goals. Second, (2) since heightened mesolimbic DA output can increase subcortical coupling between the ventral striatum, amygdala, and hippocampus while concurrently attenuating PFC input implicated in action monitoring and risk-assessment, disinhibited psychopaths are expected to show impaired neural registration of error- and punishment-feedback and lower levels of response modulation than their controlled counterparts. Finally, (3) because increased tonic DA activity in dorsal striatal structures may reduce the signal-to-noise ratio, disinhibited psychopaths are expected to show dampened striatal responses to reward-feedback, reduced attentional re-orienting to peripheral stimuli, and an impairment of action-contingent learning.

In support, striatal and mPFC reactivity to reward-predictive cues as a measure of phasic DA responsiveness is positively related to an antisocial lifestyle (right NAcc; $r = 0.38$, left NAcc; $r = 0.52$) but not to the interpersonal/affective traits (Bjork et al., 2012; Buckholtz et al., 2010). These positive associations were especially pronounced when the predicted reward was uncertain rather than guaranteed (Bjork et al., 2012). In contrast, in both offender and community samples, psychopathic traits were unrelated to ventral striatal reactivity to reward-feedback (Bjork et al., 2012; Buckholtz et al., 2010; Pujara et al., 2014). However, Bjork, Buckholtz, and Pujara did not differentiate between the antisocial facet and the impulsive/irresponsible lifestyle facet of psychopathy since Carré et al. (2013) found a significant negative association between the lifestyle facet and left ventral striatal reactivity to reward feedback, but a trend positive relationship with the antisocial facet. Other studies in psychopathic youth also report lower levels of reward responsivity (Cohn et al., 2015; Marini and Stickle, 2010).

Taken together, these data in disinhibited psychopaths consistently reveal higher levels of ventral striatal reactivity to reward-anticipation, especially towards uncertain rewards, but normal to low ventral striatal sensitivity to actual reward receipt. These findings are coherent with the theory that high DA activity increases reward-anticipatory drive and novelty-exploration but reduces the amplitude of the prediction-error. For example, enhanced ventral striatal DA efflux produced by levodopa in Parkinson patties correlated with higher levels
of wanting and hyperfocus towards another dose of L-DOPA despite increasing tolerance towards its pleasurable effects (Evans et al., 2006). Similar to their human counterparts, hyperdopaminergic mice also display increased “wanting” and demonstrate enhanced acquisition, sustained attention, goal-directed behavior, vigor, and greater incentive performance for a short-term sweet reward but lower levels of “liking” to actual intake and impaired Pavlovian or operant learning (Berridge. 2003, 2007; Cagniard et al., 2006; De Jong et al., 2015; Peciña et al., 2003). In a similar way, dampened DA activity mainly decreases the willingness to expend energy towards rewards (“wanting”) but has less impact on the ability to enjoy readily available, effortless, and guaranteed rewards (“liking”) which is more closely related to noradrenergic, opioid, and endocannabinoid mechanisms (Berridge, 2003, 2007; Berridge and Kringelbach, 2013; Mahler et al., 2007; Peciña et al., 2003).

One possibility is that due to this insatiable drive to explore and pursue novel and increasingly higher rewards, and their inability to learn and follow any particular path of action, disinhibited psychopaths may get “stuck” in a perennial need for more exciting, novel, and profitable alternatives to satisfy projected expectations (multiple life-partners, broken work-history, sensation seeking, criminal versatility, intolerance for routine or boredom; Hare, 1993).

Second, behaviorally disordered youth with psychopathic traits showed a significant dampening of dorsal striatal reactivity to reward-feedback, thus demonstrating a lower learning curve of the action response required to acquire reinforcements (Finger et al., 2011). Also, adolescents with externalizing behaviors and psychopathic traits have been found to display increased dorsal striatal blood oxygen level dependent (BOLD) responses to reward-predictive cues that persist on trials when reward is unexpectedly omitted (Finger et al., 2008; Gatzke-Kopp et al., 2009). Similarly, a significant and substantial negative correlation between ventral striatal deactivation to monetary loss (punishment) \( (r = -0.61) \) was reported exclusively in psychopathic inmates suggesting response perseverance despite repeated punishments or errors (Pujara et al., 2014).

In conjunction with the aforementioned findings, it is tempting to speculate that although disinhibited psychopaths may be less moved by guaranteed rewards, and more likely to continuously and impetuously explore novel alternatives, those habits that are formed are likely to be persevered, no matter how many times they end in failure, and no matter how grave the warnings of potential punishment. However, since higher levels of salience are likely needed to instill habit forming in psychopaths, only those actions leading
to strong and salient rewards such as illicit drugs, cheap thrills, promiscuous sex, and fast money may lead to habit forming and likely to be persevered.

Contrastingly, adolescents with high levels of externalizing behaviors but without psychopathy showed heightened ventral striatal and vmPFC activation to reward-feedback in particular (Bjork et al., 2010), similar to findings in ADHD patients, who additionally show striatal hyporesponsivity to reward-predictive cues (Scheres et al., 2007; Ströhle et al., 2008; Tripp and Wickens, 2008, 2009). Indeed, early life adversity associated with the development of ADHD impacted differentially on reward processing in adulthood, leading to hyporesponsiveness during reward anticipation and hyperresponsiveness when receiving a reward (Boecker et al., 2014). Externalizing and impulsive but non-psychopathic individuals may thus be characterized by a lower tonic DA activity and a consequent increase in the signal-to-noise ratio of positive prediction-errors, thereby potently boosting behavioral responses to a wide range of environmental stimuli and increasing the risk for impulse-driven disinhibition (Sikström and Söderlund, 2007; Tripp and Wickens, 2008, 2009).

**Mesolimbic dopamine genetics in primary psychopathy**

When studied on the level of synaptic neurodynamics (e.g., receptors, transporters, synthesis enzymes), the DA system is an elegant but at times ‘paradoxical’ system that does not allow for simple and straightforward deductions. Many inconsistent findings and contradictory perspectives of interpretation are present in the contemporary literature, especially when it comes to the functional relevance of various DA genotypes. Therefore, I will shortly review which DA neuronal components might be relevant, clarify how they might interactively mediate tonic and phasic DA functioning, and examine how different genotypes may regulate their expression and functionality, before examining which genotypes may contribute to the etiology of psychopathy.

**DA turnover (tyrosine hydroxylase);** DA synthesis begins with the ingestion of the essential amino acid phenylalanine which is converted to tyrosine, or by the ingestion of tyrosine-rich foods directly. Tyrosine is transported to DA neurons where it is converted to L-DOPA by the rate-limiting enzyme tyrosine hydroxylase (TH) and subsequently converted into DA through an enzymatic reaction by L-amino acid decarboxylase (AAAD) (also known as DOPA decarboxylase)
(Stahl, 2008). If the body is depleted of phenylalanine, tyrosine, or if either of these enzymatic steps is compromised, DA neuronal availability and corresponding release is decreased and subsequent variations in DA components are rendered less relevant. In other words, a higher ongoing DA activity is first and foremost dependent on higher turnover rates. Lawrence and Brooks (2014) reported a strong positive correlation between DA synthesis capacity, as indexed by FDOPA Ki values, and levels of trait disinhibition \((r = 0.78)\), especially tendencies to financial irresponsibility and extravagance (components of novelty seeking), which, are in turn related to externalizing behavior (Krueger et al., 2007). These results are reported in both Parkinson patients as well as healthy individuals (Lawrence et al., 2013; Lawrence and Brooks, 2014).

There has been a scarcity of research into the gene that controls for TH expression despite that a number of common polymorphisms have been identified (Rao et al., 2007; Wei et al., 1997). The available research, however, does evince a role for these polymorphisms in various psychological traits. Certain alleles of TH polymorphisms that result in higher promoter activity and increased DA synthesis, such as the T-allele for the C(-824)T single nucleotide polymorphism (SNP) in the TH gene (Rao et al., 2007), have been associated with higher levels of persistence in psychiatric patients and higher levels of novelty seeking in healthy males (Fukuda et al., 2013; Sadahiro et al., 2010). These findings support the previously stated premise that higher DA activity can improve delay/effort tolerance during goal-directed behaviors (persistence) and attenuate the bias to select behavioral responses based on previous experiences (novelty-seeking).

In sum, although research is still scarce, polymorphisms within the TH gene might prove a relevant venue for future research on the genetics of psychopathy. In line with the above-mentioned hypotheses on the relationship between DA dynamics and behavior, it might be speculated that higher TH expression genotypes, resulting in higher DA synthesis, may increase assertive reward pursuit and novelty-seeking more generally, but may also contribute to the risk for psychopathy, antisocial behavior, and externalizing symptomatology when coupled to additional DA risk-factors described below.

**DA receptor configuration (D2-receptors);** After DA is released and has stimulated postsynaptic receptor sites, it escapes the synaptic cleft and engages D2S-autoreceptors on presynaptic DA terminals which serve to downregulate the excitability of the presynaptic membrane (Grace, 1991). D2S-autoreceptor
activation not only provides an immediate inhibitory feedback to neuronal excitation, but on a longer timescale also increases dopamine transporter (DAT) expression and inhibits TH activity and in so doing homeostatically downregulates DA functioning during longer term increases in neurotransmission, such as during long-term allostatic states (see figure 4.6) (Best et al., 2009; Bolan et al., 2007; Ford, 2014; Lee et al., 2007; Pothos et al., 1998). In accordance, synaptic DA levels and corresponding neural activation patterns show greater fluctuations in the context of reduced D2S functioning (Bertolino et al., 2009). For example, inhibiting D2-receptors led to a greater evoked DA response without affecting the tonic-to-phasic ratio, indicating that the increase of phasic DA responses was accompanied by an equally strong increase of tonic DA activity (Zhang et al., 2009). Conversely, mice with overexpression of D2-receptors in the striatum show a particular reduction of tonic and phasic VTA DA signaling and a depressive phenotype (Krabbe et al., 2015). D2-receptor expression partly varies as a function of extracellular DA levels. Persistently elevated DA levels and concomitant stimulation of D2S-autoreceptors and D2L-receptors results in a downregulation of these receptors (Chou et al., 2000; Ginovart et al., 1999; Jones et al., 1999; Wanat et al., 2009), which might paradoxically increase DA activity but only if DAT-driven DA clearance is not adequately upregulated or TH-driven DA synthesis is not properly downregulated.

The widely studied TaqIA single nucleotide polymorphism (SNP) has been long thought to reside on the promoter region of the D2-receptor gene (DRD2) and directly influence D2-receptor expression. This initial assumption was seemingly supported by various studies reporting a 30 to 40% reduction of D2-receptor binding in the striatum of A1-allele carriers (Jönsson et al., 1999; Pohjalainen et al., 1998; Hirvonen et al., 2009b; Noble, 2000; Ritchie and Noble, 1996, 2003; Thompson et al., 1997). However, it has been clarified that the TaqIA is actually located in the coding region of the ankyrin repeat and kinase domain containing 1 (ANKK1) gene (Neville et al., 2004). Similar to the functions of other ankyrin repeats, the TaqIA-ANKK1 mainly controls protein stability, folding and unfolding, and binding specificity (Li et al., 2006). In other words, the TaqIA-ANKK1 polymorphism may especially influence how well the D2-receptor can perform its molecular functions.

Since the TaqIA does not reside on the DRD2 gene, its reported effect on D2-receptor densities is likely mediated through its linkage with other SNPs within the DRD2 gene. For example, the A1-allele is closely linked to the C-allele of the C(957)T SNP, and this A1/C haplotype has been related to the
lowest levels of striatal D2-receptor binding compared to other configurations (Frank and Hutchison, 2009; Hirvonen et al., 2009a). In addition, the TaqIA-ANKK1 also shows linkage to various intronic SNPs that specifically affect D2S-autoreceptor expression (Zhang et al., 2007). Lower D2S-autoreceptor functioning has been related to impaired autoregulatory modulation of TH and DAT activity in the striatum in response to DA release (impaired downregulation of TH or upregulation of DAT) (Dickinson et al., 1999; Håkansson et al., 2004). In accordance, the A1-allele, particularly when homozygous (A1/A1), leads to higher DA turnover and tonic activity as evinced by its association to increased aromatic L-amino acid decarboxylase (AAAD) activity, higher levels of [18F] FDOPA uptake in the striatum, higher urinary and cerebrospinal fluid HVA levels, and higher levels of DA release during gambling tasks (Joutsa et al., 2014; Jönsson et al., 1996; Laakso et al., 2005; Ponce et al., 2004). Nonetheless, one study failed to find an effect of the TaqIA-ANKK1 on HVA levels in violent alcoholics, although long-term substance dependence could have skewed the results (Goldman et al., 1992).

Other findings also suggest higher tonic DA activity in A1-carriers. That is, the A1-allele has been related to an increase of ventral striatal and anterior insular reactivity to reinforcement-predictive cues (both reward and punishment), but attenuation of orbitofrontal cortex (OFC) reactivity to reward feedback (Cohen et al., 2005; Richter et al., 2013; Stice et al., 2012). Thus, although A1-carriers may experience lower levels of reward in the here-and-now due to a lower appraisal of reward-feedback (reward deficiency), they may be more inclined to overestimate the probability and value of cued future rewards and thus at a higher risk for gain-oriented impulsivity and risk-taking (Blum et al., 2008). Furthermore, A1-allele carriers were less efficient in learning to avoid punished actions and these impairments were reflected by reduced dynamic interactions between the PFC and hippocampus during feedback-based learning, thereby also indicating higher mesolimbic DA activity (Klein et al., 2007).

Taken together, at this point it is yet unclear how the TaqIA-ANKK1 precisely influences synaptic DA neurodynamics and DA neural components and more research is needed to make empirically substantiated and theoretically coherent claims. In light of the data that is available, however, it can be safely deduced that the A1 genotype is associated with D2-receptor subsensitivity (both D2S and D2L), higher levels of DA turnover, and higher levels of tonic DA activity in striatal regions.

It has been reported in rodents that D2S- and D2L-receptor subsensitivity,
higher levels of DA synthesis, and higher extracellular DA are related to novelty-seeking, addictive behaviors, aggression, incentive motivation, behavioral sensitization to reward-predictive cues, response perseveration, and lower levels of anxiety (Beiderbeck et al., 2013; De Jong et al., 2015; De Miguel et al., 2011; Holroyd et al., 2015; Lehner et al., 2014; Mällo et al., 2007; Tournier et al., 2013), suggesting that the A1-allele of the TaqIA-ANKK1 SNP may relate to analogous traits in humans. In agreement, A1-allele carriers display higher levels of childhood antisocial behavior, bipolar disorder with low anxiety, impulsivity, novelty/stimulus seeking, aggression, antisocial/borderline traits, faster habituation to positive feedback (decoupling behavior from experience), and substance abuse/dependence but also adaptive traits such as extraversion, behavioral activation, low depression or harm avoidance, and improved cognitive performance (Althaus et al., 2009; Barskiĭ et al., 2010; Bartrés-Faz et al., 2002; Eisenberg et al., 2007; Esposito-Smythers et al., 2009; Hoenicka et al., 2007; Kazantseva et al., 2011; Lu et al., 2012; Nemoda et al., 2010; Noble et al., 1998; Ponce et al., 2008, 2009; Smillie et al., 2010; Stelzel et al., 2010; Thaler et al., 2012; Wang et al., 2013a, 2014; Zai et al., 2012). A1-carriers also showed significantly lower levels of risk for depression and higher engagement bias towards positive social stimuli, thus evincing a more stable and higher DA functioning (Elovainio et al., 2007; Gong et al., 2013).

Four different studies have tested the relationship between the TaqIA-ANKK1 polymorphism and psychopathy directly (Hoenicka et al., 2007; Ponce et al., 2008; Smith et al., 1993; Wu and Barnes, 2013). Two of these studies found significant associations between the A1-allele and psychopathy scores (Hoenicka et al., 2007; Ponce et al., 2008). Carriers of the A1-allele showed more pronounced core features and higher total psychopathy scores but did not differ with respect to antisocial lifestyle scores. In contrast, Smith et al. (1993) failed to find a relationship between the TaqIA-ANKK1 polymorphism and psychopathy as assessed through the PCL-R in a sample of 80 incarcerated male criminals. All three studies used men with alcohol dependence but Smith compared male criminals that varied in psychopathy scores whereas Ponce and Hoenicka compared psychopathic delinquents and alcoholics with healthy controls, indicating that the participants in these latter samples were more varied in their psychopathy scores. Since the A1-allele has been found to be a risk gene for a general defect in self-control such as observed in antisocial behavior, addiction, and psychopathy (Hoenicka et al., 2007; Ponce et al., 2008), the variability between the participants in the Smith study could have been too small.
to detect differences (both groups were substance abusing criminals).

The most recent study by Wu and Barnes (2013) reported a strong positive association between the number of A1-alleles and psychopathic personality scores in a large sample of healthy adults from the community. Despite significant results, Wu and Barnes (2013) used a non-conventional method for assessing psychopathy (i.e., self-constructed scale of correlated questions from the Five Factor Method Questionnaire) and included subjects in the psychopathy group if they scored above the 90th percentile, thus effectively classifying 10% of an healthy population as being psychopathic (226 subjects in a sample of 2,123). Since the actual prevalence of psychopathy is much lower, around 0.6% in a healthy population of adults (Coid et al., 2009, 2012), Wu may have included other antisocial and narcissistic populations that are not necessarily psychopathic, thereby diluting the validity of findings when generalized to psychopathy.

Another widely examined SNP within the DRD2 is the C(957)T (rs6277), which has also been studied in relation to psychopathy and has been found to play a complementary role to the TaqIA-ANKK1 polymorphism. Different studies reported strong linkage disequilibrium of the C-allele carriers with the A1-allele (Duan et al., 2003; Hirvonen et al., 2009a). The C(957)T SNP, probably in concert with the TaqIA-ANKK1, impacts primarily on receptor affinity (BP) rather than density (Bmax) and is associated with a putative alteration in the receptor mRNA folding pattern leading to a decrease in D2 mRNA stability and synthesis (Duan et al., 2003; Hirvonen et al., 2004, 2009a, 2009b). Haplotype analyses also showed that subjects with the A2-/T-homozygosity have the highest, whereas those with A1-/C-homozygosity have the lowest striatal D2 binding potentials (Hirvonen et al., 2009a). The A1/C genotype could thus synergistically downregulate D2-receptor functionality, thereby strongly boosting striatal DA activity while also decreasing the neural registration of reinforcement-feedback.

It has been reported that C-homozygotes show a higher reward responsivity after psychosocial stressors and lower avoidance of stimuli that are probabilistically associated with punishment indicative of higher DA activity (Frank et al., 2007), whereas T-homozygotes display higher levels of dysfunctional impulsivity and more difficulty in inhibiting dominant response tendencies indicative of lower DA functioning (Colzato et al., 2010). In accordance, Ponce et al. (2008) found that C-homozygosity was strongly associated with total, interpersonal/affective, and antisocial/lifestyle scores on the PCL-R but only in the presence of the A1-allele (Ponce et al., 2008). The A1-allele and C-homozygosity may thus work
in tandem by additively or synergistically downregulating D2S-autoreceptor expression and thereby boosting striatal DA activity. In addition, the A1/C genotype has been related to the highest risk for alcohol dependence (Swagell et al., 2012), and both alcohol intake and dependence is specifically related to lower D2-type receptors in the striatum (Martinez et al., 2005; Thanos et al., 2001). These genotypes could therefore interactively contribute to psychopathy, antisocial behavior, and substance abuse.

Taken together, since genotypes associated with lower D2-receptor expression/higher tonic DA activity (e.g., A1/C-haplotype for the TaqIA-ANKK1 and C(957)T SNP) are related to both the core and antisocial domains of psychopathy, these genotypes may increase the risk for psychopathy but also antisocial behavior, substance abuse, and risk-taking more generally.

**DA reuptake, recycling, and release (dopamine transporter):** The dopamine transporter (DAT) plays a pivotal part in the homeostatic regulation of both neuronal and synaptic DA levels and is expressed predominantly in the striatum, olfactory tubercle, nigrostriatal bundle, lateral habenula, mPFC, hippocampus, and the amygdala (Ciliax et al., 1995; Hoffman et al., 1998). The DAT is responsible for 95% of striatal and 40% of mPFC DA clearance after release (Wayment et al., 2001), serving as a regulator of both tonic and phasic DA neurotransmission (Zhang et al., 2009). Indeed, acutely inhibiting the DAT led to both higher basal DA activity and a stronger phasic DA release (Zhang et al., 2009).

![Figure 4.5](image.png) The DAT1 VNTR visualized. As the name suggests a variable number tandem repeat is a polymorphism whereby not single base pairs are substituted but whereby a specific sequence is repeated a variable number of times in different individuals. Here, it is either repeated 9 or 10 times in about 99% of the population.
al., 2009). Due to its location slightly distant from the site of release, the DAT mainly controls the diffusion and duration of elevated synaptic DA levels after release, and this clearance is most needed after phasic DA burst firing when synaptic and extracellular DA levels are substantially heightened (Chergui et al., 1994; Floresco et al., 2003; Grace, 1991). Lower DAT functioning has been related to a hyperdopaminergic state and higher DAT to a lower dopaminergic activity (Laasonen-Balk et al., 1999; Van Enkhuizen et al., 2014). However, without optimal clearance due to lower DAT affinity or expression, DA release more readily diffuses into extrasynaptic space where it can also provide strong feedback inhibition and dampen DA turnover and thus the final outcome is likely dependent on modulatory variables such as D2S-receptor sensitivity (Dickinson et al., 1999; Jones et al., 1999).

Also, adequate inward transport of released DA (i.e., recycling) through the DAT, rather than the much slower refilling of DA storage pools through synthesis, facilitates a homeostatic balance in neuronal DA levels since emptied storage pools can be refilled at a faster rate and healthy levels of DA neurotransmission can be maintained over prolonged bouts of neurotransmission (Caron and Gainetdinov, 2009). Therefore, moderately higher levels of DAT expression (within optimal ranges), instead of resulting in DA hypoactivity, would rather stabilize DA neuron firing frequencies due to faster refill and more efficient sustenance of readily releasable pools (RRP) of vesicles, which can be released at low levels of stimulation and mediate ongoing basal DA activity (Denker and Rizzoli, 2010; Rizzoli and Betz, 2005). After refilling smaller pools of RRP to an adequate extent, surplus DA vesicles that are not needed for immediate release are organized into reserve pools which are engaged at higher levels of neuron stimulation, such as during phasic responses and prolonged allostatic states (Denker and Rizzoli, 2010; Rizzoli and Betz, 2005). Thus, more efficient refill may also boost phasic DA responses due to a higher intraneuronal accumulation of releasable vesicles.

The gene encoding the dopamine transporter (DAT) is located on chromosome 7 position q31.2 (SLC6A3 or DAT1) and contains a variable number tandem repeat polymorphism (VNTR; see figure 4.5) in the 3’untranslated region (3’UTR) (see figure 4.5). The 9R and 10R allele of this VNTR are by far the most prevalent, especially in Caucasian populations (prevalence≈29% and ≈70% respectively). There have been only two studies to date that have examined the association of this VNTR to psychopathy, one in a community sample (N = 2,574) and the other in alcohol-dependent inpatients (N=137), and both have
failed to find significant results (Hoenicka et al., 2007; Wu and Barnes, 2013). However, Wu and Barnes may have unintentionally included non-psychopathic antisocial individuals, as discussed above, whereas Hoenicka used alcohol-dependent patients, who are characteristically dysregulated in DA transmission (both lower and higher DAT densities have been reported in alcoholics; Tiihonen et al., 1995). To understand through which pathways DAT1 genotypes may relate to psychopathic, antisocial, and impulsive traits more specifically, the functional relevance of these alleles must first be clarified.

VNTR polymorphisms such as DAT1, which reside in the 3’UTR region, do not directly affect the protein’s amino acid sequence but have a particular influence on mRNA transcription, stability, and protein synthesis, thus mainly influencing gene expression rather than modulating the cellular functionality of the expressed enzyme (Conne et al., 2000; Nakamura et al., 1998). Some studies that examine DAT1 mRNA levels \textit{in vitro} report that the 10R-allele expresses higher levels of protein material when prompted (Fuke et al., 2001; Kanno and Ishiura, 2012; Mill et al., 2002; VanNess et al., 2005), while others report higher expression in the 9R-allele (Michelhaugh et al., 2001; Miller and Madras, 2002), and others still, find no significant differences (Greenwood and Kelsoe, 2003). However, \textit{in vivo} studies with healthy subjects consistently report higher DAT densities in 9R-carriers (Costa et al., 2011; Jacobsen et al., 2000; Shumay et al., 2011; Spencer et al., 2013; Van de Giessen et al., 2009; Van Dyck et al., 2005), whereas those in psychiatric patients with schizophrenia, ADHD, or substance dependence, report higher DAT densities in 10R-homozygotes (e.g. Cheon et al., 2005; Heinz et al., 2000; Wonodi et al., 2009).

The common denominator in subjects with schizophrenia, ADHD, and substance abuse is that these conditions are characterized by pathological dysregulations of neuronal DA levels in mesolimbic projections (Stahl, 2008). Because 10R-homozygotes likely show lower DAT expression at baseline (pre-exposure to the risk factor), as indicated in healthy samples, DA dysregulations might result in higher and more prolonged increases of extracellular DA levels, thereby potently engaging D2S-driven autoinhibition and, on a longer time-scale, also triggering heightened DAT expression in order to re-establish a homeostatic equilibrium (Best et al., 2009; Bolan et al., 2007; Dickinson et al., 1999; Lee et al., 2007). Considering the \textit{in vitro} findings, in response to such D2S-driven upregulation of DAT expression, 10R-homozygotes might display a higher gene transcription, ultimately engendering a greater risk for DA hypofunctioning and increasing the risk for low DA conditions such as ADD/ADHD, substance
Dopaminergic risks towards an antisocial lifestyle
Figure 4.6 Visualization of how different DAT1 VNTR genotype, TaqIA-ANKK1/C(957)T haplotype, and TH C(-824)T genotype profiles may interact to influence dopaminergic activity in response to short- and long-term allostatic states. The below mentioned descriptions apply most closely to individuals with normal to high population activity of VTA DA projections.

Upper row (impetuous risk-taking); Visualization of what happens when someone with a low basal DAT (as observed in 10R-homozygotes), low D2S-sensitivity (A1/C-haplotype), and higher DA synthesis (A1/C-haplotype and T-allele for TH) is confronted with stressors, exogenous substances, or life events that deregulate DA activity. Because of a lower D2S-mediated feedback regulation of DAT and TH activity, heightened neurotransmission is not sufficiently counterbalanced and may lead to a continuous overdrive of the DA system (hyperdopaminergic state). Due to this rise in tonic DA activity, postsynaptic DA receptors are further downregulated thereby preventing their dynamic activation and thus phasic DA responses as a function of the prediction error are desensitized and behavior is energized, grandiose, irritable, manic, instrumentally aggressive, selfish, and risk-taking. Note; this description applies predominantly to individuals with a strong emotional resiliency such as primary psychopathy or emotional numbing as observed in some secondary psychopathic subtypes (detached variants) (see Yildirim and Derksen, 2015).

Bottom row (delay/effort discounting); The bottom row represents the other extreme of DA adaptation to allostatic states. That is, in the context of a low basal DAT (as observed in 10R-homozygotes) but also lower DA synthesis and higher D2S-sensitivity (A2/T-homozygosity and C-allele for TH), allostatic states strongly boost extrasynaptic DA levels and sensitively activate D2S-autoreceptors. In due time, this heightened D2S stimulation profoundly increases DAT receptor expression (especially in 10R-homozygotes) and attenuates TH synthesis thereby predisposing towards an intersynaptic hypodopaminergia. However, due to a strong D2S-autoinhibition and high DAT expression, the neuron more steadily builds up intraneuronal DA levels, which are released at higher levels of excitation such as phasic burst. In conjunction with low synaptic DA levels and the accompanying upregulation of postsynaptic DA receptors, phasic burst excitation of the postsynaptic membrane is sensitized and behavior is hyperactive, reactive aggressive, anxious, impulsive, paranoid, and short-sighted (delay/effort discounting). Note; this description applies mainly to individuals with emotional dysregulation due to serotonin deficiency such as observed in some variants of secondary psychopathy (unstable variants) (see Yildirim and Derksen, 2015).

Middle row (maximizing reward focus); The middle row represents a stable dopaminergic homeostasis. Due to slightly higher basal DAT levels (as observed in 9R-allele carriers), synaptic dopamine levels are better kept in balance thus precluding a strong D2S-mediated feedback. This effect is especially pronounced in individuals with an additional downregulation of D2S-sensitivity (A1/C-homozygotes) and stable high DA turnover rate (T-allele for TH). In addition, due to a lower upregulation of the DAT in response to D2S-stimulation (especially in 9R-allele carriers) the DA system does not undergo significant changes other than a slight desensitization of postsynaptic receptor sites. These individuals show an active, persistent, and assertive coping response, are less likely to show destabilizations during prolonged stressful states, and more capable of controlling their drives and behavior.
abuse, and anxiety/depression (see figure 4.6 bottom row).

However, the adequate upregulation of DAT in response to increased extracellular DA is highly dependent on adequate D2S-autoreceptor functioning. For example, mice with a specific D2S-knockout show lower DAT functioning, and those with DAT-knockout show lower D2S functioning, evincing that the expression of both DAT and D2S is somehow linked and likely work in concert to regulate synaptic DA activity (Dickinson et al., 1999; Jones et al., 1999). Various studies have reported disturbed upregulation of DAT in subjects with reduced or blocked D2S functionality (Lee et al., 2007; Meiergerd et al., 1993). Therefore, in the context of D2S subsensitivity, heightened synaptic DA levels might not adequately provoke DAT gene expression in already low expressing 10R-homozygotes, thereby failing to counterbalance chronically increased levels of DA activity and predisposing towards high mesolimbic DA conditions such as ADHD, antisocial behavior, and substance abuse (see figure 4.6 upper row).

In other words, 10R-homozygotes may be more sensitive to DA boosting risk factors and at higher risk for both dopaminergic extremes, namely DA hypoactivity in normative to high D2S expressing subjects but hyperactivity in low D2S expressing subjects (see figure 4.6 bottom and upper row respectively). Indeed, 10R-homozygosity has been identified as the ‘plasticity’ genotype and results in more profound fluctuations of DA functioning when predisposed towards environmental risk factors, whereas the 9R-allele carriers show a more stable DA functioning (Beaver and Belsky, 2012; Watts and McNulty, 2014). Also, autistic children carrying the 10R-allele show higher levels of emotional dysregulation compared to those carrying 9R-homozygosity, suggesting a more profound dysregulation of internal physiology (Gadow et al., 2014).

Regarding phasic DA responsivity, different studies found that 9R-carriers showed a stronger striatal reactivity to reward-predictive cues or to reward-receipt, more difficulties switching response tendencies when anticipating rewards, and higher perseveration rates (reward focus) (Aarts et al., 2010; Dreher et al., 2009; Forbes et al., 2009; Paloyelis et al., 2012; Nikolova et al., 2011; den Ouden et al., 2013). In line with these findings, subjects with 9R-homozygosity showed a stronger approach/avoidance tendency towards positive and negative social stimuli respectively (Enter et al., 2012). These findings suggest higher DA activity in 9R-carriers. In contrast, other studies reported that 10R-homozygotes showed greater striatal reactivity during reward-anticipation or to reward-receipt and more difficulties stopping ongoing response tendencies (Aarts et al., 2010; Mata et al., 2012; Paloyelis et al., 2012; Wittman et al., 2013).
Nevertheless, despite that both alleles have been associated with stronger striatal responses to anticipated rewards, 10R-homozygotes showed a strong positive relationship between ventral striatal reactivity during reward-anticipation and levels of reward sensitivity and impulsivity, whereas in 9R-allele carriers this correlation was absent (Hahn et al., 2011). Therefore, the increase of phasic DA in 10R-carriers could signify a more deregulated state of DA functioning and predispose towards more dysfunctional forms of impulsivity, whether that is due to hypo- (delay or effort discounting) or hypertonic DA activity (impetuous risk-taking, impaired error-learning, perseveration). Conversely, in 9R-carriers, higher reward-related striatal activity in healthy subjects may particularly reflect higher levels of task-engagement and reward-maximizing focus which can increase propensity for risk-taking but not necessarily impetuous behavior (deliberate risk-taking, functional impulsivity) (Poythress and Hall, 2011; Smillie and Jackson, 2006). This specific dissociation regarding the endophenotypes associated with DAT1 genotypes is also reflected in tasks that assess behavioral responses toward potential gains. Specifically, the 10R-allele confers risk-taking when the safe option requires one to disengage or stop his dominant response tendency (lower behavioral flexibility), whereas 9R-allele confers risk-taking when there is a choice between different probability options that yield varying rewards (maximizing reward tendency) (Braet et al., 2011; Cornish et al., 2005; Heitland et al., 2012; Mata et al., 2012; Zhong et al., 2009, 2012).

Furthermore, 9R-carriers also present with adaptive characteristics indicative of a higher and more stable DA functioning such as lower levels of delay and uncertainty discounting and a better efficiency of executive functions such as working memory, cognitive flexibility, executive attention, response modulation, and response inhibition (Belgrove et al., 2005; Braet et al., 2011; Fagundo et al., 2014; Heitland et al., 2012; Loo et al., 2003; Paloyelis et al., 2010; Stollstorff et al., 2010). Also, in the presence of the A1-allele for the TaqIA-ANKK1 SNP, the 9R-allele has been related to a stronger error related negativity (ERN) of the mPFC in response to a NoGo signal demonstrating better error-learning and behavioral flexibility, whereas 10R-homozygotes showed the weakest ERN in the context of the A1-allele (Meyer et al., 2012). As discussed, in the context of D2S-subsensitivity, 10R-homozygosity might lead to increased levels of DA activity and, thus, have a stronger impact on error-learning and behavioral flexibility.

Interestingly, studies that examine the relation of DAT1 genotypes to externalizing and impulsive behaviors report varying findings dependent on the age of the subject population. Beginning in childhood, when mesolimbic DA
Dopaminergic risks towards an antisocial lifestyle

activity and D2-receptor expression are still in their pre-adolescent ranges, the 9R-allele is related to higher levels of externalizing behavior and hostility (Hayden et al., 2013; Young et al., 2002). However, this difference slowly disappears at 9 years old, when transitioning into puberty (Young et al., 2002). Indeed, in adolescent and young-adult males, when mesolimbic DA activity is boosted and D2-receptor expression downregulated (McCutcheon and Marinelli, 2009; Luciana et al., 2012; Rothmond et al., 2012; Steinberg, 2008), the 10R-allele is more consistently related to antisocial behavior, impetuous risk-taking behavior, and delinquency (Beaver et al. 2008a, 2008b; Burt and Mikolaiewski, 2008; Guo et al., 2007a, 2007b, 2008; 2010; O’Brien et al., 2013). Therefore, samples that include both children and adolescents, or that do not differentiate between different age groups, fail to find a significant association between DAT1 and externalizing or impulsive behavior (Schulz-Heik et al., 2008; Richards et al., 2014; Sonuga-Barke et al., 2009). When transitioning into adulthood and DA levels steadily decline again, it is the 9R-allele that is associated with angry-impulsive personality traits, more severe ADHD symptoms, and increased levels of antisocial behavior in addicts (Franke et al., 2008, 2010; Gera et al., 2005; Joyce et al., 2009; Reese et al., 2010; Yang et al., 2012). The pattern here suggests that at normative ranges of DA activity or D2S-receptor activation as found in children and adults, the 9R-allele is more strongly associated with externalizing and antisocial behavior, whereas at higher ranges of DA activity and D2-receptor subsensitivity as found in adolescents, it is the 10R-allele that is associated with antisocial and aggressive behaviors.

Taken together, although the results are somewhat inconsistent, it might be speculated that DAT expression is less stable in 10R-homozygotes, resulting in lower expression at low levels of D2S-autoreceptor activation but higher expression at normative to high D2S-autoreceptor activation. Since psychopathy is likely related to a D2-receptor subsensitivity, psychopathic 10R-homozygotes might show a more deregulated DA activity and higher levels of impetuous risk-taking, novelty-seeking, and antisocial behavior, whereas psychopathic 9R-homozygotes would show moderately increased levels of DA activity enabling a greater self-control and more deliberate forms of risk-taking. In addition, since the 10R-homozygosity has also been related to emotional dysregulation and antisocial behavior more generally, it may also be a risk marker for secondary psychopathy. Future studies may thus find interesting results if they would focus on the interaction between DAT1 and DRD2 genotype variants and expression profiles in both primary and secondary psychopathic subtypes.
Dopaminergic projections to the PFC are involved in a range of cognitive and emotional skills that together facilitate adaptive goal-directed behavior (Assadi et al., 2009; Diekhof et al., 2012; Floresco, 2013; Floresco et al., 2006; Floresco and Magyar, 2006; Kayser et al., 2012; Seamans and Yang, 2004). The different executive processes that are crucially regulated through DA functionality in the PFC rely on varying patterns of DA receptor activation in both overlapping and non-overlapping PFC networks (Floresco, 2013; Floresco and Magyar, 2006). Opposite to DA dynamics in striatal and amygdalar projections, phasic and tonic modes of DA activity have different effects on D1- and D2-type receptors in the PFC. That is, excitatory D1-receptors in the PFC are primarily located extrasynaptically and activated through volume transmission, whereas the inhibitory D2-type receptors (D2L and D4) are mainly located intrasynaptically and activated during both tonic and phasic modes of DA release (Assadi et al., 2009; Seamans and Yang, 2004).

The functions of the PFC DA system can be categorized into three interlocking phases that each play a crucial role in adaptive goal-directed behavior. Phase 1; cognitive appraisal of novel contingencies and evaluation of possible courses of action when confronted with prediction-errors or reinforcement-predictive cues (mediated by D2-type receptors, both D2L and D4), Phase 2; choosing the most relevant course of action and stabilizing attention towards executing that decision despite competing distractions (mediated by D1-receptors), and Phase 3; resetting the system and terminating goal pursuit whenever contingencies change, behavior needs to be adjusted, or when repeatedly frustrated to reach set goal, in order to begin the cycle anew (mediated by D2-type receptors, mainly D4). I will shortly clarify these phases before going into their potential relevance for psychopathy. See figure 4.7 for a step-by-step visual representation of the first
Dopaminergic risks towards an antisocial lifestyle
**Figure 4.7** A step-by-step visual representation of the first two interlocking phases of PFC DA modulation that play a crucial role in adaptive goal-directed behavior.

**Phase 1: appraisal and evaluation:** During automated modes of ongoing behavior, mesocortical DA neurons are homeostatically stabilized at a low tonic firing rate that enables alertness and working-memory. However, as discussed, whenever we encounter an unexpected event that might require a novel behavioral strategy, VTA DA projections show a phasic burst of activity which encodes a neural prediction-error (nr. 1). Phasic activation of VTA mesocortical projections immediately activates intrasynaptic inhibitory D2L-receptors on GABAergic interneurons in the PFC (nr. 2) which inhibits the GABAergic autoregulatory tone on the PFC neural membrane (nr. 3) and thus sensitizes PFC pyramidal neurons to both sensory and bottom-up limbic input (nr. 4). The PFC neural membrane is now excited (nr. 5) and intra-cortical neural communication enhanced (nr. 6). As can be seen from the slab at the bottom-left corner, during this D2-dominated state, multiple sensory and limbic inputs can enter the PFC and conjure up a variety of associational mental representations which are now compared to one-and-other by the vmPFC regarding their effort costs, payout, affective consequences, and moral considerations. If the cued or confronted reinforcement is appraised as salient, important, and needing of a response, the ensuing glutamatergic activity in the PFC crosses the threshold at which it can induce a self-sustaining DA supply to the PFC (nr. 7) and engage goal-directed executive functions situated in the more lateral parts of the PFC such as planning and organization.

**Phase 2: goal-directed focus:** Eventually, tonically released DA escapes the synaptic cleft and engages extrasynaptic D1-receptors (nr. 8). The representation that is most active at this moment will be further stabilized and enhanced by the engagement of D1-receptors on pyramidal neurons (nr. 9) while those that are less active are now actively suppressed by the activation of D1-receptors on GABAergic interneurons (nr. 10). This further reverberation of neural cell ensembles that mediate representations of the chosen course of action strongly activates a recurrent loop between the PFC and VTA (nr. 11) thereby ensuring a stable a high tonic DA operating range in the PFC and ultimately stabilizing long-term goal directed focus, planning, and effort. As can be seen in the slab on the bottom-right corner, during this D1-dominated state, only the most active representations are boosted while competing and distracting representations are actively dampened. The PFC is now in a mode of focusing all attention and energy towards completing the task at hand and peripheral or distracting input is thus attenuated. In addition, if the chosen line of action or the goal that is being pursued is stressful or otherwise contains emotional components, the PFC activates VTA mesoamygdaloid projections (nr. 12) which aid goal-directed behavior by adequately sensitizing the emotional processing of relevant stimuli. However, glutamatergic efferents from the PFC also directly innervate the amygdala where they can boost DA processing and sensitize emotional processing (nr. 13).
two phases. The numbers within parentheses throughout the following text refer to the corresponding numbers in figure 4.7.

*Mesocortical DA functioning: stability and flexibility of goal-directed behaviors; Phase 1:* The PFC DA system comes first online in response to phasic DA signals evoked by reward-predictive cues or prediction-errors (see figure 4.7, nr. 1). Such phasic burst firing of VTA DA neurons activates inhibitory D2-type receptors on GABAergic interneurons within the PFC (nr. 2), thereby reducing network inhibition (nr. 3) and labilizing neural membrane excitability to support simultaneously activated neural representations (nr. 4-6 but see bottom-left PFC slab) (Assadi et al., 2009; Durstewitz and Seamans, 2008; Seamans and Yang, 2004). During this D2-dominated 'appraisal' phase, multiple representations can gain access to the PFC, allowing parallel processing of different action-outcome contingencies and facilitating performance monitoring, decision-making, and adjustment of behavior (Assadi et al., 2009; Durstewitz and Seamans, 2008; Seamans and Yang, 2004). D2-receptor mechanisms in the PFC are thus paramount for the adequate cognitive appraisal of phasic DA evoking events, and facilitate the flexible evaluation and adaptation of behavioral strategies to such events (Floresco et al., 2006; Floresco, 2013; Seamans and Yang, 2004). Accordingly, lower D2-type receptor expression in the brain or administration of the D2-type receptor antagonist haloperidol have been consistently found to lower sensitivity to performance-feedback, impair behavioral flexibility, and engender perseveration of automated or dominant but erroneous responses (Biehl et al., 2011; De Bruijn et al., 2006; Frank et al., 2007; Kumari et al., 1997).

*Phase 2:* If these cue evoked contingencies are appraised as relevant and thus requiring of attention, the ensuing reverberation of PFC cell ensembles that mediate relevant representations activates top-down glutamatergic efferents to pools of VTA DA neurons that project back to the PFC (nr. 7 and 11), thereby inducing a self-sustaining recurrent excitation of tonic DA release rates in the PFC and slowly increasing synaptic DA concentrations (nr. 8) (Carr and Sesack, 2000). Network dynamics are now slowly changed from a phasically-induced and parallel mode of processing (D2-dominated state) to a tonically-maintained and serial mode of processing (D1-dominated state), thereby stabilizing goal-relevant representations and shielding them from distracting influences (see figure 4.7 bottom-right PFC slab) (Delgado et al., 2008; Diekhof et al., 2012; Floresco and Magyar, 2006; Kayser et al., 2012; Kober et al., 2010; Seamans and Yang, 2004; Stock et al., 2014; Tsutsui-Kimura et al., 2013; Williams and Castner,
In so doing, sustained tonic PFC DA activity serves to stabilize attention and motivation towards the chosen course of action in order to resist immediate temptations and adaptively guide behavior towards task-completion (Delgado et al., 2008; Diekhof et al., 2012; Kayser et al., 2012; Kober et al., 2010; Tsutsui-Kimura et al., 2013). For example, acutely depleting OFC DA levels in marmoset monkey’s has been found to disinhibit DA functioning in striatal structures and result in higher responsivity to immediate reward (Clarke et al., 2014), whereas stimulating the PFC at tonically relevant ranges has been found to inhibit DA release in mesolimbic projections (Jackson et al., 2001; Louilot et al., 1989). Indeed, elevating mesocortical DA activity or the administration of D2-agonists in the PFC led to a decrease of striatal DA activity (Chen and Pan, 2000; Louilot et al., 1989).

This process of switching between a labile to a stable state is crucially mediated by the overflow of DA from the synaptic cleft (nr. 8). During heightened tonic activity, DA is enabled to escape the synaptic cleft and capable of activating excitatory D1-receptors on principal pyramidal neurons through volume transmission, which sensitizes the recurrent activation of suprathreshold signals through NMDA mechanisms (enhancing the ‘signal’) (nr. 9), whereas parallel activation of D1-receptors on GABAergic interneurons inhibits subthreshold signals and increases competition between different active cell ensembles (reducing the ‘noise’) (nr. 10) (Assadi et al., 2009; Durstewitz and Seamans, 2008; Lisman et al., 2008; Seamans and Yang, 2004; Wang et al., 2013b).

Optimal stability of working memory, attention, and goal-directed behavior is dependent on median ranges D1-receptor activation as indicated by an inverted U-shaped relationship (Frank and Fossella, 2011; Grace et al., 2007; Lodge, 2011). Blockade of D1-receptors in the orbitofrontal and lateral prefrontal cortex (OFC and lPFC) reduces the signal-to-noise ratio and deteriorates performance on working memory tasks that require maintenance or retrieval of task-relevant representations, thus leading to distractibility and shortsightedness (non-optimal labilization of the neural membrane). Conversely, acute administration of D1-agonists increases this ratio and stabilizes task-relevant representations, but may also induce task-relevant perseveration and hyperfocus despite error- or punishment-feedback (non-optimal stabilization) (Dreher and Burnod, 2002; Floresco, 2013; Floresco and Magyar, 2006; Pardey et al., 2013; Sawaguchi and Goldman-Rakic, 1994; Tsutsui-Kimura et al., 2013).

The natural strength of D1-receptor stimulation depends partly on interindividual differences in synaptic DA levels. Higher catechol-O-
methyltransferase (COMT) activity increases the metabolization of synaptic DA in the PFC, attenuates synaptic overflow of DA during tonic modes, and eventually triggers a compensatory upregulation of extrasynaptic D1-receptors (Slifstein et al., 2008). Higher DA degradation in the PFC may therefore hinder appropriate stimulation of extrasynaptic D1-receptors during tonic release rates, thus decreasing cognitive stability and working memory performance towards longer-term goals (Heinz and Smolka, 2006). However, stronger DA activations to novel and salient reward-predictive cues may still be able to escape the synaptic cleft and engage the now upregulated D1-receptors, thereby provoking strong attentional hyperfocus and goal-engagement to short-term contingencies at the cost of longer-term but more profitable alternatives. For example, adolescence, which is a period associated with stronger DA-driven risk-taking, impulsivity, and novelty-seeking (Luciana et al., 2012), is marked by a transient increase of specifically the D1-receptors on PFC output neurons to the striatum, and administering D1-antagonists directly in the PFC of adolescent rats dampened their impulsivity to immediate rewards (Brenhouse et al., 2008). This also holds true for adulthood since D1 over-expression on PFC output neurons in adult rats has been found to increase effort to obtain and increase hunger to consume cocaine, bias towards a need for immediate satisfaction, and decrease anxiety (Sonntag et al., 2014). In other words, a low PFC DA activity and non-optimally high D1-to-D2-receptor ratio in the PFC boosts attention and motivation towards short-term rewards and dampens the D2-triggered anxiety since network dynamics are not labile enough to become aware about all sorts of possible outcomes, whereas a non-optimally low ratio increases D2-mediated labilization of PFC neural membranes and leads to distractibility, rumination, and impulsive responding to environmental stimuli.

Phase 3; Finally, the last phase is entered only when the temporal order of events do not work out as they were initially predicted and expectations need to be adjusted. Both D2- and D4-receptors are paramount in the neurophysiological modulation of PFC neural excitability in reaction to such prediction-errors but the difference is that D4-receptors display affinity for both DA and norepinephrine (NE), although their affinity for NE is much lower (Lanau et al., 1997). Therefore, whereas DA is likely to engage D4-receptors during both tonic and phasic modes, NE might particularly have a functional role at D4-receptors during phasic responses. As such, D4-receptors modulate PFC neural membranes in response to both positive prediction-errors encoded by phasic DA (better than expected) and negative prediction-errors encoded by phasic NE
(worse than expected) (Harley, 2004; Lauzon and Laviolette, 2010). Activation of D4-receptors has a bidirectional influence on PFC neurons, namely sensitizing those that are silent by reducing network inhibition, but inhibiting those that are active by preventing recurrent activation of dominant neural ensembles, thereby homeostatically regulating PFC arousal (Wang et al., 2003; Seamans and Yang, 2004; Yuen et al., 2010, 2013; Yuen and Yan, 2011). This is the exact opposite of D1-receptor dynamics in the PFC. It might be speculated that upon D4-activation, the PFC “resets” the neural system by destabilizing D1-mediated dominant representations, terminating goal-pursuit, and sensitizing neural receptivity to alternative possibilities. Without such adaptive modulation of the excitability of PFC membranes to subcortical signals, dominant representations mediated by D1-type receptors are insufficiently inhibited when confronted with error, risk, or punishment, thus resulting in goal-directed hyperfocus and response perseveration once a course of action is chosen (i.e., impaired response modulation).

Mesocortical DA functioning in primary psychopathy: From these basic propositions regarding the functions of DA at its various receptors in the PFC new hypotheses can be extrapolated about PFC DA functioning in disinhibited and controlled psychopaths. (1) Increasingly disinhibited psychopaths are suggested to show lower levels of synaptic PFC DA activity and higher D1-to-D2-type receptor ratios (i.e., higher D1 and lower D2L and D4). This dopaminergic profile may impair stability towards long-term goals (reduced synaptic activity), increase reward-hyperfocus and impetuous responding to short-term rewards (higher D1-type receptors), and reduce attentional sensitivity and behavioral adjustment in response to reward-, error-, or punishment-feedback (lower D2-type receptors).

Unfortunately, the empirical literature on mesocortical DA functioning in psychopathy is non-existent at the time and we have no direct means to support or refute these hypotheses. Nonetheless, although healthy PFC functioning in most executive tasks is dependent on a multitude of neurotransmitters, some PFC mediated processes depend predominantly on proper DA functioning or other specific monoamines such as norepinephrine and serotonin (Winstanley et al., 2006; Pardey et al., 2013). In line with the discussion above, I will review performance of psychopathic samples on neuropsychological tasks that depend on adequate mesocortical DA functioning, including aspects of cognitive stability and flexibility.

First, different studies in psychopathic subjects inform specifically on
PFC mediated cognitive stability, which influences the ability to successfully complete tasks that require neural information to remain active and attention to remain alert. When compared to non-psychopathic controls, disinhibited “unsuccessful” psychopaths showed reduced P300 amplitudes to target stimuli at parietal regions, whereas controlled “successful” psychopaths showed shorter frontal P300 latency and larger parietal P300 amplitude to nontarget stimuli (Gao et al., 2011). The authors argue that shorter frontal P300 latency assesses faster information processing and better information storage capability, whereas the enhanced parietal P300 amplitudes to nontarget stimuli in similar oddball tasks has been related to the capacity to inhibit inappropriate responses in lieu of ongoing goal-directed behavior (Gao et al., 2011; Polich, 2007; Polich et al., 1983). Psychopaths who are better at evading capture for their crimes could therefore benefit from an enhanced capacity for retaining information in working memory and inhibiting goal-irrelevant tendencies. In line with these electrophysiological findings, different studies report that core psychopathy features are consistently associated with normative or higher cognitive stability and control (i.e., executive attention, delayed response accuracy, verbal working memory, digit span, letter-number sequencing), whereas the antisocial lifestyle traits relate to lower scores on these executive measures in community, student, and offender samples (De Brito et al., 2013; Hansen et al., 2007; Hoppenbrouwers et al., 2013; Sadeh and Verona, 2008; Zeier et al., 2012). In addition, delay of gratification deficits in psychopathic individuals are mainly found in incarcerated but not community samples (Newman et al., 1987; Widom, 1977). However, similar findings of reduced cognitive stability have also been reported in antisocial subjects without psychopathy (De Brito et al., 2013; Dolan, 2012; Zeier et al., 2012). Therefore, lower levels of cognitive stability likely increase the risk for antisocial behavior and impulsivity (immediate response bias) more generally.

Second, an important aspect of behavioral flexibility and reinforcement-based learning that is crucially controlled by D2-type receptors, is the PFC mediated ability to evaluate one’s behavior through feedback (Gremel and Costa, 2013; Rushworth et al., 2011). Adolescents with conduct disorder or oppositional defiant disorder comorbid with a high level of core psychopathic features (callous/unemotional traits) show significantly dampened PFC reactivity to both early stimulus-reinforcement exposure and to reward-feedback (Finger et al., 2011). Indeed, perseveration in disinhibited psychopathic offenders was strongly and specifically associated with the antisocial lifestyle factor, and mediated by a lack of evaluative reflection after both punishing and rewarding outcomes (Moltó et
al., 2007). Other studies have also demonstrated that psychopathic offenders show a trend towards higher levels of preservative errors compared to non-psychopathic offenders (Lapierre et al., 1995), and more difficulties in response reversal on the intradimensional/ extradimensional shift task (Mitchell et al., 2002). Nonetheless, some studies report that regardless of psychopathy score, offenders with antisocial personality disorder show general deficits in attentional set-shifting (Dolan, 2012). Mitchell et al. (2002) also reported that offenders with or without psychopathy did not differ with regard to the attentional set-shifting task (although psychopaths showed slightly more errors). Since similar findings have been reported in antisocial subjects with and without psychopathy, lower levels of PFC mediated cognitive flexibility could confer a general risk factor for antisocial behavior more generally.

On the other hand, psychopaths from the community show similar PFC responses to reinforcement-feedback as healthy controls (Bjork et al., 2012; Buckholtz et al., 2010). After comprehensive review, Gao and Raine (2010) argue that the more controlled psychopaths show intact or even enhanced error-learning and punishment sensitivity compared to disinhibited and criminal variants. For example, Ishikawa et al. (2001) reported that while convicted psychopaths were impaired at response modulation when reinforcements changed on the Wisconsin card sorting task (WCST), non-convicted psychopaths actually showed better performance compared to controls, indicating improved error-learning and a more sensitive change of behavioral strategies in response to a change in the value of a response. Therefore, controlled psychopaths likely show a more adequate flexibility in ongoing behavior and are more sensitive to change strategies whenever confronted with erroneous feedback.

In light of the above review, it can be deduced that disinhibited psychopathy may indeed be associated with non-optimally low tonic PFC DA levels and non-optimally high ratios of D1-to-D2-type receptors in the PFC. Such a dopaminergic profile may impair both the stability and flexibility of PFC neural dynamics and impact negatively on attentional sensitivity, working-memory, and behavioral adjustment to (peripheral) feedback, ultimately contributing to impetuous risk-taking and behavioral disinhibition. Conversely, controlled psychopathic personalities show normal learning curves and shifting of attentional sets in response to feedback, evincing a more healthy PFC DA functionality in learning about reinforcement schedules, maintaining focus on long-term goals, and representing experience-dependent changes in contingencies. However, since psychopathy is likely associated with a reduction of D2-type
receptors more generally, both disinhibited and controlled psychopaths may be likely to persevere towards coveted goals and show a particular assertiveness, competitiveness, and unwillingness to back down (they ‘keep their eyes on the prize’). Nevertheless, controlled psychopaths might show more optimal levels of tonic PFC DA activity and a moderately increased D1-to-D2-type receptor ratio that is still within the confines of normal variation, enabling them to pursue their goals in a more strategic, deliberate, and calculated manner (deliberate gain-oriented risk-taking/functional impulsivity), successfully navigate society, and perpetuate criminal acts without being caught.

Fronto-amygdalar dopamine in primary psychopathy; attentional sensitivity as an important source of heterogeneity

Dynamic fluctuations of DA output in fronto-amygdalar circuitry may be more closely involved in the attentional sensitivity, nervousness, and evaluative rumination when anticipating or preparing for stressful events (i.e., anxiety, paranoia), rather than the intuitive fear-sensation and impromptu fight-or-flight response when acutely confronted with stressors or threat (i.e., fear), which has been more strongly related to phasic NE and serotonin reactivity (Boureau and Dayan, 2011; Grossmann et al., 2011; Harley, 2004; Hurlemann et al., 2010; Park et al., 2015; Schultz, 1998, 2002, 2007). In fact, unexpected threats, errors, and punishments that drive negative prediction-errors are strong phasic inhibitors of tonic DA activity and serve to stop ongoing behavior in order to react appropriately to such salient events (Boureau and Dayan, 2011; Park et al., 2015; Schultz, 1998, 2002, 2007). In other words, the role of DA in emotion is likely evaluative, attention-mediated, and anticipatory (stronger role towards conditioned stimuli), rather than acute, intuitive, and automated (both conditioned and unconditioned stimuli), which corresponds to the distinction between, respectively, anxiety and fear (Grillon, 2008). Nonetheless, to nuance this statement, basal DA activity does seem to have a passive role in the gating of unconditioned aversive material (Brandão et al., 2015). For example, antagonism of D2-receptors in the midbrain (VTA and NS), which increases fronto-amygdalar DA output may lower the sensori-motor gating of incoming environmental stimuli thus heightening their salience (Brandão et al., 2015).
Fronto-amygdalar dopamine and predictive allostasis in psychopathy

**Fronto-amygdalar DA functioning; attentional sensitivity and anticipatory arousal;** Dynamic fluctuations in the rate of tonic DA release in the fronto-amygdalar complex, and the corresponding stimulation of in particular D2-receptors, mediate to what degree future contingencies and task-relevant stimuli are anticipated, processed, and incorporated in mental models and ongoing behavior (Nagano-Saito et al., 2013; Pezze and Feldon, 2004). For example, it has been reported in rodents that amygdalar DA levels rise substantially in response to fear-conditioned stimuli and dynamically activate postsynaptic D2-receptors to boost anxiety (de Oliveira et al., 2013; de Souza Caetano et al., 2013; Yokoyama et al., 2005). Since higher basal DA levels naturally desensitize high-affinity D2-receptors and allow for less fluctuations (ceiling effect), this dynamic increase and accompanying D2-activation is stronger in rats with lower basal DA activity (Oshibuchi et al., 2009). In fact, low anxiety rats have higher basal amygdalar DA activity, and antipsychotics, such as Haloperidol partly work to decrease paranoia, anxiety, and restlessness by dampening the amygdalar rise of DA and increasing basal DA levels in the amygdala, whereas estradiol treatment increases anxiety and depression-like behavior likely through a decrease of basal amygdalar DA levels (Balasubramanian et al., 2014; Lehner et al., 2014; Oshibuchi et al., 2009; Scholl et al., 2010).

When released in the amygdala, DA dampens the GABAergic autoinhibition of amygdalar processing and induces long-term potentiation of its neural membrane while simultaneously suppressing task-irrelevant inputs, thereby specifically sensitizing amygdalar excitability to relevant or salient sensory stimuli (Bissiere et al., 2003; Chu et al., 2012; de Oliveira et al., 2011; Grace and Rosenkranz, 2002; Kröner et al., 2005; Rosenkranz and Grace, 1999, 2001, 2002a, 2002b). Amygdalar excitability is increased by the D1-agonist but not the D2-agonist yet pre-application of either a D1- or a D2-antagonist blocked the effects of DA on excitability (Kröner et al., 2005). Therefore, it has been argued that “D1-mediated effects of DA depend on, or are enhanced by, a tonic D2-receptor activation” (pp. 1607, Kröner et al., 2005). Dynamic activation of amygdalar D2-receptors likely suppresses task-irrelevant behavior and prepares attention, emotion, and coping responses to deal effectively with the task or goal at hand, especially when there is an affective or stressful component, whereas D1-receptors participate in danger recognition, instrumental learning, and facilitate the retrieval of the affective properties of conditioned and unconditioned stimuli (Pérez de la Mora et al., 2010; Tye et al., 2010).

In sum, increasingly anxious, paranoid, and psychotic individuals are
likely characterized by a more sensitive increase of amygdalar DA and a stronger D2-receptor activation during potentially salient events, resulting in hyper-anticipaton and sensitized processing of sensory stimuli (fear-potentiated startle, increased salience attribution, and rumination) (Greba et al., 2001; Kienast et al., 2008; Kim et al., 2014; Reynolds, 1983). These anxious subjects would likely present with lower levels of basal DA activity in the amygdala, which then leads to an upregulation of D2-receptors in this structure and results in a more dynamic and stronger activation of these receptors in response DA boosting events, such as when anticipating future reinforcements or in response to prediction-errors. Conversely, higher basal DA levels and reduced D2-receptor sensitivity in the amygdala may impair dynamic stimulation of amygdalar DA receptors in response to aversive future contingencies and thus decrease attentional sensitivity towards punishment and risk, ultimately resulting a certain cognitive detachment and hyposensitivity for aversive contingencies.

Remarkably, there is scant information on which neurophysiological cascades and which afferent inputs, other than direct VTA-projections, can modulate tonic DA release rates in the amygdala. However, empirical evidence demonstrates a dissociation of bottom-up and top-control controls of emotional processes arising from limbic and PFC regions respectively (McRae et al., 2012; Ochsner et al., 2009). That is, when cognitively processed cues, instructions, and computations about upcoming events trigger emotionally relevant or stressful representations, top-down modulation of amygdalar responsivity could prime the attentional/emotional processing of relevant sensory stimuli (McRae et al., 2012; Ochsner et al., 2009; Onoda et al., 2008). Since this sensitization of amygdalar function is crucially mediated by DA release (Pérez de la Mora et al., 2010), the PFC may dynamically regulate amygdalar DA output in response to aversive or stressful cognitive representations, thereby serving a complementary role to adaptive goal-directed behavior by readying/priming the attentional and emotional processing of salient and relevant stimuli (i.e., anxiety and apprehension) (e.g., Pérez de la Mora et al., 2010; Pezze and Feldon, 2004; Schaefer and Gray, 2007; Tye et al., 2010). In so doing, the mesoamygdaloid DA circuitry may complement mesocortical DA in adaptive goal-directed behavior.

In support of this hypothesis, different tasks and stimuli that activate PFC neural networks and increase mesocortical DA release, such as stressful and novel cognitive tasks, aversively conditioned stimuli, psychosocial stressors, and novel contexts, also increase DA release in the amygdala (Fadok et al., 2010; Fried et al., 2001; Inglis and Moghaddam 1999; Lataster et al., 2011;
Nader and LeDoux, 1999; Nagano-Saito et al., 2013; Schaefer and Gray, 2007). Furthermore, empirical research has demonstrated that the PFC sends projections to VTA DA cell bodies which project back to the PFC, but also sends glutamatergic projections that synapse onto VTA DA neurons that project to sites other than the striatum or PFC (see figure 4.7, nr. 12) (Carr and Sesack, 2000). Selective pools of VTA DA neurons have indeed been found to project to both the PFC and the amygdala (Lammel et al., 2008), indicating that there is some degree of overlap between the mesocortical and mesoamygdaloid DA circuitry. Recurrent activation of PFC-VTA DA loops during the maintenance of stressful or emotional representations could therefore increase tonic DA release in both the amygdala and PFC which may then in turn decrease DA output in the striatum (stopping behavior to evaluate new contingencies) (Jackson et al., 2001; Louilot et al., 1985, 1989). In addition, PFC glutamatergic projections also heavily innervate the basolateral amygdala directly (nr. 13) (Cassell and Wright, 1986; Leichnetz et al., 1976), where, comparable to findings in the striatum (Grace, 1991), they might modulate tonic DA release rates through volumetransmission activation of glutamatergic receptors on presynaptic DA terminals (Likhtik et al., 2005; Ohmori et al., 1992; Sesack et al., 2003; Stalnaker and Berridge, 2003; Walker and Davis, 2002).

Franto-amygdalar dopamine and predictive allostasis in psychopathy; In response to these propositions it can be hypothesized that controlled and disinhibited psychopaths show differential fronto-amygdalar DA functioning. (1) Controlled psychopaths may be characterized by a more moderated increase of basal amygdalar DA level, a more sensitized tonic mesocortical DA activity, and a more dynamic activation of D2-receptors in amygdalar circuitry, thereby enabling them to anticipate the possible outcomes of their actions and sensitize their attentional/emotional system to notice peripheral warning cues when they occur, partly counterbalancing the deficit of intuitive emotional activations. In contrast, disinhibited psychopaths, due to their chronically increased tonic DA levels in mesolimbic projections and lower tonic mesocortical DA activity, may be characterized by a downregulated D2-receptor state in the amygdala and an impaired PFC-mediated dynamic activation of these receptors, which reduces attentional sensitivity for future contingencies and engenders a reckless pursuit of reward regardless of potential failure, risk, threat, or punishment.

Unfortunately, there is only one study that examined anticipatory stress reactions in controlled and disinhibited psychopaths. Ishikawa et al. (2001)
found that although both controlled and disinhibited psychopaths (termed successful and unsuccessful psychopathy by the authors) differed in mean skin conductance responses in the expected direction during anticipatory stress moments (i.e., 90-120sec preparation period for upcoming social speech), these differences did not reach significance (disinhibited: 4.86±2.74μs, controlled: 5.96±1.83μs, healthy controls: 6.52±3.48μs). However, both healthy subjects and controlled psychopaths showed a significant increase of heart rate during anticipatory stress moments such as preparing or giving a speech while the disinhibited psychopaths did not. Although more research is needed to make valid claims, these preliminary findings illustrate that disinhibited psychopaths might display greater deficits in the sensitization of attention and emotion when anticipating potentially salient events.

Nonetheless, when disinhibited psychopathic subjects are verbally instructed to direct their attention to socio-emotional stimuli, their initial hyporesponsivity and insensitivity is no longer observed (Meffert et al., 2013; Newman et al., 2010). Thus a more nuanced hypothesis would be that although controlled psychopaths show a more automatic sensitization of attentional processes when presented with novel, aversively conditioned, or stressful contingencies, disinhibited psychopaths could be able to achieve similar states of anticipation and sensitivity but may need more cognitive resources, more concrete cues (verbal instruction), and/or higher levels of salience.

Finally, since disinhibited psychopaths are the only group that consistently shows morphological alterations of the PFC, amygdala, and hippocampus, Gao and Raine (2010) argue that “given that autonomic fear conditioning deficits have been consistently found among incarcerated psychopaths…and that the amygdala and hippocampus are critically involved in fear-conditioning…it is hypothesized that fear-conditioning deficits characterize unsuccessful psychopaths in particular” (pp. 203). Despite that fear is generally reduced in psychopathic individuals alike, specific aspects of fear-conditioning might still be intact in controlled psychopathy such as a normative attentional sensitivity towards conditioned, potentially salient, or novel stimuli, which then sensitizes cognitive appraisal and may partly counterbalance the lack of intuitive emotional input.
Mesocortical dopamine genetics in primary psychopathy

**DA metabolization (Catechol-O-methyltransferase):** DAT activity is highest in subcortical structures and parts of the mPFC but nearly absent in higher order PFC structures, such as the OFC and lPFC, where clearance of synaptic DA is largely dependent on Catechol-O-methyltransferase (COMT) (Chen et al., 2004; Ciliax et al., 1995; Garris et al., 1993; Gogos et al., 1998; Hoffman et al., 1998; Hong et al., 1998; Huotari et al., 2002; Matsumoto et al., 2003; Tunbridge et al., 2004). Lower rates of PFC DA catabolism following neurotransmitter release, due to a lower COMT activity, increases the overflow of synaptic DA into the extrasynaptic space where it can stimulate extrasynaptic D1-receptors, thereby stabilizing cognitive performance (Garris et al., 1993; Lapish et al., 2009; Tunbridge et al., 2004; Winterer and Weinberger, 2004). In addition, as discussed, this increase in tonic PFC activity may also dynamically increase tonic DA output in the amygdala, which in turn sensitizes emotional processing (Drabant et al., 2006; Hashimoto et al., 2007; Heinz and Smolka, 2006; Smolka et al., 2005, 2007; Williams et al., 2010).

The COMT gene is located on chromosome 22 section q11.2, with a common functional polymorphism at codon 158 (rs4680) whereby valine (Val) and methionine (Met) are inter-exchangeable. Met-allele carriers show a three- to four-fold decrease of COMT expression compared to Val-homozygotes. Keep in mind, however, that there are multiple sites within the COMT gene that contains potential for SNP’s, and the specific allelic configurations at these different sites are in a transmission disequilibrium with each other (i.e., haplotypes) (e.g., Belfer et al., 2013; Pap et al., 2012; Jugurnauth et al., 2011; Nackley et al., 2006; Tunbridge, 2010; Xu et al., 2011). Some studies even report a 18 to 25 fold variation in COMT activity when considering haplotypes rather than low and high expressing alleles (Jugurnauth et al., 2011; Nackley et al., 2006; Xu et al., 2011). Nonetheless, I will use Met- and Val-homozygosity as a model for understanding through which endophenotypic pathways high and low catecholaminergic activity in the PFC, respectively, may predispose towards dysregulatory pathology in primary psychopathy.

It has been asserted that the Met-allele results in higher stability of goal-directed behaviors and better executive functionality but at the cost of cognitive flexibility and emotional regulation, whereas the Val-allele is associated with lower emotionality and higher stress resilience but at the cost of executive functionality (Bilder et al., 2004; Heinz and Smolka, 2006; Mier et al., 2010). However,
although the findings of heightened cognitive stability and lower emotional regulation in Met-carriers are consistent, its supposedly negative effects on cognitive flexibility are less robust in both healthy and patient samples (Heinz and Smolka, 2006; Mier et al., 2010; Rosa et al., 2010), and are instead more dependent on D2-receptor mechanisms (Garcia-Garcia et al., 2011; Mueller et al., 2011, 2014; Stelzel et al., 2010). In accordance, while the stability enhancing D1-receptors in cortical structures vary as a function of COMT genotype, with Val-homozygotes showing higher binding values (presumably reflecting receptor upregulation in response to lower extrasynaptic DA levels), the flexibility mediating D2-receptors in both striatal as well as cortical regions does not differ as a function of COMT genotype in healthy subjects (Hirvonen et al., 2010; Slifstein et al., 2008). In other words, while COMT influences the activation of extrasynaptic D1-receptors by regulating the synaptic accumulation and overflow of DA, it has less effect on processes that rely on more acute synaptic dynamics, such as sudden phasic DA bursts. The effect of these phasic DA activations in the PFC on physiology and behavior is more strongly mediated by corresponding DA receptors, such as the D2-type receptors.

Therefore, I will start off by a thorough examination on how gene-gene interactions between the COMT Val158Met and TaqIA-ANKK1 polymorphisms may affect cognitive stability, cognitive flexibility, and behavioral activation/impulsivity. Since the A1-allele of the TaqIA-ANKK1 polymorphism has been consistently associated with lower D2-densities, higher striatal DA activity, and core psychopathic features in imprisoned, forensic, and community subjects (Hoenicka et al., 2007; Ponce et al., 2008; Wu and Barnes, 2013), we will specifically examine interactive effects between this allele and COMT genotypes to deduce which genetic profiles might serve as risk or protective factors in psychopathic individuals.

First, regarding fronto-striatal genetics, gene-gene interactive effects between the COMT polymorphism and the TaqIA-ANKK1 polymorphism are consistently reported in working memory tasks (Berryhill et al., 2013; Garcia-Garcia et al., 2011; Gosso et al., 2008; Reuter et al., 2005; Stelzel et al., 2009, 2010; Wishart et al., 2011). Two studies reported higher stability and accuracy of task-relevant representations during delays and lower interference in Met/A1 carriers compared to Val/A1 carriers. That is, when the A1-allele was present, Met-homozygotes showed better Stroop and more accurate delayed response performance (Berryhill et al., 2013; Reuter et al., 2005). These data complement the findings on PFC DA dynamics and demonstrate that in the presence of
the A1-allele, lower COMT activity increases stability of attention and working memory. Furthermore, Met/A1 status was associated with superior cognitive performance on two trail making tests of which one required stability of task-relevant representations (which trail to follow in Trail A task), and the other also depended on cognitive flexibility (alternating between following numbers and letters in Trail B task), while Val/A1 carriers showed the worst performance (Wishart et al., 2011).

Others reported that the COMT x TaqIA-ANKK1 interaction is not significant for tasks that assess working memory maintenance during delays (stability) but found significant effects regarding the adequate arrangements of working memory contents according certain rules (working memory manipulation) such as during letter-number sequencing task or digit span backwards (Stelzel et al., 2009). In these tasks, results are more varied. For example, Val/A1 carriers showed a better working memory manipulation compared to Met/A1 carriers (Stelzel et al., 2009). Furthermore, Garcia-Garcia et al. (2011) reported that Val/A1 carriers showed updating of task-set representations and novelty-P300 amplitude enhancements only to task-relevant rule-shifts, but not to task-irrelevant cue-switches, thus showing strong focus and sensitivity to stimuli that are central to task-performance and lower sensitivity to peripheral distractors. In contrast, Met/A1 subjects showed updating of task-set representations to novel cues that was independent of their actual relevance for the task, thus evincing higher attentional sensitivity and breadth but lower differentiation between task-relevant and task-irrelevant shifts. However, although the Val/A1 group showed more selective shifts of task-set representations to relevant cues only, the actual accuracy of switching when task-rules shifted did not differ between various genotypes and Met/A1 carriers actually showed the fastest response times, whereas Val/A1 carriers showed the longest response times—a significant finding that was not adequately addressed by the authors. In fact, during task switch trials, Met/A1 individuals showed the highest accuracy scores compared to all other groups, but these values did not reach statistical significance. Therefore, compared to Val/A1, the strategy of the Met/A1 carriers resembling a sort of “it’s better to be safe than sorry” approach, may have increased sensitivity to novel, peripheral, and unexpected cues, boosted reaction speed, and possibly even improved accuracy. Finally, Gosso et al. (2008) found that the Val/A1 group showed the most deteriorated performance on a letter-number sequencing task whereas heterozygous subjects showed the best performance when the A1-allele was present.
These studies into the effect of COMT on executive functioning suggest that when D2-receptor sensitivity is downregulated and tonic striatal DA activity increased (e.g., A1-allele), lower COMT activity (e.g., Met-homozygosity) may improve both cognitive stability and flexibility, and thus serve as an important protective factor against impetuous and shortsighted behavior, whereas higher COMT activity (e.g., Val-homozygosity) may have a more negative effect on these cognitive skills and increase the risk for disinhibitory psychopathology.

In accordance, COMT genotypes have been found to interact with the TaqIA-ANKK1 polymorphism in reward processing and behavioral disinhibition. Since both Met- and Val-homozygosity have been related to increased striatal DA activations to reward-feedback or reward-predictive cues (Camara et al., 2010; Dreher et al., 2009; Lancaster et al., 2012; Katz et al., 2014; Yacubian et al., 2007), immediate response bias/delay discounting (Boettiger et al., 2007; Gianotti et al., 2012; Paloyelis et al., 2010; Smith and Boettiger, 2012), impulsivity (Groleau et al., 2012; Guillot et al., 2014; Malloy-Diniz et al., 2013; Salo et al., 2010; Soeiro-De-Souza et al., 2013; Varga et al., 2012), and aggression (Albaugh et al., 2010; Brennan et al., 2011; Caspi et al., 2008; Rujescu et al., 2003; Wagner et al., 2010), the effect of COMT genotypes on disinhibitory traits is likely modulated by other factors such as tonic striatal DA activity and D2-receptor densities. For example, Reuter et al. (2006) demonstrated that BAS scores correlate with the relative ratio between PFC DA activity as mediated by COMT, and striatal DA activity/D2-receptor functioning as mediated by the TaqIA-ANKK1 SNP. Behavioral activation was increased in males with either the Val/A1 or Met/A2 genotype, whereas Met/A1 and Val/A2 carriers showed normal BAS scores (Reuter et al., 2006). Val/A1 carriers also showed higher levels of BAS fun seeking, stimulus seeking (i.e., novelty seeking or quest for excitement), and behavioral impulsivity compared to Met/A1 carriers but these differences did not reach significance (Reuter et al., 2006; Thaler et al., 2012). In fact, the Met/A1 carriers showed the lowest scores on all measures of BAS and impulsivity compared to the other genotype groups (Met/A2, Val/A1, Val/A2) (Reuter et al., 2006). In line with these findings, Mueller et al. (2011, 2014) reported that although the error-related negativity (ERN) and feedback-related negativity (FRN) (which are inversely related to measures of impulsivity; Onoda et al., 2010; Pailing et al., 2002) was initially stronger in Val-allele carriers compared to Met-homozygotes, thus indicating higher flexibility, this effect was completely reversed after administration of the D2-receptor antagonist sulpiride. In other words, during normal D2-receptor functioning, Val-allele carriers may be more
sensitive to error feedback, whereas at lower levels of D2-receptor activation, Met-homozygotes may be more sensitive and thus more likely to adjust ongoing behavior in response to error or punishment.

Taken together, these findings indicate that when tonic striatal DA activity is normal or decreased and D2-receptor density normal or increased, disinhibitory psychopathology may be higher in lower COMT activity individuals (e.g., Met-homozygotes), whereas in the context of high tonic striatal DA activity and low D2-receptor activation, disinhibitory psychopathology might be higher in higher COMT expressing subjects (e.g., Val-homozygotes).

Second, COMT has also been found to interact with other DA components, such as the DAT, in modulating cognitive stability/flexibility and reward processing. However, interactions between COMT and DAT1 in working memory performance have been non-significant in preliminary studies (Blanchard et al., 2011). Nevertheless, other studies that indirectly assessed cognitive processes did find significant results. Met-homozygosity was associated with a stronger prefrontal P300a, whereas both 9R-allele and Met-homozygosity were related to a higher target related P300b at midfrontal electrodes (Heitland et al., 2013). These results evince that both Met- and 9R-allele carriers show heightened attentional sensitivity to salient events. More specifically, Met-homozygotes show a particular attentional sensitivity to novel cues, whereas both 9R- and Met-carriers display increased sensitivity to primed task-relevant stimuli (Heitland et al., 2013). Therefore, although both 9R- and Met-alleles are related to cognitive stability in task-performance, only COMT genotypes modulate the level of involuntary orienting to novel or peripheral stimuli, with Met-homozygotes showing higher levels of this form of cognitive/attentional flexibility.

In addition, COMT has also been found to interact with DAT1 in the prediction of reward related striatal reactivity. Subjects with Val-homozygosity coupled with the 10R-allele of DAT1 or the opposite profile (Met-homozygosity coupled with the 9R-allele) showed normal to high increases in ventral striatal activation during the anticipation of increasingly higher rewards, indicative of normal to higher behavioral activation, whereas genotype groups in which mesolimbic DA was not in balance with PFC DA (Met-/10R-allele and Val-/9R-allele) showed blunted striatal activity to increasingly higher rewards (Yacubian et al., 2007). With respect to previous findings, heightened BAS and reward-cue reactivity in Val/10R genotypes may reflect a particular hyperfocus to immediate rewards, and thus increase the risk for impulsivity and externalizing disorders.
when effortful self-control is lacking (dysfunctional impulsivity) (Claes et al., 2009; Congdon et al., 2009; Hundt et al., 2008; Kimbrel et al., 2012), whereas in Met/9R-carriers, heightened BAS and reward reactivity may represent a general drive to strategically maximize rewards (functional impulsivity) (Lancaster et al., 2012; Smillie and Jackson, 2006).

Third, COMT genotypes also impact on attentional processes during emotional events. For example, Met-homozygosity has been associated with an increased distractibility and reduced efficiency of task performance when a peripheral aversive stimulus is presented, demonstrating a greater attentional breadth and sensitivity to peripheral and/or subthreshold stimuli (Bishop et al., 2006). Met-homozygosity was also related to increased PFC-to-amygdalar coupling, increased activation in the amygdala towards consciously processed conditioned (i.e., unmasked unpleasant pictures) and unconditioned threatening stimuli (i.e., unmasked facial expression of fear), tendency to focus on aversive stimuli (i.e., negativity bias), heightened harm avoidance, and lower novelty seeking (Drabant et al., 2006; Hashimoto et al., 2007; Heinz and Smolka, 2006; Smolka et al., 2005, 2007; Williams et al., 2010). This COMT-mediated sensitization of the mPFC-amygdala circuitry in response to reinforcing cues and events is also apparent in psychophysiological findings. Contrasting COMT allele groups, individuals with Met-homozygosity show significantly augmented startle responses during unpleasant but also during neutral pictures, and a trend towards increased behavioral inhibition towards novelty, threat, and punishment (higher BIS-score) (Montag et al., 2008). The associated increase in startle potentiation during neutral pictures in Met-homozygotes demonstrates that this group displays a sensitized emotional response to novel stimuli in general and a potentiated response to stimuli that are associated with unpleasant or aversive emotions.

Finally, Val-homozygotes display a heightened mu-opioid response to a pain stressor compared with heterozygotes or Met-homozygotes, indicating a stronger endogenous opioid regulation of pain signals (Zubieta et al., 2003). Enhanced mu-opioid functionality, which significantly dampens physical pain sensitivity, is also closely linked to the regulation of psychological pain in response to social rejection (Eisenberger, 2012). Increased mu-opioid functioning signals a social reward state and reduces the drive to seek out these rewards externally, whereas low activity produces greater feelings of pain and isolation (loneliness) and thus increases the drive to seek out social rewards (Burkett and Young, 2012). Thus, functionality of the mu-opioid system has been theoretically and
empirically associated with the strength with which both primate and human infants attach to their parents and adults attach to their romantic partners on the basis of rewarding interactions (Barr et al., 2008; Burkett and Young, 2012; Copeland et al., 2011; Curley, 2011). These findings demonstrate that COMT polymorphisms can also influence the subjective pain of social rejection/isolation and underlie differences in social sensitivity or reward dependence.

In accordance, Val-homozygosity strongly modulated the pathway from ADHD to extreme antisocial behavior through the endophenotype of impaired social cognition in a large group of children aged around 7 years, and was associated with worse performance on social WM tasks compared to Met-homozygotes (Dumontheil et al., 2014; Langley et al., 2010). Furthermore, Val-homozygotes performed worse on different aspects of social cognition such as openness to feelings and the ability to modulate feelings in oneself and others so as to promote personal understanding and growth (Lin et al., 2013). Also, since DA activity in the mPFC crucially contributes to self-awareness and metacognition (Joensson et al., 2015), Met-carriers might show higher levels of self-consciousness in social situations.

Interestingly, Val-homozygosity has been related to callous-unemotional traits in male adolescents with ADHD (Fowler et al., 2009) and lower mPFC activation in response to empathy-eliciting stimuli in schizophrenics (Poletti et al., 2013), indicative of attentional hyposensitivity and low physiological sensitization in response to socio-emotional stimuli. Val-homozygotes are thus likely to have a lower social sensitivity and cognition and to display a lower motivation to change their behavior in response to social punishment (e.g. by parents or teachers) or social rejection (e.g. by peers) which can negatively affect the “social malleability” of behavior (Deuker et al., 2013). Therefore, Val-homozygotes may have a higher propensity towards social detachment. Met-homozygotes, on the other hand, could be more susceptible to socializing influences because of a higher dependency on social reward to regulate negative feelings (Deuker et al., 2013; Kok et al., 2013). Moreover, because Met-homozygotes are more susceptible to “painful” social experiences such as abandonment, rejection, and criticism they might be more likely to react fiercely and aggressively to these events. Aggression may thus be especially increased in Met-homozygotes in the context of a reduced emotional regulation, as found in secondary psychopathy, whereas it may be increased in Val-homozygotes in the context of emotional deficiency as found in primary psychopathy.

Concluding, higher levels of PFC DA functionality as associated with
lower COMT activity (e.g., Met-homozygosity) may serve as an important protective factor against the development of disinhibition, aggression, and shortsightedness in psychopathic individuals by improving cognitive stability and flexibility, boosting attentional sensitivity to peripheral cues, enhancing fear-conditioning, and improving both social sensitivity and cognition, especially in the context of reduced D2-receptor densities (A1-allele of the TaqIA-ANKK1) and more stable expression of the DAT in limbic regions (9R-allele for DAT1). Therefore, in conditions marked by lower D2-receptors and higher striatal DA activity such as primary psychopathy, lower COMT activity as associated with Met-homozygosity may steer development towards a more controlled variant of the disorder whereas Val-homozygosity may be more closely related to disinhibited psychopathy. However, because the Met-allele may also significantly increase aggression and disinhibition, especially in subjects with impaired self-regulation, it is crucial to differentiate primary from secondary psychopathy before examining these associations.

**DA receptor configuration (D4-receptors);** The gene for the D4-receptor (DRD4) contains a 48-base pair tandem repeat (VNTR) polymorphism in exon III of chromosome 11 with variable lengths from 2 to 11 repeats. Around 60% of the population carry only short variants and roughly 35% carry at least one 7-repeat allele (7R-allele) (Beaver et al., 2007; Garpenstrand et al., 2001). The 7R-allele has been associated with lower D4 mRNA expression (Simpson et al., 2010), lower D4 densities in neocortex (Schoots and Van Tol, 2003; Van Tol et al., 1992), and decreased ligand binding (Asghari et al., 1994, 1995).

As discussed, lower D4-receptor functioning can attenuate attentional sensitivity for alternative response possibilities once a dominant response tendency has been set, whereas non-optimally strong D4-receptor functioning can lead to distractibility and increased flexibility of conditioned material. Roussos et al. (2009, 2010) demonstrated in two independent studies that 7R-carriers showed significantly more risky decisions in the IOWA gambling tasks and less capacity to learn from repeated mistakes. In accord, 7R-allele subjects slow down their dominant responses to a lesser degree when confronted with errors (Fossella et al., 2002). Furthermore, Krämer et al. (2007) showed that DRD4 genotypes are predictive of error-related prefrontal activity and the behavioral adjustments following these errors. In addition to impaired flexibility to a worse-than-expected change in contingencies, the opposite, namely impaired flexibility to a better-than-expected change, also holds true in 7R carriers. That is, Garpenstrand et al.
(2001) reported that 7R and non-7R carriers did not differ in skin conductance responses during the acquisition phase of aversive conditioning but individuals with at least one 7R-allele showed significantly delayed extinction of learned aversive associations with a large effect size.

Second, dopaminergic functioning interacts with social experiences in shaping personality, and beginning in early childhood, could have a profound impact on attachment formation. Infants carrying 7R-alleles might have more difficulty in adapting flexibly to irregular, abusive, or erratic parenting, which can result in confusion and disorganization of attachment schemas. Indeed, prevalence of disorganized attachment is more than fourfold increased in children carrying the 7R-allele (Bakermans-Kranenburg et al., 2011; Gervai et al., 2005, 2007; Van IJzendoorn and Bakermans-Kranenburg, 2006; Lakatos et al., 2000, 2002). These findings are not consistent, however, and some studies report no associations between DRD4 genotypes and attachment (Luijk et al., 2011), while other demonstrate a positive association between the 7R-allele and secure attachment (Das et al., 2011; Reiner and Spangler, 2010). The presence of 7R-alleles may therefore promote secure attachment in favorable and sensitive environments, but also increase the risk for psychopathology in the case of insensitive treatment.

Third, the 7R-allele has been related to various antisocial personality traits and behaviors, such as substance abuse, novelty seeking, increased risk for anger related affect, aggression, impulsivity, and behavioral disorders (Congdon et al., 2008; Dmitrieva et al., 2011; Kang et al., 2008; Kirley et al., 2004; Laucht et al., 2007; Schmidt et al., 2002). A recent study in a large community sample reported a strong association between the 7R-allele and psychopathic personality characteristics (d = 1.00) (Wu and Barnes, 2013). Furthermore, 7R-carriers showed lower anxiety to novel events as infants, and higher levels of behavioral activation (BAS) and sensation-/novelty-seeking throughout life (Campbell et al., 2010; Congdon et al., 2008; Das et al., 2011; Dmitrieva et al., 2011; Lakatos et al., 2003; Munafò et al., 2008; Roussos et al., 2009; Schinka et al., 2002). However, meta-analyses reported an absence or very weak association between the 7R-allele and novelty seeking, and other factors, such as environment and socialization, may strongly modulate the final phenotypical expression in 7R-carriers (Schinka et al., 2002; Munafò et al., 2008). In support of this environment-contingent adaptation, the relationship between the 7R-allele and externalizing behavior in childhood is exclusively found in children who have experienced insensitive parenting, and not in carriers who
Dopaminergic risks towards an antisocial lifestyle

have experienced rewarding and sensitive attachment relationships with their caregivers (Bakermans-Kranenburg and Van Ijzendoorn, 2006; Propper et al., 2007; Sheese et al., 2007). Moreover, although the 7R-allele increases the risk for externalizing behaviors, if intervened early enough when dominant patterns have not yet been crystallized, such as during toddlerhood and early childhood, 7R-carriers are actually more responsive to positive and sensitive discipline techniques in decreasing these behaviors (Bakermans-Kranenburg et al., 2008; Propper et al., 2007). These results suggest that lower D4-receptor functioning increases the social malleability of emotional development during the first decade of life, resonating with both negative as well as positive experiences. In studies with adults, the 7R-allele has been found to increase emotional resiliency regardless of childhood adversities, but this result was largely explained by the interactional effect of DRD4 genotypes and childhood adversity on BIS/BAS scores (Das et al., 2011). Individuals carrying the 7R-allele were more likely to report and display high levels of BAS in addition to high levels of BIS, especially under the condition of childhood adversities, thus balancing the strengthening effect of childhood adversity on BIS scores (Das et al., 2011).

Fourth, the findings on risk-taking in 7R-carriers are also modulated by different psychological and biological variables. For example, 7R carriers take more risks and invest more money but only when they focus on potential reward and expect a positive return, suggesting that individuals who have higher levels of reward-expectancy or reward-focus may take more risks when carrying the 7R-allele (Dreber et al., 2009; Kuhnen and Chiao, 2009). Interestingly, Eisenegger et al. (2010) reported that risk-taking as a function of the 7R-allele increased as baseline DA activity increased through the administration of L-DOPA. As discussed, lower levels of D4-mediated response modulation may lead to reduced PFC-driven adjustments to reward-expectancies thereby increasing risk-taking, which is likely more pronounced in individuals with a higher DA driven reward-hyperfocus and optimism-bias. Also, Dreber et al. (2011) found that male 7R-carriers with more bridge skill take more good risks and fewer bad risks during a bridge game, while the opposite is found for less-expert 7R men, suggesting that whether functional or dysfunctional forms of impulsivity arise in 7R-carriers is also dependent on adequate foresight regarding the possible consequences. In short, whether the 7R-allele leads to functional or dysfunctional impulsivity is dependent on a host of modulatory variables such as adequate insight, foresight, and the level of reward-focus/reward-expectancy.

Fifth, the DRD4 has been reported to interact with polymorphisms at
other DA genes such as COMT, DAT, and TaqIA-ANKK1 SNP. Interactions between COMT and DRD4 have been reported for response inhibition and associated neural correlates in controls and adult ADHD subjects (Heinzel et al., 2013). When the 7R-allele was present in ADHD subjects, the NoGo anteriorization was stronger (which reflects the “NoGo” activation of the mPFC) and Go-reaction times were less variable (which reflects less lapses in sustained attention) in both Met- and Val-homozygotes compared to heterozygotes (Heinzel et al., 2013). When the 7R-allele was present in healthy controls, however, no significant differences were noted, although the Met-homozygotes consistently showed better performance (lower errors, faster reaction time) (Heinzel et al., 2013). These results also attest for a plasticity role of the 7R-allele with stronger effects on goal-directed behavior in the context of dysregulatory pathology (ADHD) but little effect in healthy controls. Also, when interactions with DAT genotypes are examined in young adults it is found that 7R-allele carriers show the highest stop-signal response times (SSRT) in a response inhibition task but only in the context of 10R-homozygosity, demonstrating a lower ability to stop ongoing behavior or dominant response tendencies and an increased risk for dysfunctional impulsivity (Congdon et al., 2008). In agreement, only children carrying both the 10R/7R risk genotype showed strong negative relationships between intelligence and externalizing behavior (Kebir et al., 2009). Furthermore, logistic regression analysis showed that the simultaneous absence of the 10R-homozygosity and 7R-allele predicts membership to the group of ADHD patients with increased levels of internalized comorbidities (e.g. anxiety, depression) (Gabriela et al., 2009). Regarding interactions with D2-receptors, it was reported in a large study of adolescent males that carriers of the A1-allele of the TaqIA-ANKK1 and the 7R-allele showed synergistically increased risk of lifetime conduct problems and composite index of antisocial behaviors, whereas adolescents carrying only one of these two alleles showed no significantly increased levels of antisocial behavior, indicating a synergistic epistatic effect of both alleles on antisocial behaviors in adolescents (Beaver et al., 2007).

Finally, two studies have examined the interactional effects of COMT and DRD4 with the serotonin polymorphism 5HTTLPR on novelty-seeking in adults (Benjamin et al., 2000; Strobel et al., 2003). The main finding of both studies was that in the presence of l-homozygosity for 5HTTLPR and Val-homozygosity for COMT, 7R-allele carriers show substantially higher novelty-seeking scores than other non-7R-allele carriers and these scores together with those of the
l-homozy./Met-homozy./7R-allele group were the highest of all genotype groups (Benjamin et al., 2000; Strobel et al., 2003). Indeed, psychopathy has been closely related to l-homozygosity for 5HTTLPR (Glenn, 2011; Yildirim and Derksen, 2013), indicating that individuals with this genotype and an additional 7R-allele are most likely to develop novelty-seeking, independent of COMT genotype.

Taken together, the 7R-allele might be considered a “plasticity” gene and its influence on both externalizing and internalizing psychopathology is strongly dependent on other biological and social variables. That is, lower density and functionality of the D4-receptor as associated with the 7R-allele, especially when homozygous, may increase the risk for reward/sensation-driven risk-taking, novelty-seeking, dysfunctional impulsivity, and antisocial behaviors, but primarily when baseline DA activity is high, when maltreated, or when additionally carrying l-homozygosity for 5HTTLPR, A1-allele for the TaqIa-ANKK1, and/or 10R-homozygosity for the DAT VNTR. The 7R-allele may also decrease the risk for these behaviors in the context of sensitive and responsive parenting, more moderate levels of baseline DA activity, and less dopaminergic risk-alleles. Therefore, the 7R-allele might bias psychopathic development towards controlled variants with functional impulsivity in the context of a positive environment, moderate levels of DA activity, and other protective genotypes (e.g., 9R-allele for DAT1) but also increase the risk for disinhibited variants and dysfunctional impulsivity in the context a negative environment, higher levels of baseline DA activity, and/or other risk genotypes (e.g., 10R-allele for DAT1).

One overarching hypothesis is that PFC DA influences the specific manner with which an individual adapts to its (social)environment. It is asserted that differences in adaptive strategies between low and high PFC DA individuals reflect differences in evolutionary strategies both having advantages and disadvantages. Individuals with higher levels of synaptic DA in PFC circuits, as associated with the Met-allele and no-7R-alleles, are designated as being “worriers” (i.e. increased sensitivity to pain and social rejection, higher social cognition, higher altruism, stronger anticipatory stress and anxiety, and sensitized threat processing), whereas individuals with lower levels of synaptic DA modulation in these structures, such as in Val-homozygotes and 7R-allele carriers, are termed “warriors” (i.e. decreased sensitivity to pain and social rejection, lower social sensitivity, higher egotism, weaker anticipatory stress and anxiety, and desensitized threat processing) (e.g., Jiang et al., 2013; Lackner et al., 2012; Langley et al., 2010; Mier et al., 2010; Stein et al., 2006; Zubieta et
When extrapolating to psychopathic subtypes, it can be deduced that controlled psychopathy is likely related to a more optimal DA functioning in the PFC, partly offsetting the deficient emotional control over behavior by increasing attentional awareness of potential errors and punishments and sensitizing the processing of socio-emotional stimuli. Therefore, although psychopathic individuals alike might rigidly pursue money and power as the primary gateways to the fulfillment of these needs (inflexibility in goal-selection), the controlled subtype is potentially more apt in choosing appropriate courses of action, persist long-term endeavors despite distracting influences, and more skilled in adapting long-term strategies according feedback (flexibility in strategies), whereas the disinhibited psychopath may impulsively persevere inappropriate, repeatedly punished, and maladaptive strategies to achieve those ends (inflexibility in strategies).

4.3 Serotonin x Dopamine Interactions: Explaining Interhemispheric Imbalances in Primary Psychopathy

Serotonin has potent modulatory influences over fronto-striatal DA neurotransmission via direct projections from raphe nuclei to the VTA (Adell et al., 2010; Higgins and Fletcher, 2003). Serotonergic activity at 5HT2C receptors on GABAergic interneurons in the VTA exerts a tonically mediated autoregulation of mesolimbic DA output, and counterbalances dynamic increases of striatal DA activity (Adell et al., 2010; Bubar and Cunningham, 2007; Di Giovanni et al., 2000, 2001; Di Matteo et al., 1999, 2000; Dremencov et al., 2005, 2006; Eberle-Wang et al., 1997; Higgins and Fletcher, 2003; Millan et al., 1998; Pompeiano et al., 1994; Pozzi et al., 2002; Prisco et al., 1994; Visser et al., 2014). In accordance, higher 5HT2C activation is related to decreased reward-seeking behaviors and a depressive/anxious phenotype (Dremencov et al., 2005, 2006; Grottick et al., 2000; Higgins and Fletcher, 2003). Furthermore, 5HT2C receptors mediate the excitatory effects of serotonin on amygdalar and HPA-axis responsivity, indicating that heightened expression of this receptor subtype can increase the risk for stress-related disorders (Christianson et al., 2010; Holmes, 2008; Li et al., 2012). Since psychopathic individuals demonstrate a higher stress resilience but also increased reward sensitivity, they might be characterized by
Dopaminergic risks towards an antisocial lifestyle

Figure 4.8 Serotonin x dopamine interactions in the fronto-amygdalar circuitry of emotionally resilient individuals (higher ratio of regulatory [5HT1A + 5HT2A] to excitatory [5HT2C + 5HT3] serotonin receptor balance). First, serotonin has direct inhibitory effects on mesoamygdaloid DA activity through 5HT2C receptors on GABAergic interneurons within the VTA (1). Second, serotonin has an indirect autoregulatory effect on amygdalar reactivity via tonic activation of its excitatory 5HT2A receptors located on mPFC output neurons (2) that synapse onto GABAergic interneurons in the lateral intercalated paracapsular islands (LIp) (3), which, in turn provide a continuous inhibitory influence over basolateral amygdala (BLA) excitability (4). Serotonin also has tonic inhibitory effects on intra-amygdalar information flow and central amygdalar (CeA) output via 5HT2A receptors that are located on GABAergic interneurons in the medial intercalated paracapsular islands (MIp) (5), the main intercalated island (Im) (6), and those located directly on GABAergic interneurons
within the CeA (7) and BLA (8). Finally, serotonin provides a strong counter balancing mechanism to allostatic regulations during acute threat and stressful states through high-affinity inhibitory 5HT1A receptors that are located on CeA output neurons (9). All these serotonin mediated neural processes ensure a stable physiological balance in fronto-amygdalar reactivity to salient events.

As can be seen, DA needs to override serotonin mediated autoinhibitory effects to sensitize amygdalar processing. DA D1-receptors that are located on GABAergic neurons in the MIp (10) and the Im (11) which dampen GABAergic neurons to the CeA (12) and thereby sensitize its neural membrane (13), have the capacity to sensitize emotional processing but need to override the serotonin 5HT2A mediated excitatory effects on the same or surrounding GABAergic interneurons (5 and 6). Similarly, DA D2L-receptors located directly on GABAergic neurons within the CeA (14) and LIp (15) also need to override serotonin mediated excitatory effects (7 and 2 respectively) in order to sensitize amygdalar output. Finally, DA also has the capacity to labilize the mPFC neural membrane through activation of D2L receptors on GABAergic interneurons (16) but this modulation may only increase anxiety and attentional sensitivity in the context of a sensitized BLA output (17). In sum, in the context of a strong serotonergic regulation of the amygdalar neural membrane, DA may not be able to sufficiently sensitize the amygdalar membrane in response to predicted or immediately salient events. It may be speculated that the inability of DA to properly sensitize emotional processing is related to lower levels of anxiety and nervousness but also a lower emotional response to unexpected reward-feedback (which is also driven by the phasic DA activation of the fronto-amygdalar complex), which are both directly associated with psychopathy.

a specific reduction of 5HT2C receptors on GABAergic neurons in the VTA (see Yildirim and Derksen, 2013 for discussion). However, in addition to direct effects on VTA DA neuron firing via 5HT2C receptors, serotonin can also modulate the functional effects of DA in overlapping brain structures. In fact, some ‘paradoxical’ effects of DA on measures of fear and anxiety might be reconciled when considering its modulation by serotonin.

That is, although DA serves to sensitize amygdalar processing to salient predictions, enhancing DA neurotransmission through pharmacological manipulations shows widely varying, even opposite effects on amygdalar reactivity and other measures of fear, sometimes leading to an increase in such measures and other times a decrease. For example, administration of D-amphetamine boosts amygdalar reactivity to fearful and angry facial expressions, which fits nicely with the finding that dampened amygdalar reactivity in hypodopaminergic Parkinson patients can be restored back to normal levels by administering L-DOPA (Hariri et al., 2002; Kawamura and Kowayakaba, 2009; Tessitore et al., 2002). In sharp contrast, however, administration of L-DOPA or D-amphetamine have also been
found to dampen aversive emotional reactions such as amygdalar reactivity to fearful faces and fear-potentiated startle to unpleasant stimuli (Corr and Kumari, 2013; Delaveau et al., 2005, 2007, 2009). This apparent inconsistency may be clarified when considering that increasing DA activity through pharmacological

*Also see Jill Bolte Taylor’s TED talk “a stroke of insight” for a wonderful and moving explanation on the right versus the left brain.*
interventions only has anxiogenic effects in high-anxiety individuals, whereas in low-anxiety subjects, the same DA increase has an anxiolytic effect (Mizuki et al., 1997). Similarly, high-anxiety rats are less sensitive to the rewarding effects of amphetamine compared to low-anxiety rats, indicating that levels of trait-anxiety may also modulate the actual reward-enhancing effects of DA (Lehner et al., 2014).

Therefore, the level of trait anxiety, mediated crucially through serotonergic pathways (e.g., Balestri et al., 2014; Caio, 2012; Hariri et al., 2006; Hariri and Holmes, 2006; Hariri and Weinberger, 2003; Yildirim and Derksen, 2013), might modulate the relationship between DA release and anxiety or reward-seeking (e.g., Deakin, 2003; Nikolaus et al., 2010; Seo and Patrick, 2008). In accordance, excitation of amygdala-driven emotional processes is strongly counterbalanced through pacemaker-like excitation of high affinity 5HT2A receptors on mPFC glutamatergic efferents to GABAergic interneurons in the amygdala (see figure 4.8) (Amargós-Bosch et al., 2004; Fisher et al., 2009, 2011; Holmes, 2008; Marek, 2010; Quirk et al., 2003). Furthermore, high densities of serotonergic neurons have also been found to directly innervate the intercalated islands of the amygdala, where serotonin can regulate the flow of information within the amygdala, likely via GABAergic mechanisms (Caio, 2012; O’Rourke and Fudge, 2006; Pérez de la Mora et al., 2010). Finally, serotonin also directly regulates amygdalar output neurons through inhibitory 5HT1A receptors (Caio, 2012; Yildirim and Derksen, 2013). Therefore, when potentially threatening, stressful, and salient events are cued or anticipated, the ensuing increase of DA and/or NE activity needs to override these serotonin/GABA-driven brakes on amygdalar processing in order to sensitize the fronto-amygdalar complex towards salient cues and stimuli (see figure 4.8) (Bryden et al., 2011; Grace and Rosenkranz, 2002; Marowsky et al., 2005; Pérez de la Mora et al., 2010). In other words, a higher baseline stability of tonic serotonergic activity at 5HT2A and 5HT1A receptors in the amygdala may render catecholamines such as DA and NE less effective in this fronto-amygdalar sensitization and thereby counterbalance their anxiety-boosting effects (see Yildirim and Derksen, 2013).

In line with these expectations, Lonsdorf et al. (2009) found an interactional effect of COMT and 5HTTLPR on startle potentiation during aversive conditioning, but only s-allele carriers (who consistently evince lower serotonergic activity and impaired self-regulation; Yildirim and Derksen, 2013) were selected for an exploratory within-subjects analysis because l-homozygotes did not show reliable startle potentiation during conditioning, regardless of
COMT genotype. When interactional effects were considered, those individuals with s-alleles and Met-homozygosity showed the greatest potentiation of startle responses during conditioning and the slowest rates in extinction. Furthermore, Met-allele carriers showed lowest fronto-limbic functional connectivity during emotional reactions reflecting less efficient emotional regulation strategies but only in the presence of the s-allele (Surguladse et al., 2012). The fact that in the presence of l-homozygosity, fear potentiated startle was dampened in both Val- and Met-allele carriers further demonstrates the primacy of the serotonin system in trait-anxiety (see also Balestri et al., 2014). Indeed, findings of higher emotional resiliency in Val-homozygotes may also be explained when considering that Val-homozygosity is directly associated with higher 5HT1A receptor densities in fronto-limbic structures (Baldinger et al., 2014; Yildirim and Derksen, 2013).

In sum, although higher PFC DA functioning may increase attention-driven vigilance and orienting to aversive stimuli, this may not necessarily translate into anxiety when serotonergic regulation of emotional processes is strong and stable. However, the presence of both l- and Val-homozygosity in the same individual does have a more detrimental effect on emotional processing than either risk factors apart (Radua et al., 2014; Smolka et al., 2007), which supports the findings of a more serious deficiency of emotion in disinhibited compared to controlled psychopaths (Gao and Raine, 2010; Yildirim and Derksen, 2015).

Nonetheless, this serotonin x DA interaction still does not explain why increasing DA in low anxious subjects should lead to lower anxiety and higher novelty-seeking since it mainly predicts that higher serotonergic regulation of limbic processes would dampen DA-driven emotional processing. In this context, it is important to consider that serotonergic and GABAergic processes show a right-ward lateralization bias (Fitzgerald, 2012; Glick et al., 1982) and thus especially influence right-lateralized emotional processes driven by DA. That is, right fronto-limbic structures show higher levels of serotonin 5HT1A receptors, serotonin metabolite 5HIAA, and serotonin transporter binding sites (Arató et al., 1991; Fink et al., 2009; Kranz et al., 2014), and serotonergic effects on mPFC-amygdalar processes are stronger and most consistently reported in the right hemisphere (e.g., Fisher et al., 2009, 2011; Hariri and Holmes, 2006; Hariri and Weinberger, 2003; Hariri et al., 2006; Lonsdorf et al., 2011; Previc, 2009). For example, Lonsdorf et al. (2011) failed to find additive effects between 5HTTLPR and COMT polymorphisms but did report lateralized effects of both genotypes, with effects of 5HTTLPR genotypes on right amygdalar reactivity and COMT genotypes on left amygdalar reactivity. Higher serotonergic
regulation of right sided emotional processes may impair appropriate emotional modulation of left-hemisphere activity during goal-directed behavior, which may dampen anxiety and possibly increase DA-driven novelty-seeking and behavioral activation (Hecht, 2011; McGilchrist, 2010; Previc, 2009; Tomer et al., 2014).

In line with this interhemispheric lateralization of the functional effects of DA, male rodents show a stronger right-lateralized amygdala and mPFC DA reactivity to stressors, stronger dysregulation of right hemisphere DA in response to perinatal stress, and depletion of right amygdala DA produces an anxiolytic effect (Brake et al., 2000; Carlson et al., 1993; Stevenson et al., 2003; Sullivan et al., 2009a, 2009b; Sullivan and Gratton, 1998). Interindividual variation in the dominant hemisphere where DA is lateralized has also been reported in humans (Martin-Soelch et al., 2011; Simonyan et al., 2013). Some have argued that DA-related reward processing is more pronounced in the left-hemisphere (Previc, 2009; Tomer et al., 2014). In support of this hypothesis, reward related fronto-striatal activations have been found to be stronger in the left-hemisphere (Hamann and Mao, 2002; Schott et al., 2008; Weiland et al., 2014) and Parkinson patients with relatively greater DA loss in the left hemisphere display in particular incentive-approach deficits (less effort to increase gain than to avoid loss) (Porat et al., 2014). Also in Parkinson patients, the increased effort to maximize gain after L-DOPA administration was associated with improved DA function in the left hemisphere, while increased effort to avoid loss was related to right hemisphere DA improvement (Porat et al., 2014). Furthermore, higher levels of novelty-seeking and incentive motivation are related with a greater left-ward bias of DA activity in the brain (Tomer, 2008; Tomer et al., 2008), and patients with Parkinson’s disease show reduced novelty-seeking and higher levels of anxiety and depression when DA functioning is specifically degraded in the left hemisphere (Menza et al., 1995; Tomer and Aharon-Peretz, 2004; Weintraub et al., 2005). Finally, Parkinson patients with greater DA loss in the right-hemisphere display increased levels of novelty-seeking and impulsivity when taking L-DOPA likely because of a non-optimal increase of DA signaling in an otherwise healthy left-hemisphere (Harris et al., 2015).

Synthesizing these foregoing findings, we suggest that serotonin deficiency biases DA-mediated excitation of fronto-amygdalar pathways to the right side and increases anxiety, whereas a hyperstable serotonergic regulation of emotional fluctuations decreases anxiety and biases DA driven fronto-limbic...
activity to the left-side, thereby promoting reward- and novelty-seeking. This can be nicely reconciled with the consistent finding that a left-ward bias in resting brain activity is associated with behavioral approach and reduced anxiety, and a right-ward bias with behavioral inhibition and increased anxiety (Balconi and Mazza, 2009, 2010; Coan and Allen, 2003; Fox et al., 1995; Harmon-Jones and Allen, 1997; Kagan and Snidman, 2004). Also, the left mPFC-amygdala complex is predominantly reactive to positive stimuli in subjects that focused on obtaining goals (promotional context), whereas higher bilateral mPFC-amygdala reactivity to negative stimuli was found in subjects that focused on avoiding failure (prevention context) (Cunningham et al., 2005). Moreover, kindling the left amygdala in rats decreased anxiety up to a week after, whereas kindling the right amygdala increased anxiety (Adamec and Morgan, 1994).

It might thus be speculated that administration of dopaminergic agents in low-anxiety subjects predominantly causes a left-hemispheric fronto-amygdalar activation, which results in increased behavioral activation towards reward and reduced sensitivity towards risk (novelty-seeking), whereas in high-anxiety subjects, the same agents may boost both left- and right-hemispheric fronto-amygdalar processes and sensitize reinforcement-processing as well as emotional functioning thereby also increasing the motivation to avoid aversive states (harm avoidance). Serotonin functioning could thus partly modulate whether DA-driven coping behaviors serve to decrease uncertainty, apprehension, and anxiety (serotonin deficiency; higher right- and left-sided DA-driven neural fluctuations; harm avoidance, risk-averseness), or to increase reward and pleasure (serotonin stability; higher left-sided, lower right-sided DA-driven neural fluctuations; novelty-seeking, incentive motivation) (Aznar and Klein, 2013).

When applied to psychopathic individuals, these foregoing interpretations also make sense. That is, callous-unemotional traits and core psychopathic traits are mainly associated with right amygdalar abnormalities and hyporeactivity to aversive stimuli or when processing moral emotions (Carré et al., 2013; Fairchild et al., 2013; Glenn et al., 2009; Gordon et al., 2004; Harenski et al., 2009, 2010; Jones et al., 2009; Kiehl et al., 2001; Kosson et al., 2002; Marsh et al., 2011; Marsh and Cardinale, 2012; Viding et al., 2012), whereas the antisocial traits of psychopathy have been mainly related to left hemisphere hyperactivity to rewards (see Buckholtz et al., 2010; Carré et al., 2013; Hecht, 2012). Hoppenbrouwers et al. (2014) reported that right to left connectivity is affected in psychopathic offenders, whereas left to right connectivity is intact. In other words, the left hemisphere does not adequately process input from the right
hemisphere in psychopathic offenders. Stronger left-lateralized attentional focus on primary task-demands and relevant sub-goals, accompanied by a lower input of right-lateralized emotional processes, can contribute to reward hyperfocus while concomitantly dampening the impact of socio-emotional signals and consequences that are not directly within the primary field of focus, such as peripheral warning cues that signal potential punishment, failure, or risk (Baskin-Sommers et al., 2010; Hoppenbrouwers et al., 2014; Kruschwitz et al., 2012; McGilchrist, 2010; Newman and Lorenz, 2003). Intriguingly, when participants are not afraid of being punished (which is inherent to psychopathy and related to a more stable serotonin functioning; Yildirim and Derksen, 2013, 2015), increasing DA activity through L-DOPA administration led to more selfish behavior, whereas L-DOPA administration had no significant effect on behavior when participants were threatened with punishment for selfishness (Pedroni et al., 2014).

In light of these findings the following hypotheses may be constructed which can be tested in future empirical research; (1) Without the parallel fluctuations of the right fronto-limbic circuitry due to a stronger serotonergic autoregulation amygdalar excitations in this hemisphere, reward pursuit, as driven by DA activity in the left hemisphere, may be devoid of socio-emotional input and depend solely on calculated instrumental outcomes, thereby resulting in selfishness, moral utilitarianism, callous insouciance, heightened risk-taking, and goal-directed forms of antisocial behavior (primary psychopathy). (2) Whether these traits are being expressed in an aggressive, impetuous, and overt manner (disinhibited subtype) or whether they are shrewdly concealed and deployed in a calculated manner (controlled subtype) is partly determined by the level of mesolimbic DA dysregulation and mesocortical DA functionality in the left-hemisphere.

4.4 Therapeutic Implications

The hypotheses brought forward indicate that pharmacological interventions can be designed to specifically reduce the risk of impulsivity, risk-taking, aggression, and persistent criminality in disinhibited primary psychopaths by (1) reducing striatal DA hyperactivity, (2) improving DA functionality in PFC circuits, and (3) normalizing D1-to-D2-type receptor activation patterns in fronto-striatal
pathways.

Intriguingly, recent findings have indicated that the DA regulating antipsychotic Clozapine, which shows among the highest D1-to-D2 receptor occupancy ratio compared to other antipsychotics (see Tauscher et al., 2004), substantially reduced impulsive violence, aggression, and anger in forensic psychiatric inpatients with high levels of psychopathy (Brown et al., 2014). In fact, Clozapine mainly works by improving the tonic stimulation of D1-receptors in the PFC (Ahlenius, 1999), which may normalize D1-to-D2 receptor activation and thereby improve cognitive stability and control of immediate tendencies in primary psychopathy. Similarly, preliminary results in rats showed that high levels of impulsive aggressiveness is associated with lower PFC DA levels (Patki et al., 2015), suggesting that increasing PFC DA levels may improve control of aggressive tendencies. In other words, when given to severely disinhibited psychopaths, Clozapine may bias their mesocortical DA profile towards a more controlled psychopathic profile. In another attempt to regulate fronto-limbic activity in severely disinhibited psychopaths, Konicar et al. (2015) applied neurofeedback mediated learning of brain arousal regulation and reported a significant reduction in aggression, impulsivity and behavioral approach tendencies as well as improvements in behavioral inhibition and increased cortical sensitivity for error-processing, possibly indicating higher PFC DA functionality and strengthened regulation of mesolimbic DA processes. Pharmacological or neurofeedback interventions which help regulate DA activity in fronto-limbic regions may thus be an interesting venue for further research.
Hendrick Goltzius
“Hercules and Cacus”
CHAPTER 5
THE ROLE OF TESTOSTERONE
A Real Man is Shaped by his Environment
ABSTRACT

Psychopathic traits are more prevalent in males and it has been suggested that testosterone levels could account for this gender bias. Preliminary reports of fetal testosterone assessed through 2D:4D ratios find inconsistent associations with psychopathic traits. However, circulating testosterone consistently shows positive associations with antisocial behaviors throughout childhood, adolescence, and adulthood, especially in males. It is suggested that high fetal/circulating testosterone interactively influence the maturation and functionality of mesolimbic dopaminergic circuitry, vasopressinergic/oxytocinergic circuitry, right orbitofrontal cortex, amygdalar reactivity, and fronto-limbic connectivity, resulting in a strong reward motivation, low social sensitivity, dominant interpersonal style, and dampened regulation of strong motivational/emotional processes. The link between these testosterone induced endophenotypes and actual display of antisocial behavior is strongly modulated by different social (e.g. social rejection, low SES) and genetic (e.g. MAOA, 5HTT) risk factors which can disturb socio-, psycho-, and biological development and interact with testosterone in shaping behavior. When these additional risk factors are present, the testosterone induced endophenotypes may increase the risk for a chronic antisocial lifestyle. However, behavioral endophenotypes induced by testosterone can also predispose towards socially adaptive traits such as a strong achievement motivation, leadership, fair bargaining behaviors, and social assertiveness. These adaptive traits are more likely to emerge when the high testosterone individual has positive social experiences that promote prosocial behaviors such as strong and secure attachments with his caregivers, affiliation with prosocial peers, and sufficient socioeconomic resources. A theoretical model is presented, various hypotheses are examined, and future venues for research are discussed.

Chapter 5
The Role of Testosterone
A Real Man is Shaped by his Environment

“Testosterone may not be just a ‘sexual hormone’; it has a lot to do with the way men interact socially. It is indeed sad that testosterone – especially when used as a steroidal supplement – has been maligned beyond belief. So much so, that we tend to associate testosterone supplementation with ‘aggression’ and ‘doping’ or ‘cheating’ more readily than ‘truthfulness’ or ‘prosocial’ behaviour. In fact, a very small number of people have ever known (or would ever know) about the positive social influences of testosterone” (Deepak Hiwale).

There are few topics in the behavioral sciences which incite as much heated debate as the issue of gender-differences. Despite much disagreement, one thing that can be reliably established as scientific fact is that across nearly all cultures and ethnicities, males are much more likely to commit violent and criminal acts (Steffensmeier and Allan, 1996). In fact, men are responsible for 76% of all criminal arrests in the United States and commit 89% of all homicides, 88% of all robberies, 78% of all aggravated assaults, and 82% of all violent crimes in general (U.S. Department of Crime, 2009). Similarly, the prevalence of persistent antisociality, physical/overt aggressive behavior (violence), and severe forms of psychopathy is disproportionately higher in adult men compared to women (Archer, 2004; Blair, 2006a; Eme, 2009; Hare, 1993; Moffit, 2003, 2006; Moffit et al., 2001; Verona and Vitale, 2006).

The temperamental and personality precursors to antisocial and aggressive behaviors are more evident in boys compared to girls, even at an early age. For example, beginning at the age of 2 to 3, and continuing throughout their childhood, boys are quicker to show physical aggression, uncooperativeness, and non-compliance, while also exhibiting lower empathy, prosociality, social skills, remorse, and understanding of others’ intentions and feelings (Sanson et al., 1993; Zahn-Waxler et al., 2008).
In light of these robust gender differences in antisociality and socio-emotional functioning, scholars now show increasing interest in masculine gonadal hormones such as testosterone (abbreviated as T) (Eme, 2009; Martel, 2013; Stålenheim et al., 1998; Terburg et al., 2009; Van Honk and Schutter, 2006; Van Wingen et al., 2011; Yildirim and Derksen, 2012a, 2012b). The idea that gonadal hormones play an important role in antisocial behavior is not new and was first detailed during the 1940’s by the American microbiologist Paul Henry de Kruif. In his book *The Male Hormone*, de Kruif described the curious case of a 3-year-old boy who was given T treatment in a mistaken attempt to treat tumors on his larynx (De Kruif, 1945). After treatment, although the tumor did not shrink, the personality of the boy changed dramatically. He became hyper-sexualized and started to aggressively dominate other children on his ward. He was extraordinarily violent and oppositional and quickly became notorious for his actions. Remarkably, after stopping the T treatment the boy slowly returned to his former self, becoming gentle, thoughtful of others, and his hyper-sexuality waned (De Kruif, 1945).

Despite these early discoveries, thorough empirical research on the role of T in behavior has only been conducted in the last two decades. In this chapter I want to discuss the potential role of T in the etiology of antisocial behavior more generally, but also how it may act as a modulatory factor, which, when present, leads to a more severe expression of primary or secondary psychopathy (i.e., more severe violence, impulsivity, sexual deviancy, and criminality). However, before going into this comprehensive discussion, it may be refreshing to start off with a short introduction on T and introduce the organizational-activational hypothesis of gonadal hormones and discuss the validity of various methods of measuring T exposure.

### 5.1 Organizational-Activational Hypothesis of Testosterone

Levels of circulating T rise prominently during short-lived situational events, especially during competitive, socially stressful, or sexually arousing situations, and serve to modulate the behavioral response to these events, but T also rises more chronically during adolescence when it facilitates the development of adult masculine features (Archer, 2006; Buchanan et al., 1992; Geniole et al., 2013;
Roelofs et al., 2010; Sayegh et al., 1990). However, there is a high inter-individual heterogeneity in the typical behavioral response to a surge of T, which is most evident in the difference with which males or females react to T administration (e.g., compare results of: Zak et al., 2009; Zak, 2011, with the findings of: Eisenegger et al., 2010; Zethraeus et al., 2009). This heterogeneity may be partly explained when considering that the behavioral response to T is dependent on the specific ways that fetal T exposure has influenced the maturation of underlying neural circuitry (e.g., Arnold and Breedlove, 1985; Phoenix et al., 1959; Van Honk et al., 2011a). This phenomenon is called the organizational–activational hypothesis of gonadal hormones and states that gender- and individual-specific responses to a surge of circulating T throughout the lifespan are initially programmed during prenatal development and depend on the strength of fetal T induced maturation of underlying neural circuitry (organization of the specific T-behavior response). Higher levels of fetal T exposure lead to a sensitized and more “masculinized” behavioral responses to a surge of T throughout life (Arnold and Breedlove, 1985; Phoenix et al., 1959).

For example, in the aforementioned case example of the 3-year-old boy who was given T, the doctors may have unintentionally activated the dormant and prenatally organized masculinity, which is usually naturally activated by the surge of T that comes with puberty. In other words, the little boy may have experienced a chemically induced but profound bout of acute puberty complete with the hyper-sexualization and oppositionality that characterizes adolescent boys, but without the much more evolved cognitive skills of a normal adolescent; a dangerous combination for such a little child and a testament to the power that hormones can exert on behavior.

Furthermore, some researchers have questioned whether permanent influences occur only prenatally, arguing that there appear to be several sensitive periods throughout life when T might have permanent effects on neurobiology (Arnold and Breedlove, 1985; Lürzel et al., 2010; Schulz et al., 2009). Nonetheless, maturation of most brain structures is predominantly prenatal (Stahl, 2008). Therefore, the strongest and most permanent effects of gonadal hormones on neurodevelopment and neurobiological (dys)functioning are likely to be seen prenatally. In addition, male-biased disorders such as autism and life-course persistent antisocial behavior characteristically arise early in childhood, whereas female-biased conditions such as depression mainly show an adolescent onset, indicating that males may be especially vulnerable to prenatal and early childhood risk factors (Martel, 2013; Martel and Roberts, 2014).
Consequently, organizing effects of fetal T might set up the neurobiological wiring which may later play an important role in shaping antisocial behavior in response to a strong and persistent rise of T levels during adolescence and young-adulthood. Thus, in discussing the role of T in antisocial pathology, I will focus on how fetal and circulating T may interactively contribute to socio-emotional development and motivational responding.

5.2 Measurement of Fetal and Circulating Testosterone Exposure

Fetal T can be indexed through a variety of different measures. Amniotic fluid assessment, which is a direct and valid measure of fetal T (Van de Beek et al., 2004), is mainly examined in the context of more broad personality measures (e.g., empathy, cognitive abilities) but has not been conducted with regard to antisocial behaviors or psychopathic traits. The dominant measure as a proxy for fetal T that has been related to antisocial behavior and psychopathy is the second-to-fourth digit ratio (2D:4D), or, in other words, the length of the index finger divided by the length of the ring finger. Lower values represent higher levels of masculinization. The validity of the 2D:4D measure as a proxy for fetal T has been confirmed in both rodents (Zheng and Cohn, 2011) as well as humans (Brown et al., 2002; Lutchmaya et al., 2004; McIntyre, 2006; Ökten et al., 2002), indicating that lower ratios are associated with higher levels of fetal T exposure. Furthermore, as is hypothesized by the organizational–activational theory of T, it has been demonstrated that the 2D:4D ratio modulates the effect of circulating T on behavioral measures such as cognitive empathy (Van Honk et al., 2011a). Nonetheless, further research is still needed to replicate and validate these preliminary findings since gender-differences in 2D:4D ratios in newborns are smaller than in adults, become more pronounced during the first years of life, and show significant associations with postnatal levels of T (Knickmeyer et al., 2011; but see McIntyre, 2006 for a critical discussion).

Other insights on the effects of fetal T can be obtained by examining the behavior of individuals who are naturally exposed to higher levels of fetal T. First, women with the genetic disorder Congenital Adrenal Hyperplasia (CAH) are exposed to abnormally high levels of fetal androgens because of an enzyme defect. In males, CAH is less valid as an indicator of heightened fetal T exposure
since uncontrolled adrenal androgen secretion can result in increased neural feedback and inhibition of testicular T production (via the aromatization of T into estrogens) which may lead to secondary hypogonadotrophic hypogonadism (Brown-Grant et al., 1975; Mathews et al., 2009). Since females do not produce testicular T, the high levels of fetal androgen exposure cannot be counterbalanced and thus result in masculinization of brain and behavior (Brown-Grant et al., 1975; Mathews et al., 2009). Other psychological effects of the disorder that are more pronounced in males can also strongly modulate the T-behavior relationship. That is, CAH is often discovered at a later age in males compared to females because of the absence of clear physical deformities (Hines and Kaufman, 1994). Males with CAH are therefore less preventively treated from birth and thus more often hospitalized for salt-losing crises at early ages (Hines and Kaufman, 1994). These traumatic hospitalizations show an inverse relationship with levels of aggression and rough-and-tumble play demonstrating a significant effect of the illness on personality development, especially in males (Hines and Kaufman, 1994). Therefore, I will exclusively concentrate on findings in women with CAH.

A second potentially interesting condition which may inform on how fetal T influences behavior is by examining women with Polycystic Ovary Syndrome (PCOS). Interestingly, while CAH subjects are mainly exposed to high levels of fetal androgens but usually show normal to low levels of T throughout the life-span, the etiology of PCOS has been explained though an interaction between high fetal T but also high circulating T later in life (Abbott et al., 2005, 2008a, 2008b). Thus, PCOS may provide an unique insight into how high levels of both fetal and circulating T may interactively affect behavior. Unfortunately, research with this group is scarce.

A third natural experiment to investigate the effects of fetal T is by examining the effects of fetal hormone transfer in opposite-sex twins. Female animals that co-develop next to a male twin, have been found to show increased levels of masculine behaviors (Ryan and Vandenbergh, 2002) and this is likely to be true in humans as well (Tapp et al., 2011). Simply speaking, T synthesized by a developing male fetus can diffuse across the amniotic membrane and thereby affect neighboring fetuses (i.e., masculinization of specific aspects of behavior, cognition, and morphology) (Ryan and Vandenbergh, 2002). In addition, T can also diffuse between fetuses through the mothers’ bloodstream (Meulenberg and Hofman, 1991). In this sense, females from an opposite-sex twin dyad are naturally exposed to higher levels of fetal T than same-sex female twins and the
differences in behavior between both groups could also inform on the effect of fetal T on behavior.

Activational effects of T throughout the lifespan are usually inferred through levels of circulating T which are measured through a variety of techniques. Most common methods of T measurement are through collecting saliva or blood samples and assessing T levels via enzyme- or radio immunoassay procedures. Other procedures are measuring T levels through urine and in CSF fluid although the great majority of studies use either blood draws or saliva. Salivary assessments provide a direct measure of the unbound T because the larger protein bound T molecules do not readily pass through the saliva glands (Vining and McGinley, 1984). Conversely, because a high percentage of T in the human body is bound by proteins such as sex hormone binding globulin (SHBG) and albumin that may affect its direct influence on neurobiology or behavior, T in blood samples can be measured as “total” (i.e., the percentage which is protein bound and less active) or “free” (i.e., unbound and biologically active).

However, SHBG levels vary strongly with age, substance abuse, and with bodily fat levels, whereas free-T is less affected by these parameters (e.g., Allen et al., 2002; Vermeulen et al., 1996). This is relevant because the relationship between total-T and behavior can be strongly modulated by SHBG levels. For example, Aluja and Garcia (2007) found that SHBG levels were higher in aggressive subjects compared to controls and strongly modulated the relationship between total-T and aggressiveness. When SHBG levels were controlled for, the positive correlation between T and aggression became non-significant. In addition, Stälenheim et al. (1998) also reported that total-T and SHBG were higher in subjects with antisocial personality disorder compared to controls but found no difference with regard to free-T. Aluja and Garcia (2007) suggest that not T levels but liver damage caused by an unhealthy lifestyle (e.g., substance abuse, obesity) and leading to higher levels of SHBG may be related to aggression and anger thereby confounding the relationship between T and behavior in antisocial samples. Therefore, I will also review studies of total-T levels in children and adolescents when SHBG is unlikely to be altered by liver damage, substance abuse, or age. These studies may provide more direct representations of the T-behavior relationship.
5.3 The Role of Testosterone in Psychopathic Traits

In the following section, I will focus on the potential role of T in the etiology of psychopathic traits throughout the life-span. In discussing these findings the distinction is made between core psychopathic traits (i.e., callousness, utilitarianism, and fearlessness) and the associated life-course persistent antisocial behavior (i.e., impulsivity, aggression) (Lilienfeld and Andrews, 1996; Patrick et al., 2009; Yildirim and Derksen, 2015). The following research questions will be examined; Do psychopathic or antisocial individuals have higher levels of fetal T exposure/ circulating T? Does the strength of the relationship between fetal/ circulating T and psychopathic traits vary at different life phases (childhood, adolescence, and adulthood)? And finally, which endophenotypes might mediate the relationship between T and psychopathic traits? For a detailed overview of the included studies in the form of a table see Yildirim and Derksen, 2012b.

Correlation between testosterone and core psychopathic traits

Fetal testosterone and psychopathy: The role of fetal T in the etiology of core psychopathic traits has been scarcely studied. Surprisingly, the sole study reported that core psychopathic traits were strongly and positively correlated with left hand 2D:4D in both genders (Blanchard and Lyons, 2010). Since higher 2D:4D ratios have been related to higher fetal estrogen exposure (see Blanchard and Lyons, 2010), this finding actually implies that the development of core psychopathic traits is facilitated by fetal estrogens rather than fetal T. In accord, T administration led to greater utilitarian decision-making in subjects with higher 2D:4D ratios (Montoya et al., 2013), suggesting a potential interactive effect between fetal estrogens and circulating T. Also, administration of oxytocin led to a larger shift of focus from self to group-serving cognition and decision-making (less egocentrism) in individuals with lower 2D:4D ratios (Kret and De Dreu, 2013).
In sum, these findings attest for a role of fetal estrogens rather than fetal T in the development of egocentrism, utilitarianism, and core psychopathic traits, possibly in concert with high circulating T. However, as discussed, the validity of the 2D:4D ratio as a proxy for fetal T has yet to be firmly established (McIntyre, 2006). These findings on fetal T and core psychopathic traits should thus be viewed as preliminary and more research, arguably with more valid measurements of fetal T, such as through amniotic fluid, is needed to deduce firmly grounded hypotheses. Nonetheless, it would be interesting to also examine the effect of fetal estrogen exposure, especially its interaction effects with T administration, on psychopathic traits. One possibility, though novel and unexpected, is that a higher fetal estrogen exposure coupled to higher levels of circulating T later in life might have a role in the development of core psychopathic traits.

Circulating testosterone and psychopathy; Though there is more research into the relationship between circulating T and core psychopathic traits, most studies to date have reported non-significant results. For example, Loney et al. (2006) found no significant correlation between T levels and callous-unemotional traits in youngsters. However, in this study, T was also unrelated to conduct disorder symptoms, which contrasts with the consistent positive correlations between T and antisocial behavior found in other studies (Yildirim and Derksen, 2012b). Nevertheless, two studies in adults also failed to find significant associations and reported that T was mainly related to an antisocial lifestyle (factor 2; PCL-R) rather than core psychopathic traits (factor 1; PCL-R) (Glenn et al., 2011; Stålenheim et al., 1998). Only Welker et al. (2014) found a small but positive effect size of T on core psychopathic traits in adult males. In sum, associations between circulating T and core psychopathic traits are non-significant or weak. Nevertheless, more research is needed to reach solid conclusions.

A further possibility to determine whether T might be involved in the etiology of core psychopathic traits is by examining whether T influences underlying endophenotypes. As discussed in chapter 2, low fear-reactivity and dampened affective empathy are the primary endophenotypes underlying the development of core psychopathic traits (Blair, 2006a; Fowles and Dindo, 2006; Hare, 1993). This finding has been replicated in children; low empathy and low fear in younger children has been directly related to the development of callous/unemotional traits later in childhood and adolescence (Frick and White, 2008; Glenn et al., 2007; Pardini et al., 2007).
Testosterone and fear; confronting your demons

It has been recognized that fear and anxiety are different constructs related to different situations and differing in their neurobiological substrates (Grillon, 2008a). Anxiety is a more chronic but consciously controllable attention process, whereas fear is an unconscious and emotionally reactive process. More specifically, anxiety can be defined as the nervous anticipation of unwanted but potential events that might happen in some future scenario (e.g., remaining unemployed, losing a job or partner, etc.). Conversely, fear is the acute, uncontrollable, and unconscious physiological reaction to imminent threat, faced within the here and now (e.g., being attacked/provoked) (Grillon, 2008a). As discussed in chapter 2, 5, and 6, primary and secondary psychopathy mainly diverge regarding unconscious fear mechanisms with primary variants being fearless and secondary variants being fearful. Attention-driven anxiety is less strongly related to either forms of psychopathy and although primary psychopaths generally show lower levels of anxiety compared to secondary variants, anxiety can also be reduced in some secondary psychopaths such as those of the detached subtype. Therefore, I will mainly focus on the role of T in fear and acute threat-responsivity.

Gender differences in fear are weak, non-consistent, and dependent on how it is measured (Grillon, 2008b; McLean and Anderson, 2009). For example, men and women are equally sensitive to fear-conditioning and show similar physiological responses to threat or social stress (Frederikson et al., 1976; Katkin and Hoffman, 1976; Kelly et al., 2008). In contrast to fear, boys show slightly lower levels of anxiety towards novel surroundings and people or when left alone compared to girls (age 1-13) (Else-Quest et al., 2006). Indeed, this difference in anxiety also extents to adulthood and generalized anxiety disorder is more common in women (Anderson et al., 1987; McLean and Anderson, 2009; Walsh et al., 2004). In other words, while men and women show similar physiological responses to immediate threat (fear), males do tend to show lower levels of nervous anticipation and worrying (anxiety).

Association T and fear in humans; The absence of a gender difference in fear is also reflected by inconsistent findings regarding T and fear-reactivity. Beginning in utero, some studies report a positive association between T exposure and fear-reactivity in 6-18-month-old boys (sudden exposure to a novel toy) ($r = 0.34$) (Bergman et al., 2010), whereas others report a negative association (Jacklin et al., 1983), and others still, find no differences (Marcus et al., 1985). However,
the Bergman study is the only one which used an established and validated measure to determine fetal T exposure (amniotic fluid), while Jacklin and Marcus both used umbilical cord blood. Van de Beek et al. (2004) have demonstrated that amniotic fluid assessment of fetal T is superior to umbilical cord blood assessments and these finding thus mainly attest for a null or positive effects of fetal T on fear. Finally, Alexander and Saenz (2011) reported that circulating T in male and female infants (3–4 months old) did not show a significant association with fear-reactivity as measured by the Infant Behavior Questionnaire-Revised.

Despite that correlative research between T and fear in adolescents and adults is simply lacking, which is remarkable, there are some studies that do assess fear in response to direct T administration. For example, Hermans et al. (2006a) found that a single sublingual administration of 0.5 mg of T attenuated fear-potentiated startle in females but the effect was small. That is, threat still had a strong effect on startle reactivity but slightly less than it did in the control group. Furthermore, Van Honk et al. (2005) found that a single administration of T reduced attentional bias toward fearful facial expressions but did not affect consciously experienced anxiety.

In sum, although T has some effect on processes implicated in fear (attention to threat) and is capable to dampen fear-potentiated startle compared to placebo, these effects are weak and the role of T in the fear deficit observed in primary psychopathic individuals is likely to be modulatory rather than necessary. That is, in the context of an already hyporesponsive emotional system, high T individuals may show a more pronounced fearlessness and this effect might be especially mediated through a dampening of emotional appraisal rather than responsivity (see below).

Association testosterone and fear in animals; Changing T levels in rodents, cows, and primates does not affect their physiological reactivity to immediate threat (Anagnostaras et al., 1998; Bouissy and Bouissou, 1994; Dalla and Shors, 2009; McDermott et al., 2012; Morris et al., 2009; Toufexis et al., 2005). For example, prepubertal castration of rhesus macaques did not affect fear-conditioning both before and after puberty, indicating that altering T exposure throughout development does not influence fear (Morris et al., 2009). Bouissy and Bouissou (1994) concluded after a thorough investigation with heifers that T influences the coping but not physiological response to threat; T treated heifers did not show altered physiological responses to threat (heart rate) or fear-conditioning but were nonetheless more daring and confronting when entering an unknown
area and examining a novel object (Bouissy and Bouissou, 1994). Archer (1976b) found similar results when he examined the effect of T on fear behaviors in male chicks. He observed that T did not affect the intensity of fear-responses; both T-treated and control chicks showed similar levels of freezing, defecating, and burrowing when startled. Nevertheless, T-treated chicks were less careful and approached, attacked, picked, and touched the bell which startled them more often than controls, indicating a more confronting and aggressive reaction to the source of threat. Other studies conducted by Archer (1973a,b,c, 1976a) also demonstrated that T reduces fear-related behaviors such as avoidance, distress calls, and behavioral inhibition to a novel environment but does not directly alter emotional responsivity to fear-eliciting situations. Similarly, T treated macaques spend more time watching violent videos in which conspecifics engaged in aggressive behavior, suggesting that T increased attention and behavioral approach towards normally aversive stimuli (Lacreuse et al., 2010).

Testosterone and fear in the brain; The amygdala is among the core structures regulating fear-reactivity and fear-behaviors (Grillon, 2008b). In the adult human brain, the amygdala is significantly larger in men, even after controlling for whole brain volume, and this difference is thought to be shaped primarily by gonadal steroids (Goldstein et al., 2001). In accord, T increases amygdalar reactivity to fearful and angry faces, and higher levels of salivary T are associated with higher amygdala responsivity in general ($r = 0.40$) (Bos et al., 2013; Derntl et al., 2009; Ernst et al., 2007; Goetz et al., 2014; Hermans et al., 2008; Manuck et al., 2010; Van Wingen et al., 2009). Derntl et al. (2009) also observed a substantial negative relationship between T levels in blood samples and reaction time to fearful faces ($r = -0.598$) suggesting that the increase in amygdalar threat-reactivity is also translated in a faster behavioral response. Finally, female adolescents with CAH show higher amygdalar reactivity to emotional facial expressions (anger, fear), indicating a sensitizing organizing effect of fetal T on amygdalar reactivity (Ernst et al., 2007).

These findings suggest increased rather than decreased fear reactivity in high T individuals. One possibility that provides an explanation for both the neural and behavioral findings might be that T changes the coping response to threat. That is, since T increases psychological dominance (Mazur and Booth, 1998), it might also boost neural reactivity to threat originating from other members in the hierarchy in order to react appropriately to social competition (Van Honk et al., 1999, 2001; Van Honk and Schutter, 2007b). In accord, T
augments vasopressinergic activity in limbic areas (Rasri et al., 2008), which is associated with increased power-motivation (dominance) and intermale aggression (Compaan et al., 1991; Morrison and Melloni, 2014; Sowards and Sowards, 2003). In other words, when threatened or provoked, subjects with a stronger increase of T may react with strong emotions but more likely to confront the source of threat and enter a fight rather than flight mode (Carré and Olmstead, 2015; Chichinadze et al., 2012; Geniole et al., 2013). Thus, the heightened amygdalar reactivity to angry and fearful facial expressions in high T individuals might particularly indicate that they are more easily angered or frustrated by social threat and more easily triggered into aggression. For example, in violent subjects, T and impulsivity correlate positively with the level of anticipatory skin conductance response to a social stress task, which is mediated primarily by a higher level of anger expression, suggesting that the increased emotionality in high T subjects is mainly expressed as impulsive anger (Romero-Martínez et al., 2013b). In addition, higher levels of basal T are related to a worse mood and higher levels of anger and anxiety (Romero-Martínez et al., 2013a).

These propositions are also supported by research into the effects of T on fronto-limbic connectivity. That is, the PFC and the limbic system bidirectionally affect each other’s influence over behavior. This bi-directional flow of information (i.e., cross-talk) is an important prerequisite for healthy emotion regulation and emotional decision-making (Knyazev and Slobodskaya, 2003; Van Honk and Schutter, 2006; Van Peer et al., 2008). Administration of T down-regulates fronto-limbic interactions of information-flow, likely leading to a diminished ability to cognitively analyze or regulate affective signals stemming from limbic structures (Lindberg et al., 2003; Schutter and Van Honk, 2004; Van Honk et al., 2005; VanWingen et al., 2010; Volman et al., 2011). That is, when this flow of information is disturbed, capacity of the PFC to regulate emotional influences on behavior is likely reduced, and alternatively, capacity of the limbic system to infuse emotional relevance into PFC constructed action plans, is also limited.

For example, T administration enhanced amygdalar reactivity but dampened orbitofrontal reactivity to cues of threat (Bos et al., 2013; Goetz et al., 2014; Van Wingen et al., 2009), which may be explained by the negative influence of T on fronto-limbic cross-talk (Van Wingen et al., 2010). In a longitudinal study, a higher rise of T throughout adolescence correlated with a stronger level of fronto-limbic uncoupling in adolescents (Spielberg et al., 2014a, 2014b). Interestingly, Spielberg et al. (2014b) also found that in addition to increased
amygdalar reactivity, the T rise during adolescence is also associated with increased nucleus accumbens activations towards threat, which complements the above-mentioned behavioral findings and implies a more vigorous behavioral response towards threats. In a more complex task, Mehta and Beer (2009) showed that T was negatively associated ($r = -0.55$) with orbitofrontal cortex (OFC) activation to rejection in a social game (ultimatum game) and this hyporesponsivity was related to higher levels of reactive aggressive responding on the task.

**Synthesis;** Instead of influencing fear-reactivity directly, T likely changes the way an environmental threat is handled after detection, increasing the probability for reacting with approach behaviors (e.g., dominant/aggressive response) instead of avoidance behaviors. That is, T increases sensitivity to threat by sensitizing amygdalar reactivity but it also concomitantly boosts vasopressinergic and nucleus accumbens reactivity (dominance and behavioral approach) and dampens OFC sensitivity (reduced emotional appraisal/regulation) which may interactively engender a more vigorous, aggressive, and confrontational response to threat. Thus, one possibility is that high levels of amygdalar reactivity may lead to either

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*Figure 5.1* The proposed relationship between T and threat-related behavior.
anger and aggression or anxiety and avoidance, strongly depending on other mediating neurobiological factors such as vasopressinergic reactivity and the degree to which the amygdala is capable of activating PFC areas implicated in emotional appraisal/regulation. The effect of T on amygdalar, vasopressinergic, and vmPFC reactivity to threat and their putative association with threat coping behaviors is schematized in figure 5.1 and 5.5.

Testosterone and empathy; an eye for an eye

Empathy is a comprehensive and layered phenomenon which does not lend itself to a simple definition or subdivision (Bird and Viding, 2014). For the sake of clarity and in line with the general literature, empathy can be understood as a three step process. Simply stated, whenever we detect another person to be in distress or pain, even before we become fully aware of the situation, our limbic system alerts our attention and kick-starts our physiological arousal response (sweating, heart rate increase, muscle tightening). This initial process is a fully unconscious and uncontrollable reaction, is usually referred to as emotional empathy, and is severely and uniquely attenuated in primary psychopathy (Blair, 2006a; Hare, 1993). After this initial rudimentary awareness, our thinking brain kicks in and tries to understand cause-and-effect (cognitive empathy). The ability to understand the behaviors and feelings of people around us, also referred to as “theory-of-mind” or social cognition, can be done purely rationally, and is usually intact in adult primary psychopaths (Dadds et al., 2009; Dolan and Fullam, 2004). After understanding the antecedents of the situation we might consciously begin to appraise and feel the other’s distress by imagining their pain (emotional appraisal), which can be described more generally as “caring” rather than “feeling” because it involves a strong cognitive component. This last component of empathy is severely affected in both primary and secondary psychopathy but arises due to divergent emotional pathologies, namely inability to feel empathy in primary psychopathy and an inability to tenderly appraise human suffering in secondary psychopathy.

The first indication that T may be involved in empathy is the consistent finding that men show both lower emotional and cognitive empathy compared to women (e.g., Baron-Cohen, 2002; Christov-Moore et al., 2014; Goldenfeld et al., 2005; Hurlemann et al., 2010; Zahn-Waxler et al., 2008). In addition, the emotional empathy response in men strongly depends on the individual being
perceived, and whether this person is likable or unlikable. That is, men show empathy-related activation in pain-related brain structures (fronto-insular and anterior cingulate cortices) only toward fair players who receive a painful electric shock, whereas women show increased empathy-related responses towards both fair and unfair players (Singer et al., 2006). In other words, compared to women, emotional empathy in men may be more strongly modulated by situational factors and less an ingrained part of personality.

Association testosterone and empathy: The extreme male brain theory of autism by Simon Baron-Cohen (2002) states that exposure to high levels of male gonadal hormones in the womb can facilitate the development of neural systems implicated in understanding rule-based systems (e.g., machines) but at the cost of neural development of socio-emotional areas. In comparison to girls, boys are therefore naturally better at the rational understanding of systems (‘systemizing’) while girls are naturally more sensitive in resonating to and understanding social processes (‘empathizing’) (Baron-Cohen, 2002).

In accord, Lutchmaya et al. (2002) reported that higher amniotic T is negatively related to eye-contact in 12-month-old infants, which is in turn associated with dampened emotional empathy and higher psychopathy in adolescence and adulthood (Bedford et al., 2014; Dadds et al., 2010). Furthermore, amniotic T is negatively related to the child version of the Empathy Quotient (EQ) in boys between 6 and 9 years of age ($r = -0.35$) (Chapman et al., 2006). The EQ in children is a measure of both cognitive (perspective-taking, $r = 0.485$) as well as emotional empathy (empathetic concern $r = 0.423$/emotional reactivity to others $r = 0.583$) (Lawrence et al., 2004). However, Romero-Martínez et al. (2013a) reported that the negative effect of fetal T and empathy was only evident in aggressive subjects but not in healthy controls suggesting that fetal T likely works in concert with other risk factors to engender more dysfunctional forms of callousness.

Furthermore, Helleday et al. (1993) found that women with CAH, who are naturally exposed to higher fetal T, scored substantially higher on the subscale “social detachment” which indicates higher levels of coldness in social interactions and lower levels of empathy and attachment towards other people. In subsequent studies, these results were supported and it was found that women with CAH also show less tender-mindedness ($d = -1.16$), less caring disposition ($d = -1.3$), and higher physical aggression ($d = 0.51$) compared to healthy controls (Mathews et al., 2009).
These results indicate that high levels of fetal T may have a small to moderate negative relationship \((r = \text{between } 0.3 \text{ and } 0.4)\) on measures of social sensitivity and empathy in children and adults.

Also, throughout the lifespan, circulating T consistently shows a negative correlation to empathy related measures. For example, in undergraduate females, salivary T showed a small negative relationship with kindness \((r = -0.21)\), having a caring attitude \((r = -0.21)\), and being helpful \((r = -0.24)\) on self-report questionnaires (Baucom et al., 1985). In support of these findings, a second study in undergraduate students found that salivary T was related to lower scores on emotional empathy, altruism, and nurturance (men; \(r = -0.44\), women; \(r = -0.29\)), and higher scores on the aggression and hostility (men; \(r = 0.36\), women; \(r = 0.41\)). After modeling of the observed associations, a causal effect model seemed to fit the data better than a correlational effect model, indicating a moderate causal effect of T on prosocial personality characteristics \((r = -0.39)\) (Harris et al., 1996).

In contrast to these findings, however, a third study with children of 5-years reported that emotional empathy (affectivity in close relationships) was positively related to salivary samples of T \((r = 0.453)\) but only in girls with low IQ (Azurmendi et al., 2006). The observed differences in findings between the Azurmendi study conducted with children (age 5) and the Baucom and Harris studies with undergraduates, may be related to the age of the participants studied. Since personality is not yet established at the age of 5 and activating effects have not yet fully occurred, relationships between T and prosocial behavior are likely to be more labile and show less stability over time compared to studies with undergraduates.

Continuing with more experimental studies on the causality between T and empathy, it was found that T administration in women reduced facial mimicry when seeing dynamic facial expressions of happy and angry faces (Hermans et al., 2006b). The automated tendency to mimic others’ emotional expressions is a strong predictor of emotional empathy (Sonnby-Borgstrom, 2002), and is significantly lower in adolescent boys who are prone to develop psychopathy in adulthood (De Wied et al., 2006). A strong interaction effect was found for degree of facial mimicry and independent condition (T and placebo), with lower mimicry in participants given T compared to placebo (happy faces; \(d = -0.96\), angry faces; \(d = -0.92\)). In reaction to these findings Hermans et al. (2006b) argue that “in sum the nature of the relationship between T and human behavior likely lies in its propensity to amplify power motives and dominance,
whilst attenuating empathy” (p. 860).

Another task designed to examine altruism and prosocial behavior in human social interactions is the ultimatum game. The participant receives a certain amount of money and is told that he may donate some of his money to another participant, who he is told, has received nothing for his enrollment. The amount of money offered to the unpaid participant is taken as a measure for fairness, generosity, and has been connected to emotional empathy (Barraza and Zak, 2009). The results of T administration on generosity in the ultimatum game are inconsistent. In the first and second study by Zak et al. (2009; Zak, 2011), T administration to undergraduate men was found to reduce their generosity by 27% in the ultimatum game. This decrease in generosity remained significant after controlling for altruism (Zak, 2011). In contrast, Zethraeus et al. (2009) found no effect of long-term T administration (4 weeks) on ultimatum game behavior in healthy women between ages 50 and 65. Moreover, another study in women with a mean age of 25 reported an increase in generosity on the ultimatum game after administration of T (Eisenegger et al., 2010), indicating an unexpected increase in prosociality and fairness in social interactions. Therefore, T administration increases fair-bargaining behaviors in middle aged women demonstrating that T can have varying behavioral associations that can be both prosocial and antisocial (Eisenegger et al., 2010).

Remarkably, the studies that report an absence or positive relationship between T and bargaining behavior are conducted only with women (Eisenegger et al., 2010; Zethraeus et al., 2009), while studies that report a negative relationship are conducted only with men (Burnham, 2007; Zak et al., 2009; Zak, 2011). Men may react differently to the activating effects of T administration because of prenatal and adolescent masculinization of underlying neural circuitry. While women may react with an increase of concern for maintaining social connections (in women status may be more defined by their social connectivity), men might react to T administration by an increase in dominance and reactive aggression to (re)establish social status (in men status may be more defined by strength and dominance). Interestingly, Van Honk et al. (2011a) found that the cognitive empathetic response in females is strongly modulated by T exposure in utero (measured through 2D:4D ratio), explaining more than 50% of the variance in the effect of T administration on empathy in females (Van Honk et al., 2011a). Nonetheless, Montoya et al. (2013) found that higher 2D:4D ratios in females predicted increased levels of utilitarian decision-making in response to T administration, which is inconsistent with the found gender-differences.
Therefore, more research is needed regarding the effect of T administration on empathy related measures, preferably through designs with equal amounts of males and females who are administered T. Also, it is highly advised that these studies take place with individuals in whom fetal T exposure has been measured through amniotic fluid at the time of pregnancy rather than 2D:4D ratios throughout life. Finally, since there are some indications that especially in males fetal estrogens may also interact with circulating T, it would be very interesting to also measure fetal estrogen exposure.

Testosterone and empathy in the brain: One of the key limbic structures regulating the strength of emotional empathy is the right-hemisphere amygdala. Proper amygdala activation in response to distress cues (distressed facial expressions) may be an important prerequisite for emotional empathy development (see for review Blair, 2006a). Accordingly, the right amygdala shows diminished activation to distress cues (sad and fearful facial and vocal expressions) in primary psychopathy (see Blair, 2006a; Yildirim and Derksen, 2015). Conversely, extraordinarily altruistic individuals (those who donated a kidney to a complete stranger) display an enlargement and enhanced responsivity of specifically the right-hemisphere amygdala to fearful faces (Marsh et al., 2014).

However, the amygdala signals affective information to the vmPFC, which is mainly involved in its appraisal. Functionality of the vmPFC during social interactions is paramount for healthy emotional appreciation of social cues (Damasio et al., 1990; Eslinger, 1998; Grattan et al., 1994). Thus, empathetic responding is processed via two pathways; the subcortical route is fast and reflexive and encompasses the basic emotional resonance with the distress of others (e.g., amygdalar reactivity to facial expressions), whereas the cortical route is slower and strongly based on self- and other awareness and the capacity to take other people’s point of view (e.g., cortical appraisal of the significance of other’s distress) (Preston and de Waal, 2002). Both the intuitive amygdalar response to social cues and the prefrontally mediated appraisal have been associated to circulating T levels.

As discussed, different studies have reported that T is both causally and associatively related to heightened responsivity of the amygdala to fearful or angry faces (Bos et al., 2013; Derrtl et al., 2009; Ernst et al., 2007; Goetz et al., 2014; Hermans et al., 2008; Manuck et al., 2010; Van Wingen et al., 2009). These results indicate that the negative effects of T on empathy are unlikely due to lower amygdalar reactivity. However, although T does not decrease amygdalar
reactivity to others’ distress cues, it might influence the emotional appraisal of those subcortically generated signals, which is largely dependent on proper vmPFC sensitivity to these affective signals (Damasio et al., 1990; Eslinger, 1998’ Grattan et al., 1994).

First, both fetal and circulating T have been found to impact on the maturation and functionality of vmPFC structures involved in socio-emotional appraisal. Males consistently show lower right OFC gray matter volumes (Lombardo et al., 2012b; Raine et al., 2012; Welborn et al., 2009; Xu et al., 2000), and reduced functionality of this structure during emotional decision making (Lee et al., 2009c). Raine et al. (2012), found that lower OFC gray matter volumes in males explained 77.3% of the gender-difference in antisocial personality/behaviors. Moreover, this reduction was not a function of psychiatric comorbidity, psychosocial risk factors, head injury, or trauma exposure. In other words, sexual differentiation may partly underlie the found differences in the right OFC gray volumes, and thus, antisocial behavior (Raine et al., 2012). Indeed, fetal T exposure as measured through amniocentesis at 13–20 weeks of gestation (i.e., a time-frame that is hypothesized to be critical in human sexual differentiation; Hines, 2004) was found to negatively predict right OFC gray volumes and this effect accounted partially for the observed gender-differences of this structure in the same study (Lombardo et al., 2012b).

Second, activational effects of T may exacerbate fetal T organized maturational weaknesses and further dampen social sensitivity. As discussed, T dampens fronto-limbic cross-talk, likely leading to a diminished ability to cognitively appraise affective signals stemming from limbic structures (Schutter and Van Honk, 2004; Van Honk et al., 2005; VanWingen et al., 2010; Volman et al., 2011). Therefore, in addition to changing fear coping behaviors, T may also impact on socio-emotional appraisal when confronted with empathy eliciting stimuli. A behavioral example illustrating the effect of a diminished fronto-limbic information flow on socio-emotional processing is the finding that T impairs conscious recognition of the affective facial emotion of anger (Van Honk and Schutter, 2007a), while it increases limbic and autonomic reactivity when confronted with an angry face (Goetz et al., 2014; Van Honk et al., 2001, 2005). In this manner, although T increases reactivity to empathy eliciting stimuli, it may reduce their cortical appraisal, thereby also dampening socio-emotional sensitivity.

Finally, the hypothesis that T might influence empathetic and prosocial behavior is also supported by its effects on the neuropeptide oxytocin. Oxytocin
is present in all mammalian species and promotes calmness, social sensitivity, trust, and empathy. It is the main hormonal system of attachment and serves to increase emotional bonding between individuals (Üvnas-Moberg, 2003). Different studies have shown strong positive effects of oxytocin administration on both emotional and cognitive empathy and oxytocinergic genotypes have been related to inherent empathetic capacity (Barraza and Zak, 2009; Hurlemann et al., 2010; Laursen et al., 2014; Zak, 2011; Zak et al., 2007). Also, callous-unemotional traits in youngsters have been associated with alterations to the oxytocinergic system and administration of oxytocin has been suggested as a potential treatment option (Rice and Derish, 2014). For example, Hurlemann et al. (2010) found that oxytocin administration enhanced self-reported emotional empathy when watching pictures of individuals in distress. Gender differences were also found in emotional empathy, with men scoring lower than women. However, after oxytocin administration, this effect disappeared indicating that the lower level of emotional empathy in men may relate to lower oxytocinergic functioning (Hurlemann et al., 2010).

In accord with this finding, steroids such as estrogens and androgens have a great influence on neuropeptide production, release, sensitivity, and gene-expression (Crowley et al., 1995; Grazzini et al., 1998; Rhodes et al., 1981). There is also evidence that gender specific levels of steroids, such as T and estrogen, alter the sensitivity and innervation of oxytocin and its receptors.
(De Vries et al., 1986; Johnson, 1992; Johnson et al., 1991). Oxytocinergic mechanisms are amplified by female sex-specific hormones such as estrogen (up-regulation of receptor sensitivity) (Grazzini et al., 1998; Johnson, 1992; Johnson et al., 1991; Rhodes et al., 1981), and are dampened by T (down-regulation of receptor sensitivity) (Francis et al., 2002; Johnson et al., 1991). Accordingly, oxytocin levels increase significantly after human touch or a trusting sign with women being more sensitive to this effect than men, who are less likely to alter their original behavior because of a trusting sign or a gentle touch from another individual (Morhenn et al., 2008).

**Synthesis;** These preliminary results indicate that the interplay between fetal and circulating T likely delays the maturation and diminishes socio-emotional appraisal by the vmPFC, ultimately resulting in lower socio-emotional sensitivity. This observation is in line with the organizational-activational theory of gonadal hormones (Phoenix et al., 1959), and the extreme male brain theory of autism which states that high levels of fetal T may lead to dampened maturation of brain structures involved in socio-emotional processing (Baron-Cohen, 2002). In addition, oxytocin might partly mediate the negative relationship between T and empathy, such that individuals exposed to higher levels of fetal T and with higher circulating T levels, might exhibit decreased oxytocinergic sensitivity and thus lower attachment and empathy towards individuals in general (maybe the focus in men is biased away from individual welfare and towards group welfare). Finally, as will be clarified later on in this chapter, although T can decrease social sensitivity, it may only lead to pathological callousness when exposed to negative social experiences such as abuse, neglect, and rejection. These interactions are schematized in figure 5.2.

**Testosterone and life-course persistent antisocial behavior**

*Correlation between testosterone and life-course persistent antisocial behavior*

*Fetal testosterone and antisociality;* Studies that examine the association between antisocial behavior and the 2D:4D ratio as an indicator of fetal T report inconsistent results. While younger samples (children aged 2–5) do not show an association between 2D:4D ratio and antisocial behavior, children who transition
into puberty (ages 7-11) usually show a negative correlation (Fink et al., 2007; Williams et al., 2003). Since circulating T levels steadily rise from early to late childhood and then peak at puberty, these findings support the organizational-activational hypothesis and suggest that when circulating T levels rise, fetal T induced developmental vulnerabilities such as vmPFC maturational delays, may be exacerbated, thereby interactively increasing the risk for deviant behavior.

Interestingly, further studies that compare clinical to healthy samples report that while children and adolescents with ADHD and oppositional deviancy demonstrate 2D:4D ratios indicative of higher fetal T exposure (De Bruijn et al., 2006; Stevenson et al., 2007), these differences are not consistently found in samples with exclusively ADHD children (McFadden et al., 2005). Nonetheless, a third study by Martel et al. (2008) reported that both ADHD and oppositional deviancy were associated with lower finger ratios compared to controls, whereas CD symptoms showed a much smaller negative but non-significant correlation. Thus, the findings are not entirely consistent and it is advisable to further study which specific types of deviancy and externalizing pathology are associated with lower 2D:4D ratios. That is, these above findings suggest that fetal T predisposes towards a mix of reward hypersensitivity (ADHD combined type/ODD) and frustration intolerance (oppositional deviancy), which may increase boyish rebellion, stubbornness, and frustration intolerance rather than being indicative of serious psychological pathology (e.g., hostility, aggression) such as found in conduct disorder, or biological pathology (e.g., cortical hypoarousal) as is characteristic of ADHD.

Further data comes from twin-studies which report that females who developed next to a male twin and were thus exposed to higher cross-membrane T in utero, show higher levels of antisocial behavior than females from a same-sex dyad (Meier et al., 2011; Tuvblad et al., 2005). Finally, a large study by Gotby et al. (2015) cross referenced individuals with hyperandrogenic cases with their criminal records obtained from the population based registers and were thus able to include 483 CAH cases, 12,730 PCOS cases, and another 583 OAD (other androgenital disorders) cases, which is impressive. It was reported that the PCOS and OAD cases showed a significantly increased risk for criminality compared to controls, whereas the CAH cases did not. From these results they concluded that circulating T is more directly related to criminality than fetal T. However, it is interesting that Gotby et al. (2015) only found an increased risk for criminal offending in PCOS patients, which has been associated to both heightened levels of fetal T and heightened T sensitivity throughout life (Abbott
et al., 2005, 2008a, 2008b, 2009), but not in those exposed to heightened fetal or circulating T exclusively (CAH and likely OAD). In other words, these results may indicate that increased risk for criminality is especially associated with a combination of high fetal and circulating T, rather than either factor alone.

Hönekopp and Watson (2011) recently confirmed in a large meta-analysis that a negative relationship exists between 2D:4D ratios and aggression, albeit small. This could also hold true for the association between 2D:4D and other antisocial behaviors. However, fetal T may not be directly related to antisocial behaviors but may indirectly increase the risk for antisocial behavior by sensitizing the T-behavior pathway. This could explain the contrasting results when studying fetal T without accounting for circulating T levels. For example, it has been demonstrated that the 2D:4D ratio strongly modulates the effect of circulating T on empathetic capacities in young adults (Van Honk et al., 2011a). This modulating effect of fetal T on empathy and probably also antisocial behaviors is likely to be mediated through intersecting neurobiological endophenotypes that interact with circulating T levels throughout life to increase the risk for antisocial behavior. Nonetheless, more research conducted with more valid indicators of fetal T is needed to deduce firmly grounded hypotheses.

Circulating testosterone and antisociality: In the study with the youngest population (ages 3 to 11) higher free-T children were more moody, upset, fussy, and more likely to wake up in a bad mood ($r = 0.35$). They were also less attached, being less cuddly and close to their parents ($r = -0.45$) (Strong and Dabbs, 2000). However, only the younger group (ages 3–8) showed a negative association with sociability ($r = -0.44$) that disappeared in the older group (ages 9–11). Conversely, the older group showed a strong positive association with moodiness ($r = 0.68$) that was not found in the younger group (Strong and Dabbs, 2000). Indeed, in clinical samples, results also vary according to the age studied. Adolescents (age 9-11) but not children (ages 5-8) with behavioral disorders show higher T compared to controls (Chance et al., 2000). Similarly, externalizing and delinquent behaviors are mainly positively related to free-T in adolescents (age 9-18) but not in younger children (age 5-8) (Booth et al., 2003; Chance et al., 2000; Granger et al., 2003; Maras et al., 2003a). A final longitudinal study in a community sample indicated that total-T levels at ages 12 to 14 predicted antisocial norm-violating behaviors at age 16 (Tarter et al., 2009).

In contrast, three other studies, in children aged 7 to 15, did not find a significant difference in free- and total-T levels between healthy controls and
children with disruptive behavioral disorders (DBD’s) (mean age 9) (Dorn et al., 2009), CD (mean age 10) (Van Goozen et al., 1998), or delinquency (mean age 13.5) (Granger et al., 2003). However, Dorn et al. (2009), did not differentiate between younger and older children which might have yielded different results. Also, Granger et al. (2003) reported a positive relationship between free-T and delinquency in boys ($r = 0.167$) but this association did not reach significance.

In addition to community samples, different studies have also found positive association between T levels and disruptive behavioral disorders in adolescent boys with psychiatric diagnoses (Maras et al., 2003a; Rowe et al., 2004). One longitudinal study reported that free-T in a group of 13-year-old boys with CD was significantly predictive of delinquency and criminal behavior at age 16 and at age 21 (Van Bokhoven et al., 2006). Similarly, incarcerated youth show higher T than healthy controls and criminals with higher T levels show higher violence, prison misconduct, recidivism risk, and a more severe criminal history than their lower T counterparts, who are more likely to be one time offenders and incarcerated for petty crimes (Dabbs et al., 1995; Mattson et al., 1980).

In sum, children with high free-T levels are less attached in general, and become more social but also more oppositional and irritable when transitioning into adolescence. Also, associations between T and antisocial behaviors become more defined and stronger when transitioning into adolescence and likely reach their peak at around ages 16-18. Again, in line with the organizational-activational hypothesis, it is at those adolescent peak ages that T shows the strongest associations to antisocial behavior. It would be interesting to see whether these associations are particularly defined in adolescents who have been exposed to higher fetal T levels. Also, T levels do not only differ between healthy controls and delinquent youth but violent and persistently criminal youngsters also show higher T than their less violent counterparts suggesting that T may exacerbate antisocial and aggressive behavior in otherwise at-risk youngsters.

The majority of studies into the role of T in antisocial behavior have been conducted with adults. T levels have been consistently associated with antisocial and borderline personality traits and diagnosis (ASPD and BPD) (Dabbs et al., 1990; Dabbs and Morris, 1990; Räsänen et al., 1999; Roepke et al., 2010; Virkkunen and Linnoila, 1993). Furthermore, T correlated significantly with the severity of antisocial behavior in both ASPD subjects and healthy controls (Aromäki et al., 1999, 2002). Within the group of personality disordered patients,
free T levels were higher in recidivists compared to non-recidivists suggesting that T may exacerbate antisocial behavior in psychiatric patients (Räsänen et al., 1999). In contrast to these studies, however, Aluja and Garcia (2007) found no differences in T levels in inmates with or without ASPD. The main difference with the other studies is that Aluja and Garcia compared inmates with ASPD to inmates without ASPD rather than subjects with ASPD to healthy controls. It is arguable that inmates generally display high levels of antisocial behavior and to differentiate between them on the basis of ASPD may be a too sensitive measure of the severity of antisocial behavior. Accordingly, the same study did find significant results when the subjects were differentiated on the basis of recidivism rather than ASPD, with recidivists showing higher levels of total-T than non-recidivists ($d = 0.12$). Nevertheless, Stålenheim et al. (1998) found that inmates with ASPD showed higher levels of total-T compared to inmates without ASPD. One possibility for these divergent findings may be that Stålenheim et al. (1998) used a more stringent measure to assess the presence of ASPD thereby mainly including the more severely disturbed criminals.

A second way to measure life-course persistent antisocial behavior is through the antisocial lifestyle items (factor 2) of the PCL-R. Three studies have examined the relationship between T and factor 2. Stålenheim et al. (1998) found that inmates who scored high on factor 2 had significantly higher total- but not free-T levels than inmates who scored low. Furthermore, Dolan et al. (2001) also reported a trend towards higher levels of total-T in both psychopathic and antisocial prison inmates compared to healthy controls. In contrast, two other studies failed to find differences in baseline free-T between low and high factor 2 scorers in both community (Glenn et al., 2011), and prison samples (Laxton, 1998). These results point out that mainly total-T and not free-T levels are associated with factor 2 scores indicating that part of this correlation may be explained by indirect biological effects such as liver damage through substance abuse or otherwise increased levels of SHBG (Stålenheim et al., 1998; Aluja and Garcia, 2007).

The third group of studies are the prison inmate and delinquent samples. Free-T levels were found to be higher in delinquent adults (from the community) compared to controls (Banks and Dabbs, 1996), and in violent criminals (imprisoned for robbery, rape, homicide) compared to non-violent criminals (imprisoned for drug possession, burglary, theft) (Dabbs et al., 1987). The results thus consistently indicate that higher free-T levels are associated with increasingly violent and criminal acts such that criminals show higher
levels than controls and violent criminals show higher levels than non-violent criminals. Indeed, higher free-T was also significantly positively associated with parole board decisions, indicating that individuals higher in free-T were rated by the parole board to be more dangerous and at more risk to recidivate, and therefore saw a greater need to contain them in prison as long as possible (Dabbs et al., 1987, 1988). Also, free-T levels were positively related to the number of charges in the criminal history \( r = 0.27 \) (Dabbs et al., 1988), and the age at first conviction for violent crimes \( r = -0.65 \) (Kreuz and Rose, 1972). Finally, higher free-T was in some studies significantly related to increased rule-breaking behavior in prison \( r = \text{between 0.30 and 0.50} \) (Dabbs et al., 1987; Dabbs and Hargrove, 1997), although other studies report non-significant result between free-T and rule-breaking in prison (Aluja and García, 2007; Dabbs et al., 1988).

The last population that has been extensively studied are the army veterans. Army veterans are characterized by the same level of SES, education, and family background as healthy community individuals. Five different studies consisting of large groups of subjects (N ranging from 4179 to 5236) have examined this population and all have found small positive associations between T and antisocial behavior. First, ASPD was found to be 1.9 times more likely to be diagnosed in a high free-T group of army veterans compared to a low free-T group (Dabbs and Morris, 1990). In accordance, Dabbs et al. (1990) also found a significant positive association between ASPD and free-T \( r = 0.18 \). In addition, different studies with veterans find a positive correlation between total-T and antisocial behaviors \( r = \text{ranging from 0.11 to 0.18} \) (Booth and Osgood, 1993; Dabbs, 1992; Mazur, 1995). Veterans higher in free-T were 1.8 times more likely to have misbehaved during military than those lower in free-T (Dabbs and Morris, 1990), and it was also found that total-T correlated positively with army misbehavior \( r = 0.10 \) and norm-breaking \( r = 0.22 \) (Mazur, 1995).

**Synthesis:** Taken together, both free and total circulating T levels have a small but positive correlation with antisocial behaviors throughout the lifespan. Furthermore, it can be deduced that age is a mediator of the relationship between T and antisocial behavior. The correlations between circulating T and antisocial behavior are lowest in childhood (ages 3 to 8) \( r = 0.10 \), and increase during the transition into adolescence (ages 9 to 12). During adolescence, the association between T and different measures of antisocial behavior is small but higher than in childhood \( r = 0.20 \).Remarkably, the found associations between T and antisocial behaviors in adulthood show a greater variety between different
samples ($r = 0.15$ in community samples and $r = 0.40$ in antisocial samples) than the associations in child and adolescent samples (see also figure 5.3). Furthermore, these positive associations between T and antisocial behavior throughout all life phases are particularly pronounced in males and not in females. Since males are naturally exposed to higher levels of fetal T, the T-antisocial behavior pathway could be modulated by fetal T exposure.

To examine in more detail through which endophenotypes the T-antisocial behavior link could be mediated it is first important to determine which personality
traits underlie most of the reviewed measures of antisocial behavior. Longitudinal studies of gender-differences in predictors of psychopathology might provide insight into the behavioral mechanisms underlying the relationship between high T and antisocial behavior. Côté et al. (2002) followed the development of a sample of 1,865 children over 6 years, from kindergarten to grade six and assessed the characteristic developmental trajectories (impulsivity, fearfulness, and helpfulness) towards potential future psychopathology. They found that boys were more likely than girls to follow a risk trajectory of high impulsiveness and low helpfulness (low empathy) towards future externalizing pathology, while girls were more likely to follow a trajectory marked by high fearfulness towards future internalizing disorders.

Therefore, part of the relationship between T and antisocial behavior might be mediated through the endophenotypes of empathy and impulsivity. Since empathy is discussed in the previous section I will focus here on impulsivity. Indeed, different studies have found lower levels of impulsivity in girls as compared to boys, when studied as a predictor of crime (LaGrange and Silverman, 1999; Moffit et al., 2001), aggression (Campbell and Muncer, 2009), substance abuse (Stoltenberg et al., 2008), gambling behaviors (Stoltenberg et al., 2008), and adolescent sexual behavior (Hope and Chapple, 2005).

Finally, another trait underlying antisocial behavior and which is disproportionately higher in males compared to females is aggression. Across a range of meta-analyses and reviews, it has been concluded that males show a higher rate of aggression, especially overt physical aggression that can cause pain or injury (Archer, 2004; Bettencourt and Kernahan, 1997; Bettencourt and Miller, 1996; Eagly and Steffen, 1986; Hyde, 1984). In addition, most psychopathy measures include items that assess aggression as part of the antisocial domain and are as a result positively correlated to aggressive behavior (Kennealy et al., 2010; Yildirim and Derksen, 2015). Therefore, the second endophenotype that could underlie part of the relationship between T and antisocial behavior may be aggression.

Testosterone and impulsivity; no risk, no reward

Impulsivity is generally defined as the inclination to spontaneously initiate behavior without adequate forethought or insight into the potential risks or consequences of this behavior. Contemporary literature often differentiates
impulsivity into two general variants; impulsive action and impulsive decision making (see for detailed conceptualization Bechara et al., 2000a; Winstanley et al., 2006a, 2006b). Impulsive action is the absence of higher order inhibitory control leading to an impetuous acting-out of internal tendencies and drives, whereas impulsive decision making is the tendency to pursue certain rewards without adequately considering evaluative feedback or more adaptive modes of action. However, although this distinction captures the larger category of impulsive behaviors it does not properly include traits such as novelty/sensation seeking and risk-taking, which are also part of the impulsivity construct (Cross et al., 2011).

Another way to deconstruct impulsivity which allows for inclusion of a wider variety of behaviors is through its endophenotypic components. The processes that can lead to impulsive behavior can be deconstructed into three components which can be present in differing degrees in various impulsive subsamples; (1) the degree to which the individual is attracted to reward, represented by the BAS, with higher values leading to a dysregulated motivational approach (e.g., risk-taking, novelty seeking, impulsive decision-making), (2) the degree to which the individual is repelled by punishment, represented by the BIS, with lower values leading to less consideration of potentially aversive consequences (e.g., risk-taking, impulsive decision-making) but higher values possibly engendering neuroticism related forms of impulsivity (negative urgency), and (3) the degree to which the individual is capable of effortful control with lower values leading to a dysregulation of behavior in general (e.g., impulsive action and decision-making).

A meta-analysis of 277 studies and 741 effect sizes reported that overall levels of impulsivity do not differ among males and females. Instead, gender differences in impulsivity are mainly manifested through a varying expression of the endophenotypic components of impulsive behavior more specifically (see Cross et al., 2011). First, gender differences have been found in psychological components of reward-sensitivity with males generally scoring higher than females. For example, males show higher sensitivity to rewards in a sample of 584 Taiwanese college students (RayLi et al., 2007), in 1,563 Spanish undergraduates (Torrubia et al., 2001), and in a sample of 360 French adolescents and young-adults (Lardi et al., 2008). In a meta-analysis by Cross et al. (2011) it was found that males were not necessarily higher in all measures of reward sensitivity but only those that assessed the degree to which individuals were willing to take risks and compete aggressively to acquire wanted rewards (success, money, status...
Conversely, women scored higher on measures that assess the dependence on social rewards (approval by others, attachment) \((d = -0.56)\) or on measures which assessed emotional responsivity to rewards \((d = -0.27)\) (Cross et al., 2011). Second, females show higher levels of punishment sensitivity than males and this effect applies to all measures included \((d = -0.32)\) (Cross et al., 2011). Indeed, the tendency for males to show higher sensitivity to rewards and lower sensitivity to punishments is reflected in a greater tendency towards risk-taking \((d = 0.36)\) and sensation-seeking \((d = 0.39)\) in males (Cross et al., 2011). Finally, when specific forms of impulsivity are examined with regard to gender-differences, males show less consideration of future consequences when making choices on how to act (impulsive decision-making) and a greater difficulty inhibiting prepotent responses (impulsive action), whereas females show a higher tendency to act impulsively to regulate negative affect states (negative urgency) (Cross et al., 2011).

In sum, males show higher levels of risk-taking, sensation-seeking, impulsive action, and impulsive decision-making and these traits are likely to be partly mediated through higher reward-sensitivity, lower punishment sensitivity, and lower levels of self-control, whereas female impulsivity is more strongly an expression of neuroticism (hostility, anger, anxiety, depression etc.) and mediated partly through higher dependence on social reward and a higher need to immediately regulate intense emotional states.

**Association testosterone and impulsivity;** Only one study to date has examined the effects of fetal T on endophenotypes of impulsivity in humans, including reward/punishment sensitivity (Lombardo et al., 2012a). Fetal T was measured through amniotic fluid sampled between 13 and 20 weeks of gestation and the children were tested at 8-11 year old. Fetal T was related to an enhanced selectivity for positive compared to negative facial expressions in reward-related regions such as the striatum. In accordance, increasing fetal T also predicted behavioral approach tendencies which was mediated by the increase of striatal reactivity to rewarding stimuli. This results indicates that fetal T may play an important role in the programming of reward-related neural circuitry, such as the dopamine circuitry, and that this influence may extent to influence also behavioral approach tendencies.

A complementary finding is that males with higher levels of fetal T exposure (measured through 2D:4D ratio) are more sensitive to prenatal risk factors in the development of disruptive behavioral disorders in childhood.
Martel and Roberts, 2014). In other words, the T induced programming of reward-circuitry may sensitize the male vulnerability to develop impulsive disorders in childhood, especially in the context of additional risk factors such as prenatal nicotine and alcohol exposure (Martel and Roberts, 2014).

Continuing with correlational studies on circulating T, Virkkunen et al. (1994a, 1994b) found that highly violent and impulsive offenders displayed higher levels of cerebrospinal fluid (CSF) T levels and lower levels of CSF 5HIAA than less violent and impulsive offenders. However, impulsivity was primarily related to low levels of CSF 5HIAA whereas T was related to high levels of aggression and interpersonal violence. In another study by Virkkunen and Linnoila (1993) CSF T concentration was also primarily associated with outward-directed aggressiveness and lack of socialization but not directly with impulsiveness in a group of alcoholic violent offenders. These results indicate that the relationship between T and impulsive violence may be mediated through its enhancing effect on aggression and its disturbing effect on socialization rather than through increasing impulsivity, which is more directly related to low serotonin levels.

Accordingly, T showed no association with impulsivity as measured by the Eysenck personality questionnaire (EPQ-II) in personality disordered men and pathological gamblers (Blanco et al., 2001; Coccaro et al., 2007), the Impulsiveness-venturesomeness-Empathy (IVE) inventory in prison inmates (Dolan et al., 2001), the Barrat Impulsivity Scale (BIS) in two different samples of rapists (Giotakos et al., 2003, 2005), the Impulsiveness Scale (IS) in a group of delinquent recidivists (Mattson et al., 1980), and the Minnesota Multiphasic Personality Inventory (MMPI) in pathological gamblers (Blanco et al., 2001). In prison inmates, T was related to less future planning \( r = -0.210 \) on the BIS (Dolan et al., 2001), and higher avoidance of monotony (Mattson et al., 1980) thus living life more in the moment, but was unrelated to more relevant subscales such as motor-(impulsive action) and cognitive impulsivity (impulsive decision making) which are more strongly related to dysfunctional forms of impulsivity (Dolan et al., 2001). In contrast, Stålenheim et al. (1998) found a small but significant relationship between T and the impulsiveness subscale \( r = 0.15 \) of the Karolinska Scales of Personality (KSP) in adult inmates.

Other associational studies have used behavioral tasks rather than questionnaires to assess the link between T and impulsivity. One study with a large group of participants found a significant association in both men and women between naturally varying T levels and risk-taking on the Iowa Gambling Testosterone and life-course persistent antisocial behavior; impulsivity
Task (IGT) (Stanton et al., 2011). However, in contrast to the other studies reviewed above which are conducted with pathologically impulsive individuals, the participants in the Stanton study were college students. It has been supported in research that in low-impulsive individuals (such as college students), disadvantageous strategies on the IGT may not reflect impulsive decision making but rather deliberate risk-taking, which are two fundamentally different constructs (Steinberg et al., 2008; Upton et al., 2011). A second difference in the design of these studies may be related to the dependent measure used to assess impulsivity. Whereas the above studies used self-report personality measures, Stanton et al. (2011) used a behavioral task, which may also account for the found differences. However, Derntl et al. (2014) found no effect of T on risk-taking behavior when participants had to choose between different options with different probabilities towards winning. Nonetheless, because the participants were all paid a fixed amount of money, which they were informed of before the study started, the choices made would not have necessarily reflected risk-taking since there was no real-life punishment involved. The only possible punishment, namely scoring lower on the game, may not have been salient enough to deter participants to refrain from choosing risky options. Furthermore, Takahashi et al. (2008) also used a behavioral task in a sample of college students and found a negative association between free-T and delay discounting in a group of male students (mean age 22), indicating that T might in fact be related to lower impulsive decision making and higher patience. T is likely not associated with impulsive decision making but may lead to higher deliberate risk-taking.

Regarding impulsive action on behavioral tasks, three different studies have examined the correlation with circulating T levels (Bjork et al., 2001; Fontani et al., 2004; Van Strien et al., 2009). Van Strien et al. (2009) measured the performance of a group of older men (mean age of 67) on the Eriksen flanker task (which measures the ability to suppress automatic behavioral tendencies) to assess the association between T levels and response inhibition. Higher levels of circulating T were positively related to the interference elicited by irrelevant incongruent flankers ($r = 0.24$). T was thus related to less inhibitory control over behavior resulting in heightened impulsive action. In a second experiment, T levels showed a significant positive association with commission errors in a the continuous performance task ($r = 0.55$) (which has been related to impaired response inhibition) in 27 women aged between 32 and 55 (Bjork et al., 2001). In contrast, Fontani et al. (2004) reported a negative relationship between T and the number of errors in a go/no-go task ($r = -0.294$), indicating a better ability...
to suppress automatic responses. Their study was done with a greatly varied population, consisting of 35 males and 33 females between the ages of 18 and 77. Regarding these varying results it may be concluded that it is unclear at this point whether T influences impulsive action but it is likely that T does affect some processes implicated in response inhibition.

Another way to study the effect of T administration on impulsivity is through individuals that use/abuse T enhancing substances. Anabolic androgenic steroids (AAS) are stimulant drugs, often taken by athletes, which chemically boost T levels and hence improve muscle building and energy. Earlier correlative studies have suggested a positive relationship between AAS and different forms of impulsive behavior, including severe violence (Pope and Katz, 1988, 1990, 1994). This has been confirmed by Galligani et al. (1996) who reported a positive relationship between AAS abuse and impulsiveness on the Karolinska Scales of Personality. Other studies have reported that impulsivity is even more profound when combining AAS with other substances that can also lower impulse control (such as GABAergic drugs) (Kindlundh et al., 1999). The above research with AAS indicate that men who abuse these compounds are more likely to be impulsive. However, most studies examine men who already abuse AAS which clouds validity. It may well be that men who are more impulsive and risk-taking are also more inclined to abuse AAS, which is in accordance with the findings that high impulsiveness is related to stimulant substance abuse (Moeller et al., 2001). Therefore, one should be wary of the causality between AAS abuse and impulsivity.

Regarding experimental designs (i.e., T administration and impulsivity in the laboratory), Goudriaan et al. (2010) observed no significant influence on IGT performance after one week of Letrozole treatment in men (which boosts T levels). Similarly, Ortner et al. (2013) reported no significant effect of T administration on delay discounting in university students. However, Van Honk et al. (2004b) report riskier, more disadvantageous decision making after a single administration of T to a group of healthy women ranging from 20 to 25 years of age. Nevertheless, it has been argued that risky decision making on the IGT by low impulsive individuals may reflect deliberate risk-taking in order to obtain rewards, rather than dysfunctional impulsivity (Upton et al., 2011), again indicating that T may in fact increase risk-taking rather than impulsivity.

Interestingly, this hypothesis is supported by rodent research. For example, a chronic high dose of T administration in male rats decreased their sensitivity towards risk and led to a greater amount of risk-taking but it did not affect levels
of impulsivity (Cooper et al., 2014). The T treated rats were more willing to risk potential foot shock to receive a larger reward and less likely to choose the smaller but safer option, also indicating an increase of reward sensitivity, but showed a normal inhibitory capacity of prepotent responses in a go/no-go task (impulsive action) (Cooper et al., 2014). In addition, T administration in rats actually led to choosing the larger delayed rewards over the smaller immediate rewards thereby also suggesting lower impulsive decision making (Wood et al., 2013).

Testosterone and impulsivity in the brain; Research has indicated that T has strong rewarding properties on the brain and this effect is mainly due to the activating effect of T on the mesolimbic dopaminergic circuitry. Hermans et al. (2010) designed a counterbalanced placebo-controlled crossover design in which 12 healthy female participants (mean age=20.4) were administered T and their ventral striatal response to a monetary incentive was assessed through blood-oxygenation level-dependent (BOLD) fMRI. Furthermore, intrinsic appetitive motivation of participants was also assessed through the Behavioral Activation System (BAS) scores. A single dose of T administration significantly increased mesolimbic BOLD responses during anticipation of the monetary incentive (reward-anticipation) (Hermans et al., 2010), which is indicative of increased mesolimbic dopaminergic release (Schott et al., 2008). Interestingly, this effect was stronger in participants with a lower intrinsic appetitive motivation, suggesting that individuals with low reward-sensitivity might be more sensitive to the rewarding effects of a single administration of T, probably because of its enhancing effect on reward-sensitivity. This result is interpreted as T shifting the balance from punishment- to reward processing thereby increasing risk-taking to obtain short-term rewards (Van Honk et al., 2004b). The finding of Hermans and colleagues also help to explain the increased risk-taking to obtain monetary rewards on the IGT after administration of T (Stanton et al., 2011; Van Honk et al., 2004b) further supporting the hypothesis that high T is more likely to be related to risk-taking in order to obtain desirable rewards than to impulsivity that arises out of an inability to control behavior, learn from feedback, or foresee adverse consequences.

In rodents, administration of T creates conditioned place preferences that can be inhibited by dopaminergic antagonists suggesting that the heightened place-preference due to T is partly modulated through its effects on dopamine (DA) processes (Alexander et al., 1994; Arnedo et al., 2000; Caldarone et al.,
289

1996; Packard et al., 1998; Schroeder and Packard, 2000). These positive hedonic effects of T have been found to be mediated by actions of its metabolites, especially 3α-androstanediol, in the nucleus accumbens (Frye et al., 2002; Rosellini et al., 2001). Chronic exposure to T has shown to alter sensitivity to DA by increasing DA metabolism in the cerebral cortex (Kurling et al., 2005). For example, anabolic androgenic steroid (AAS) treatment also increased the binding potential of the dopamine transporter (DAT), indicating a higher clearing of dopamine from the synaptic cleft (Kindlundh et al., 2002). Increased DAT binding is suggested to reflect efforts of the brain to compensate for the higher release of dopamine due to AAS use, suggesting a robust effect of T on dopaminergic functioning (Kindlundh et al., 2002). However, long-term T treatment has been found to impair reward sensitivity, likely due to the depletion of DA in response prolonged heightened neurotransmission (Zotti et al., 2014). Finally, infusion of T into the nucleus accumbens has strong rewarding properties in rodents, which can also be blocked with dopaminergic D1 antagonists (Packard et al., 1997, 1998) and long-term T treatment down-regulated D2-autoreceptor density in the nucleus accumbens (Kindlundh et al., 2001, 2003), indicating that T increases D1-receptor and decreases D2-receptor sensitivity in brain structures closely associated with reward processing. In sum, in both humans as well as in rodents, T has been found to increase mesolimbic DA activity demonstrated by an increased neural activity during reward anticipation and decreased D2-receptor mediated inhibitory control of that activity.

Figure 5.4 The proposed relationship between T, impulsivity, and antisocial behavior
**Synthesis:** Taken together, T is not directly associated with impulsivity but might aggravate such behaviors when exposed to other risk factors. T might specifically increase risk-taking through increasing reward-sensitivity and dampening punishment sensitivity. This T induced increase of reward-sensitivity is likely due to a higher activity of mesolimbic DA circuitry and decreased auto-inhibitory D2 receptor densities in neocortex and limbic structures. However, although these processes might increase risk-taking and sensation seeking in high T males, they might not directly increase impulsive behavior. Rather, T may aggravate impulsivity and lead to antisocial behavior in the context of other biological and environmental risk factors that can impair self-control. For example, the heightened reward sensitivity may engender deliberate risk-taking and sensation seeking in subjects with adequate self-control but may also engender impetuous risk-taking and reckless thrill-seeking in those who are incapable of controlling strong tendencies and drives. These interactions are schematized in figure 5.4. The modulatory effect of several biological risk-factors such as serotonin, PFC, and HPA-axis dysregulation, and environmental risk-factors such as abuse, neglect, and rejection on the T-behavior link are discussed further on in this chapter.

**Testosterone and aggression; the rule of might**

The discussion on the role of T in aggression will be different from the other three endophenotypes discussed above because there is more research available. While there have been a remarkable scarcity of reviews or theoretical papers that have examined in depth the role of T in fear, empathy, or impulsivity, and analyzed potential mechanisms of action, there have been a number of papers published that comprehensively discuss the role of T in aggression (e.g., Archer, 1991, 2006; Book et al., 2001; Carré et al., 2011; Hönekopp and Watson, 2011; Ramírez, 2003; Terburg et al., 2009; Yildirim and Derksen, 2012b). However, aggression is often divided into two forms; reactive and instrumental (Merk et al., 2005), and nearly all papers that describe the role of T in aggression focus on reactive or “provoked” aggression. In contrast to reactive aggression, which is a “hotheaded” aggressive reaction to frustration or provocation, instrumental aggression is often “cold-blooded” and driven by some future reward-anticipation (i.e., in order to obtain materials, increase status, and satisfy needs) (Merk et al., 2005).

As discussed, a surge of T in response to social threat or challenge facilitates vigor, assertiveness, and dominance and might lead to aggression
whenever provoked by a male conspecific (Archer, 2006; Batrinos, 2012; Chichinadze et al., 2012; Geniole et al., 2013). For example, a higher basal T level or a stronger T increase to social challenge promotes a confrontational style whereby the individual is more likely to react competitively and aggressively to (social) threat (see also figure 5.1) (Carré and Olmsted, 2014; Geniole et al., 2013; Montoya et al., 2012; Terburg et al., 2009; Yildirim and Derksen, 2012a). Interestingly, this surge of T is strongly facilitated by the psychological anticipation of victory and males who have learned to anticipate defeat do not show a strong T response and are as a result less competitive and more likely to avoid confrontation (Chichinadze et al., 2012).

The enhancing effect of T on aggression is likely mediated through an increased vasopressinergic and amygdalar reactivity to social threat, a lower vmPFC regulation of that activity, and an increased DA activity, which together increase vigorous/dominant responding, reduce self-regulation, and might therefore engender aggression in at-risk individuals, namely those with emotional pathologies, prenatal risk factors, and/or an abusive upbringing (see also figure 5.5) (Batrinos, 2012; Martel and Roberts, 2014; Mehta and Beer, 2009; Montoya et al., 2012; Rasri et al., 2008; Van Wingen et al., 2009, 2010). That is, although T may increase aggressive responding, it does not necessarily affect the motivation to react aggressively (Wood et al., 2013), which may be more strongly mediated through other risk-factors that increase hostility, such as abuse or rejection.

In contrast to reactive forms of aggression, the role of T in instrumental aggression is much less discussed and clarified in the literature. Therefore, I will mainly focus on the role of T in instrumental aggression. Different terms are used to indicate forms of instrumental aggression in different populations; in children and adolescents it is often referred to as proactive aggression and in animals it is named predatory aggression.

Instrumental aggression is closely tied to the need to control others and since T is associated with a heightened drive for interpersonal control (dominance) (Mazur and Booth, 1998; Winstok, 2009), it might be expected that instrumental aggression is naturally more prevalent in males. Accordingly, men are significantly more instrumentally aggressive in their interactions with other people ($d = 0.23$) (Murray-Close et al., 2010). Furthermore, even when “sex neutral” measures are used (humiliating, embarrassing, bullying, and verbally forcing others), teenage boys are rated by peers, but not teachers, to show significantly more proactive aggression ($d = 0.46$) (Salmivalli and Nieminen,
Moreover, in another large sample of healthy children between the ages of 11 and 15, proactive aggression was more prevalent in boys compared to girls at all ages (main effect; \(d = 0.17\)), and increased with age exclusively in boys (\(d = 2.68\)) (Fung et al., 2009). These results indicate that proactive aggression is not only more prevalent among boys but also shows significant age-related increases in boys as opposed to girls, which might be related to the increase in T during adolescence (see for example Ramos et al., 1998).

However, another study with 323 children from both a residential treatment center and a pediatric psychopharmacology clinic, reported no gender differences between boys and girls with respect to proactive aggression (Connor et al., 2003). The main difference between the studies that report significant relationships between male gender and proactive aggression (Fung et al., 2009; Salmivalli and Nieminen, 2002) and the one that does not (Connor et al., 2003), might be related to the populations studied. The Connor study used children and adolescents who were referred to a clinic because of disturbing behavioral problems, which is in contrast to the Fung and Salmivalli studies that used healthy children and adolescents. It can be argued that females who are referred to a clinic because of behavioral problems may not represent the typical feminine personality profile of the larger population and may also differ with respect to gonadal hormone levels from healthy girls.

In light of the above findings, it can be expected that a small to moderate effect of gender on instrumental aggression exists in the normal population, with males scoring higher, especially in interpersonal contexts.

**Association testosterone and instrumental aggression:** T levels in childhood or adolescence do not consistently correlate with direct measures of aggression, in most studies being measures of reactive aggression (see for review Ramírez, 2003). Unfortunately, very few studies have examined the relationship between T and instrumental aggression during childhood or adolescence. Van Bokhoven et al. (2006) found that at age 16, salivary T levels were significantly higher (\(d = 0.72\)) in a group of highly proactively aggressive adolescents compared to a control group. Remarkably these results were found only at age 16, which is at the peak of puberty, and not at age 13 or 21 (age-testosterone interaction effect). Thus, T might be especially related to proactive aggression at the peak of puberty when adolescents acquire adult needs and tendencies but do not yet have the self-control and foresight necessary to adaptively deal with them (somewhat resembling adults with PFC dysfunctioning). However, other studies with
adolescents found that higher T levels showed a small to moderate relationship with increased readiness to respond to provocation; physical aggression \( (r = 0.36) \), verbal aggression \( (r = 0.38) \), lack of frustration tolerance \( (r = 0.28) \), but had no effect on unprovoked aggression (Olweus et al., 1980, 1988).

Most studies in adults find significant positive associations between circulating T and instrumental aggression (e.g., Andreu et al., 2006; Dabbs et al., 1995, 2001). Andreu et al. (2006) found that salivary T in male university students was related to both reactive and instrumental aggression. Another study by Dabbs et al. (2001) found that among a group of severely violent murderers, those high in T more often knew their victims and planned their crimes ahead of time, indicating a higher inclination towards callous, premeditated, and instrumental forms of aggression. Additionally, in a study of prison inmates, it was found that higher levels of T are associated with specific crimes involving a high level of combined instrumental and reactive violence, such as rape (3.6 times more prevalent in the high vs. low T group), child molestation (2.6 times more prevalent), homicide (2.1 times more prevalent), and robbery (1.5 times more prevalent). In contrast, lower levels of T were more predictive of less violent and more covert criminal acts such as burglary, theft, and drug-dealing/possession (Dabbs et al., 1995). Other forms of highly instrumentally aggressive acts are sexually motivated assaults such as burglary, theft, and drug-dealing/possession (Dabbs et al., 1995; Giotakos et al., 2004; Rada et al., 1976). Moreover, in a small subset of child-molesters, T correlated with callousness of the crime \( (r = 0.42) \) (Dabbs et al., 2001), indicating a significant relationship with the instrumentality of the crime.

In sum, the relationship between T and instrumental and unprovoked aggression in childhood and adolescence remains to be empirically established and preliminary results are inconsistent, thereby precluding construction of powerful hypotheses. However, in adults, T seems to be consistently related to instrumental forms of aggression, especially in interpersonal contexts.

Other methods of assessing both reactive as well as instrumental aggression are through laboratory tasks such as the revised version of the Point Subtraction Aggression Paradigm (PSAP) (Carré et al., 2010). In this task participants are instructed to keep as many points as possible (which will be traded for money at the end). During the task, participants are provoked by a fictitious partner who steals points from them, and are given the opportunity to steal back points. However, the points which are stolen back are not added to the total score of
the participant, making the behavior a purely aggressive act. Reactive aggressive
that is. In a modified version by Carré et al. (2010), a new condition is added in
which participants are not provoked but do receive a reward (point) for aggressive
acts thereby differentiating between pure forms of instrumentally (not provoked/
reward) and reactively (provoked/no-reward) motivated aggression. The results
indicated that the group who were provoked but did not receive a reward, enjoyed
the task the most and demonstrated a significant increase in salivary T (increase
of 14.58%, \( d = 0.76 \)) which was directly related to the level of reactive aggression
(\( r = 0.34 \)). Importantly, such T dynamics were not observed in men who received
a reward for aggression but were not provoked (i.e., instrumental aggression)
(Carré et al., 2010). These results indicate that T levels may be more strongly
related to reactive forms of aggression than instrumental forms of aggression
and that the pleasure derived from these reactive forms of aggression is directly
related to the increase in T.

A second study which is relevant in this context, measured how T levels
would modulate decision-making on a moral dilemma involving an instrumental
act of aggression (Carney and Mason, 2010). In the task, participants were asked
whether they would kill a human being by pushing him in front of a trolley to
save five others who are about to get hit by the trolley. Individuals high in T were
more willing to make the utilitarian decision of killing a human being if it would
lead to the greater good (\( r = 0.18 \)). Importantly, mean T levels were lowest in
the participants who were unwilling to choose an aggressive option to solve the
moral dilemma. The authors conclude that high T individuals “are able – and
perhaps likely – to approach decision making in a manner that is divorced from
negative affect and disproportionally focused on outcome” (pp. 670), which is
a strong foundation for the emergence of instrumental aggression (Blair, 2006a;
Glenn and Raine, 2009). These laboratory studies indicate that although T may
be related to instrumentally aggressive decision making during hypothetical
moral dilemmas, this does not necessarily translate into real-life instrumental
aggression (Carney and Mason, 2010; Carré et al., 2010).

Testosterone and aggression in the brain: As discussed in the section on T and
fear, T enhances the responsiveness of the amygdala to fearful or angry faces
but decreases orbitofrontal reactivity to the same social cues thereby increasing
competitive, confrontational, and aggressive responding to social threat,
challenge, or provocation (Bos et al., 2013; Derntl et al., 2009; Goetz et al.,
2014; Hermans et al., 2008; Mehta and Beer, 2009; Spielberg et al., 2014a;
Van Honk et al., 2001, 2005; Van Wingen et al., 2009, 2010). In accordance, a higher T responsivity to social provocation was associated with a higher level or reactive aggression (Geniole et al., 2013).

In addition to the dysregulation of limbic emotions, T has also been found to increase mesolimbic DA reactivity (Bos et al., 2012; Hermans et al., 2010; Van Honk et al., 2004b). Research with rodents indicates that mesolimbic DA is crucial for the expression of aggression (Couppis and Kennedy, 2008; Lewis et al., 1994) and that higher levels of DA responsivity increase extreme forms of aggression (Beiderbeck et al., 2013). Also in humans, higher mesolimbic DA activity has been associated with impulsive antisocial behaviors and with externalizing symptomatology (Buckholtz et al., 2010). More specifically, the T induced increase in DA responsivity may boost vigorous responding to reinforcement-predictive cues in general and may thus heighten aggression levels when the individual is hostile and motivated to retaliate aggressively to dominance challenging cues such as provocation, derision, criticism, and rejection, but may not necessarily boost aggression in otherwise non-aggressive individuals.

Also, T also boosts vasopressinergic activity in limbic areas (Rasri et al., 2008), which is associated with increased power-motivation (dominance) and intermale aggression (Compaan et al., 1991; Morrison and Melloni, 2014; Sewards and Sewards, 2003). Indeed, depleting vasopressin suppressed aggressive behaviors of rodents (Ferris and Delville, 1994; Fodor et al., 2014). Vasopressin genotypes have been especially linked to provoked and reactive forms of aggression while showing no relationship to instrumental aggression (Luppino et al., 2014). Therefore, the T mediated boost of vasopressinergic activity may be especially tied to emotional and reactive forms of aggression and spring out of the evolutionary imperative for males to settle territorial and dominance disputes.

However, the mechanism by which T dampens fronto-limbic cross-talk can increase the risk for reactive but also instrumental aggression (Yildirim and Derksen, 2012a). That is, dampening fronto-limbic cross-talk works both ways; the prefrontal system has less regulatory influence over limbic activations thereby increasing the risk for emotional dysregulation and threat-reactivity (reactive aggression) but the limbic system also has less power over prefrontal processes leading to lower emotional input during decision-making and planning. In agreement, T has been found to increase utilitarian decision making when confronted with a moral dilemma (Carney and Mason, 2010) and it is posited that reduced limbic control of prefrontally mediated decision making processes increases the risk of instrumental forms of antisociality and aggression (Van...
Honk and Schutter, 2006; Yildirim and Derksen, 2012a). In addition, T has been found to shift attention from punishment to reward processing, thereby inducing a more instrumental way of decision making that is less dependent on emotional consequences and more focused on outcome (Carney and Mason, 2010; Stanton et al., 2011; Van Honk et al., 2004b).

**Synthesis:** T has been mainly related to reactive, provoked, and emotional forms of aggression and less strongly to instrumental and unprovoked forms. Nonetheless, T dampens fronto-limbic cross-talk and this reduction of connectivity may have a dual-action on neural processing which might increase the risk for both reactive as well as instrumental forms of aggression. That is, in conjunction with the T induced increases of limbic vasopressinergic activity, amygdalar reactivity to threat, and dopaminergic reactivity to reinforcement-predictive cues, a decreased cortical control over emotional processes may specifically increase reactive types of aggression, especially in emotionally dysregulated individuals. Conversely, in conjunction with a fearless temperament (emotional deficiency), the T induced need for interpersonal control and dampening of limbic input into the vmPFC may particularly increase utilitarianism and boost the risk for instrumental forms of aggression. Therefore, the type and degree of emotional deficit may partly influence which type of aggressive behavior is more likely in a high T individual. This modulation is schematized in figure 5.5 and will discussed in more depth in the section on T and primary/secondary psychopathy below.
5.4 Biological Interactions of Testosterone: Primary or Secondary Psychopathy?

**HPA-axis (cortisol) x HPG-axis (testosterone)**

The HPG- and HPA-axis, which respectively regulate T and cortisol (abbreviated as C) secretion, contribute interactively to the interindividual variation in social, emotional, and motivational behavior. As such, a larger variance of dominant, aggressive, antisocial, or psychopathic behavior may be explained when considering interactive rather than main effects of HPA- and HPG-axis activity (see Dabbs et al., 1991; Glenn et al., 2011; Mehta and Josephs, 2010; Terburg et al., 2009; Van Honk and Schutter, 2006). See chapter 3 for an overview of the HPA-axis profiles associated with primary and secondary psychopathy.

First, the HPG- and HPA-axis have mutually regulatory effects on each other such that dynamic fluctuations in one system directly influence the activity of the other (e.g., Bedgood et al., 2014; Viau, 2002). One demonstration of this interdependency is that men with higher HPA-axis activity show a lower T responsivity to social threat, whereas those with lower HPA-axis activity show a stronger T responsivity, which have been associated respectively with social avoidance versus confrontation (Bedgood et al., 2014). Therefore it has been asserted that the HPA- and HPA-axis directly modulate each other’s output in a mutually inhibitory manner (see Van Honk and Schutter, 2006; Viau, 2002).

However, when artificially hypogonadal males (i.e., due to Leuprolide administration) were subsequently administered T compared to placebo, they showed a significantly dampened C secretion but paradoxically also an increased CRH-stimulated ACTH secretion, indicating that the effect of T on the HPA-axis is likely to be exerted peripherally instead of centrally (Rubinow et al., 2005). In fact, since peripherally stimulated C secretion is known to provide feedback autoregulation on HPA-axis activity, this finding may actually suggest that T dampens HPA-axis feedback inhibition and thus prolongs its activation (e.g., Sharma et al., 2014). Accordingly, a number of studies have reported tight coupling between the HPA- and HPG-axis (e.g., Dismukes et al., 2014; Johnson et al., 2014; Welker et al., 2014), such that C and T levels rose and fell together throughout the day (Johnson et al., 2014). Thus, in addition to a
mutually inhibitory effect, there are likely also some mutually excitatory effects (see also Sharma et al., 2014). One possibility is that acute T surges boost HPA-axis activity and facilitate active coping, whereas trait-like increases in T that may arise due to repeated successes, victories, and a higher self-confidence, may eventually dampen HPA-axis activity. Similarly, HPA-axis fluctuations in response to acute stressors may boost T levels and facilitate dominant and competitive responding but prolonged HPA-axis activation, especially when due to inescapable social stressors and especially in males with a lower social status, may ultimately dampen T output and lead to withdrawal and depression.

T and C have differential effects within fronto-limbic regions (Wood, 1996), where they regulate motivational response profiles to both threat and reward (Hermans et al., 2010; Schulkin, 2003; Van Honk et al., 2004a). For example, while T reduces fronto-limbic coupling and may therefore lead to disinhibited behavior as discussed above, C administration increases fronto-limbic coupling which is related to behavioral inhibition (Van Peer et al., 2008). Accordingly, in a large study of male US military veterans, behavioral inhibition was positively associated with C, whereas behavioral activation was positively associated with T (Windle, 1994). In response to these findings, different scholars initially suggested that the prediction of psychopathy is more accurate when in addition to high T, low C is also incorporated in this prediction (Terburg et al., 2009; Van Honk and Schutter, 2006; Yildirim and Derksen, 2012a, 2012b). It was initially argued that high ratios of T to C levels (T>>>C) might lead to a fearless, detached, and dominant pursuit of rewards thereby representing the predatory style of psychopathy.

However, since these initial arguments, a number of contrasting results have been reported that demand a more nuanced explanation. Beginning with community and non-clinical samples, some studies report that T shows positive association with core psychopathic traits, state dominance, and reactive aggression but exclusively when basal C activity is also increased (low basal T: basal C ratio) (Denson et al., 2013; Geniole et al., 2011; Welker et al., 2014). In contrast, other studies in community samples report that T is positively correlated to psychopathic traits but only in the context of low basal C levels or a reduced C reactivity to a social stressor (high basal T: C ratio) (Glenn et al., 2011; Tackett et al., 2014). It has also been reported in youngsters that high T contributes to externalizing behavior in the context of low basal C activity but only in youth
with high levels of disagreeableness and emotional instability, suggesting that personality variables may also crucially modulate the relationship between the T:C ratio and behavior (Tackett et al., 2014). Still, in other samples with subjects of similar demographics as community samples, such as army veterans, high T levels were related to deviant behaviors but these associations were not modulated by C (Mazur and Booth, 2014).

Similarly, in incarcerated and clinical samples, some studies report that high T is related to the interpersonal domain of psychopathy and is characteristic of incarcerated youth but only when basal C activity is additionally increased (Dismukes et al., 2014; Johnson et al., 2014), whereas others report that T is more strongly related to severe conduct disorder, externalizing behavior, and callousness when C levels are low (Popma et al., 2007), or when T and C are uncoupled (Johnson et al., 2014).

In sum, these recent findings suggest that antisocial deviancy and a variety of psychopathic traits are sometimes related to low T:C ratios and other times to high T:C ratios (both in the context of high T levels). In light of the findings regarding HPA-axis functioning in primary and secondary psychopathy as discussed in chapter 3, it might be hypothesized that these divergent findings relate to the various emotional pathologies that may contribute to psychopathic behavior. Emotionally disturbed individuals may be characterized by a high T activity in the context of a more trait-like HPA-axis deregulation (either too low or too high activation patterns) which may particularly contribute to callous hostility, impulsivity, reactive forms of aggression, and secondary forms of psychopathy, whereas emotionally deficient individuals may be characterized by high T activity in the context of a HPA-axis hyporesponsivity to acute stressors, which may particularly contribute to callous insouciance, risk-taking, instrumental aggression, and primary psychopathic traits.

In accordance, several studies have reported that a high coupling of basal T and C activity is related to stressful life events such as childhood abuse and dangerous/potentially traumatic experiences (Bobadilla et al., 2014; Dismukes et al., 2014), suggesting that this pathway may be more characteristic of secondary psychopathy. In contrast, the intensity of HPA-axis reactivity to acute stressors is determined primarily by genetic factors and less by social experiences (Wüst et al., 2004), suggesting that a low HPA-axis responsivity coupled with high T may particularly characterize those with a strong genetic foundation for antisocial behavior such as observed in primary psychopathy. See figure 5.6 for a schematic representation of these interactions.
Serotonin x testosterone interactions

Dynamic interactions between monoamines such as serotonin or dopamine and gonadal/adrenal hormones constitute the building blocks of our deepest and most rudimentary drives and affects which we are born with or develop very early in life, also termed ‘temperament’. While hormones regulate central motive states (i.e., the readiness to respond to certain events in a particular way) and originate in hypothalamic-pituitary (HP) regions, monoaminergic neurotransmitters directly potentiate or de-potentiate neural processing in corresponding networks and spring from deep seated brainstem nuclei.

Baseline T sensitizes the motivation to pursue novel rewards and respond dominantly to social threat while concomitantly desensitizing social sensitivity (Schulkin, 2003, 2011; Smeets et al., 2009; Van Honk et al., 2004a, 2004b; Van Honk and Schutter, 2006; Von Dawans et al., 2012; Yildirim and Derksen, 2012a, 2012b, 2013). However, rather than directly inciting pathological callousness, overt aggression, or dysfunctional impulsivity, T is likely to increase these traits only in the context of other, more primary genetic and environmental risk-factors, namely those that can lead to emotional pathology. In other words, when the core psychopathic personality structure is additionally infused with a competitive, reward-seeking, and self-aggrandizing motive state, as associated with high T levels/reactivity, the risk for severe forms of antisocial behavior and aggression may be substantially heightened (Bos et al., 2012; Kuhn et al., 2010; Montoya et al., 2012; Sato et al., 2008; Terburg et al., 2009; Van Honk and Schutter, 2006; Yildirim and Derksen, 2012a, 2012b). Serotonin is closely involved in emotional processing and its various extremes (hyperstability vs. deficiency) have been asserted to play a principal role in the development of both primary and secondary psychopathy (see chapter 3 for extensive discussion). Serotonin may thus importantly modulate the impact of T on behavior.

As extensively explained in chapter 3, the primary role of serotonin in both mind and body is the maintenance of a homeostatic operating range in physiological processes necessary for optimal growth, development, and well-being of psychological, neural, and general physiological processes. Plasticity genotypes that decrease stability of synaptic serotonin, such as those leading to a lower serotonin re-uptake, aggravate homeostatic disruptions in response to stress-induced neurotransmission. If this homeostatic disruption is prolonged (i.e., lacking the opportunity for stress-recovery) and occurs in the developing brain, it can have life-long desensitizing effects on the serotonin circuitry, ultimately
leading to morphological changes to the system (desensitization of postsynaptic receptor sites/downregulation of serotonin synthesis etc.) and altering brain development. These processes impact in particular on right vmPFC functionality and predispose to trait-like emotional dysregulation, thereby also increasing the risk for life-course persistent neuroticism (e.g., hostility, anhedonia) and secondary psychopathic/reactive aggressive phenotypes, (Yildirim and Derksen, 2013).

Conversely, without transient homeostatic disruptions to serotonergic activity in response to stressful events, physiological processes would become disconnected from external events. That is, synergistic or additive genetic contributions that facilitate the regulatory functionality of serotonin by stabilizing its continuous turnover, output, synaptic receptivity, and re-uptake, would effectively stabilize homeostatic autoregulations and dampen internal fluctuations to salient events (Yildirim and Derksen, 2013). Such a neurophysiological profile would promote a strong psychophysiological equilibrium that is resistant to acute stressors (fearless) and prevent allostatic overload or morphological alterations of the system to prolonged stressors (emotionally resilient). In extreme cases multiple serotonin stabilizing genotypes could substantially dampen emotional activations below the threshold needed to respond adequately to aversive (socio) emotional events such as threat, punishment, and the suffering of others, thus provoking a certain “emotional insouciance” and contributing to the etiology of primary psychopathic phenotypes (see Yildirim and Derksen, 2013).

Since the effects of deficient serotonin parallel those of high T, namely leading to amygdalar hyperreactivity and vmPFC dysfunctionality, it might be expected that both risk-factors could additively or synergistically contribute to impulsive and aggressive behavior. Indeed, when serotonergic functioning is dampened, high T individuals are more likely to act out in impulsive and antisocial ways (Birger et al., 2003; Higley et al., 1996; Kuepper et al., 2010). For example, it was found that the interaction between low serotonin/high T predicted impulsivity in reactive aggressive responding more accurately than either factor alone (Kuepper et al., 2010). Furthermore, Higley et al. (1996) found in a group of adolescent primates, that subjects with low serotonin metabolism, exhibited high levels of impulsivity indicated by an increased amount of long leaps from tree to tree compared to more safe and shorter leaps (long leap ratio). However this ratio was synergistically increased if the individual also exhibited high T levels.

These results suggest that T may especially aggravate antisocial behavior.
The role of testosterone and aggression in secondary psychopathy because it is associated with a similar neural processing profile. However, since T dampens fronto-limbic cross-talk, there may in fact be two consequences; lower emotional regulation as discussed above but also lower limbic input into the PFC during goal-directed behavior. Therefore, in the case of a serotonin-mediated amygdalar hyporesponsivity, as observed in primary psychopathy, high T may further dampen the bottom-up modulation of PFC processes by limbic structures leading to decisions and behavioral tendencies that lack consideration for socio-emotional consequences, ultimately increasing the risk for instrumental aggression (Carney and Mason, 2010; Van Honk and Schutter, 2006; Yildirim and Derksen, 2012b, 2013). The effect of T on fronto-limbic cross-talk may thus partly explain why reactive and instrumental aggression co-occur so frequently and why it is difficult to properly separate these subtypes (Bushman and Anderson, 2001).

A potential genetic risk marker for psychopathic development and which interacts with T, is the gene encoding for the serotonin transporter (5HTTLPR). The difference in the three different polymorphisms (s/s, s/l, l/l) of 5HTTLPR is related to variations in serotonergic functionality, with male l-homozygotes having a higher serotonergic stability and emotional resilience independent of social experiences (Homberg and Lesch, 2011; Manuck et al., 2004; Reist et al., 2001; Yildirim and Derksen, 2013). Interestingly, it has been reported that 5HTTLPR polymorphisms strongly interact with T in the modulation of emotional processing (Josephs et al., 2011). That is, although s-allele carriers showed higher HPA-axis reactivity compared to l-homozygotes, the differences became substantially greater when T levels were included as a covariate (Josephs et al., 2011). That is, s-homozygotes showed a positive association between T and HPA-axis reactivity, suggesting that T may increase the risk for emotional disturbances in s-homozygotes and probably also the risk for secondary psychopathic development. Conversely, the more resilient l-homozygotes showed a negative association between T and cortisol reactivity, suggesting that T may additively or synergistically increase the risk for emotional deficiency in l-homozygotes and contribute to primary psychopathic development. These results suggest that T may aggravate both extremes of emotional reactivity depending on the underlying serotonergic vulnerability. However, recent research has suggested that T treatment increases the surface expression of the 5HTT in limbic regions thereby suggesting that T may in fact act synergistically with lₐ-homozygosity to stabilize serotonergic functioning and enhance emotional resiliency (Kranz et al., 2014). Conversely, the synergism between serotonin
deficiency and high T on impulsivity and aggression may be especially mediated through combined excitatory effects on emotional reactivity and negative effects on fronto-limbic coupling and might have a stronger dopaminergic basis.

In sum, individuals with serotonergic extremes (hyperstability or deficiency) and corresponding emotional pathologies (deficiency or disturbance) may show a greater risk for psychopathic development and higher rates of aggression, impulsivity, and callousness if T is also increased. Nonetheless, without such serotonergic disturbances, high T levels/reactivity may not necessarily increase the risk for psychopathic development. Therefore, T is likely modulatory of the severity of primary and secondary psychopathy rather than a necessary risk-factor (see figure 5.6). As will be discussed below, in individuals with protective factors such as a good self-regulation, strong self-control, prosocial

Figure 5.6 The proposed relationship between T, serotonin, HPA-axis, and life stressors in the prediction of primary and secondary psychopathy.
environment, and secure attachment, high T may actually predispose towards admirable and prosocial traits such as honesty, fairness, and altruism.

5.5 Interactions Testosterone and Environment: Antisocial or Prosocial?

The foregoing discussion might erroneously strengthen the already popular idea that T is inherently an ‘evil’ hormone that leads to greater selfishness, callousness, and hedonism. However, the ultimate effect of any brain chemical on psychology or behavior is naturally shaped by the environment to which that brain must adapt itself. As repeatedly stated throughout this chapter, T in and of itself is neither a necessary nor sufficient risk-factor for the full expression of any of the psychopathic traits discussed but might worsen their severity when other, more primary risk-factors are present. However, what is much less known is that T also actively boosts prosociality, assertiveness, leadership, honesty, fair bargaining, straightforwardness, and altruism when the environment is conducive (Boksem et al., 2013; Booth et al., 1989; Dabbs and Dabbs, 2000; Diekhof et al., 2014; Eisenegger et al., 2010; Kret and De Dreu, 2013; Lindman et al., 1987; Rowe et al., 2004; Van Honk et al., 2011b; Wibral et al., 2012). So instead of judging T as being an antisocial hormone, it is better to see it as a ‘social plasticity hormone’—that is, it increases the malleability of neural pathways implicated in social behavior and may thus equally well lead to prosocial personality development given a secure, loving, and resourceful environment. Below it is shortly described how varying environments may shape the developmental effect of T on social behavior.

Socio-biological interactions with testosterone

Children who are ill-treated during their earliest years and as a result develop insecure attachments to their caretakers are more likely to develop impulsivity and callousness and are thus at higher risk for becoming antisocial, delinquent, and psychopathic than securely attached children (e.g., Aguilar et al., 2000; Bowlby, 1944; Greenberg et al., 1993; Speltz et al., 1999; Van Ijzendoorn, 1997). Importantly, when controlled for the security of the parent-child attachment
relationship, the association between T and antisocial behavior in community samples becomes non-significant, demonstrating that the attachment relationship may crucially modulate the T-antisocial behavior link (Booth et al., 2003; Fang et al., 2009; Updegraff et al., 2006). This experience-dependent relationship between T and antisocial behavior can be partly explained through socio-biological processes interacting with fetal/circulating T.

First, biological maturation of neural circuitry implicated in socio-emotional behavior, such as the vmPFC, is not complete at birth and is therefore strongly dependent on environmental factors, especially social experiences (Schore, 2001a, 2001b). Early relational trauma leading to insecure attachment patterns has been suggested to disturb the healthy maturation of neural networks underlying empathy and self-control (Schore, 2001a, 2001b). Accordingly, children who are chronically abused or neglected show impaired functionality of the OFC (Chugani et al., 2001), and reduced gray matter volumes of this structure in adolescence and adulthood (Edmiston et al., 2011; Hanson et al., 2010; Thomaes et al., 2010). The destructive effect of relational trauma on the vmPFC might interact with the T induced alterations in the maturation and functionality of this structure (Lombardo et al., 2012b; Mehta and Beer, 2009; Van Wingen et al., 2009, 2010) and result in a more severe expression of callousness, aggression, and impulsivity than either factor alone.

Second, the early attachment relationship may also impact on the T-behavior link through its effect on the functioning of neurochemical and endocrinological pathways. Both serotonergic and HPA-axis functioning have been discussed as being important modulators of the T-behavior pathway, and accordingly, the maturation and functionality of both systems is strongly influenced by early attachment experiences (see chapter 3 for extensive discussion). Moreover, reduced vmPFC functionality can be partly explained through the effect that negative social experiences have on serotonergic neurochemistry (e.g., Passamonti et al., 2006; Schore, 2001a, 2001b; Siever et al., 1999; Soloff et al., 2000). Preliminary reports indicate that parenting styles and the parent-child relationship relate directly to reduced responsivity of the serotonergic circuitry throughout childhood (Crowell et al., 2008; Pine et al., 1996). Furthermore, high levels of social stress arising out of neglect and abuse during the first years of life may lastingly deregulate the set-point and activity of the HPA-axis throughout life (Bruce et al., 2009; Diamond and Fagundes, 2010; Quevedo et al., 2012; Van der Vegt et al., 2009; Wismer Fries et al., 2008, but see chapter 3 for discussion). As stated in chapter 3, these experience-dependent alterations of the brain may
The role of testosterone

not be classified necessarily as being pathological when seen through the lens of environmental adaptation. These socio-emotional alterations in response to a harsh and unforgiving environment may actually be an evolutionary adaptive process enabling the individual to relinquish the restraints of morality and attachment and fend vigorously for himself in a world where he feels that others cannot be trusted and where prosociality and cooperation are likely to be taken advantage of.

Finally, T may modulate the impact of oxytocin on social behavior. Oxytocin is an important hormone that acts as a neurotransmitter, is strongly impacted by early social experiences, and modulates both brain maturation and social functioning later in life. Oxytocin is related to attachment motivation, growth-promotion of the PFC (in particular the mPFC), and the development of social sensitivity, empathy, trust, and human connectedness (Carter, 1998; Üvnas-Moberg, 2003). Different studies with rodents indicate that the trait-like production of oxytocin and its receptors in the mPFC, and therefore its lifelong effects on social behavior, may be especially vulnerable to postnatal experiences (Champagne et al., 2001; Francis et al., 2002). In humans, there have been associational studies finding that oxytocinergic responsivity to social cues is associated with early caregiving conditions (Wismer Fries et al., 2005), and adult attachment styles (Strathearn et al., 2009). Since oxytocinergic mechanisms are desensitized by T (Francis et al., 2002; Johnson et al., 1991), a double hit dysregulation of oxytocinergic functioning because of high levels of fetal/circulating T combined with insecure attachment is likely to have a synergistic effect on socio-emotional functioning. In this sense, males may be more vulnerable to negative social experiences in the development of empathy and interpersonal connectedness (e.g., Singer et al., 2006).

Nevertheless, when attachment is successful and the child is raised in a positive environment with sufficient levels of sensitivity and love, T may mold the oxytocinergic circuitry in such ways that it eventually biases focus away from what is good for another individual or for oneself and towards what is good for the group (Kret and De Dreu, 2013). The human tendency to support and benefit fellow group members and to show an increased hostility towards outsiders (parochialism), even at potential costs for oneself such as death or mutilation (altruism), is a natural way to ensure group-survival, especially in times of war and competition (Choi and Bowles, 2007; Diekhof et al., 2014).
Accordingly, high T levels are associated to a lower punishment of in-group members but a higher hostility towards out-group members, especially when there is a competition between both (Diekhof et al., 2014). Diekhof and colleagues conclude that T “may promote group coherence in the face of external threat, even against the urge to selfishly maximize personal reward” (abstract). So the alterations to the oxytocinergic circuitry and corresponding social insensitivity as engendered by T may also enable these individuals to make hard, utilitarian, and sometimes aggressive choices against out-group members but only in order to protect the in-group and mainly when there is a potential threat from these outsiders. This is also in line with the finding that empathy processes in men are mainly biased towards fair-players but not towards unfair players (Singer et al., 2006), suggesting that males may be more inclined to select whom they will protect and care for and that this selection is partly based on the other’s ability to cooperate. In sum, T also facilitates protective behavior and ensures that males are willing to protect their families, community, and trusted in-group members against external threats even at the cost of their own needs and even in the face of potential harm to oneself.

In this sense, attachment processes may facilitate the evolving ability to identify with one’s community or the dominant in-group. When attachment processes are facilitated by a sensitive and caring environment, the male child may learn to connect emotionally to others and with time learn to care and protect his in-group members. However, when attachment processes go awry, the child may not learn to trust others, not even members of his dominant culture and he may be faster to judge others as being unfair and hostile, which may lead to social detachment and downsizing the number of individuals whom he regards as being trustworthy. These individuals may still be able to form attachments but only to a very few others while the rest is being regarded as outsiders and potential threats, thereby leading to a greater hostility and aggression towards others in general. Extreme attachment disturbances may even totally abolish social identification and thus effectively reduce the ‘in-group’ to only one member: themselves. Also, since primary psychopaths are detached by nature, due to their emotional deficiencies, studying these experience-dependent influences on social behavior may be especially relevant for understanding secondary psychopathic development. Indeed, while primary psychopaths show a profound inability for attachment from birth on, secondary psychopaths are likely born with a greater plasticity of socio-emotional pathways but have learned to distrust and distance others in order to protect themselves from betrayal and pain.
Socio-psychological interactions with testosterone

Children who are deficient in impulse control or empathy due to insecure attachment patterns and other negative social experiences, display higher levels of aggression and impulsivity than children without these risk factors (Lahey et al., 2003). As a consequence, these problematic youngsters are more likely to be rejected or bullied by peers, victimized in different settings, rejected by teachers, expelled from school, and are more likely to be abused by parents (Briscoe-Smith and Hinshaw, 2006; Chapple et al., 2005; Cook et al., 2010; Dodge, 2003; Gottfredson and Hirschi, 1990; Holmberg and Hjern, 2008; Kokkinos and Panayiotou, 2004; Shea and Wiener, 2003; Turner et al., 2010). In a sense, throughout their formative years, these youngsters are repeatedly rejected by their community at large (Shea and Wiener, 2003).

Throughout childhood, youngsters develop “multidimensional, stable and unique patterns of processing social stimuli, which form the working component of personality” (pp. 225, Dodge, 2003) and strongly determine social adjustment (Crick and Dodge, 1994). Abuse by caregivers and repeated rejections during this critical period can result in biased social information processing patterns centered around a hostile and uncaring worldview (Dodge et al., 2001, 2003). Such rejected individuals will often develop hypersensitivity to potential cues of further rejection or derision and react fiercely to these perceived provocations (Crick and Dodge, 1994; Dodge et al., 2003). With advancing age, social information processing patterns become self-perpetuating thereby evolving in stable traits and personality patterns (Dodge, 2003; Dodge and Price, 1994).

Somewhat similarly, T also increases sensitivity to social threat and engenders assertive and dominant responding to perceived injustices and slights (Archer, 2006; Bos et al., 2012; Van Honk and Schutter, 2007b; Yildirim and Derksen, 2012). Because T incites a confrontational response to social threat, hostile attributional biases may be more likely to result in dominant and aggressive reactions in high T individuals. For example, southern Americans were quicker to perceive slights and respond aggressively than northerners which was directly related to stronger increases in both C and T in response to the perceived slights (Nisbett and Cohen, 1996). Furthermore, boys demonstrate stronger hostile attributional biases, more aggressive response generation patterns, and greater confidence in aggressing and its consequences compared to girls (Coie and Dodge, 1998).

In addition, T heightens motivation towards achieving and maintaining
a high social status with the specific strategy (prosocial vs. antisocial) being
dependent on social reinforcement of behaviors that grant the desired social
status (Boksem et al., 2013; Eisenegger et al., 2010; Mazur and Booth, 1998;
Van Honk et al., 2011b). The aforementioned psychological processes which
stem from mental models of the world as harsh and hostile can bias attention
away from prosocial behaviors and towards more antisocial means to achieve and
protect the status quo, whereas in environments where it is in one’s best interest
to cooperate with others, T may induce fair bargaining behaviors to protect the
status quo (Boksem et al., 2013; Dabbs and Dabbs, 2000; Eisenegger et al.,
2010; Van Honk et al., 2011b). For example, administration of T decreased trust
but increased generosity when repaying trust (Boksem et al., 2013). Similarly,
Boksem et al. (2013) conclude that “testosterone may mediate different types of
status-seeking behavior. It may increase competitive, potentially aggressive, and
antisocial behavior when social challenges and threats (i.e., abuse of trust and
betrayal) need to be considered; however, it may promote prosocial behavior in
the absence of these threats, when high status and good reputation may be best
served by prosocial behavior” (abstract).

Repeated rejections by peers, authority figures (i.e., teachers), and abuse
by parents is predictive of rebellion towards conventional social norms and
values, and involvement and affiliation with other deviant peers (Agnew and
Brezina, 1997; Dishion et al., 1991; Lochman et al., 2010; Simons et al., 2001).
Deviant peer groups, such as street gangs, often reinforce shared activities such as
aggressive and delinquent acts through mutual respect (Burgess and Akers, 1966;
Lochman et al., 2010; Patterson et al., 2000). Indeed, as discussed above, while
T may increase in-group protection, it is dependent on who is being regarded
as being part of one’s in-group. If high T individuals befriend deviant peers and
form bonds with such individuals, they may be more likely to conform to the
social norms and values of these youngsters, which are centered around taking
care of the group while rebelling and aggressing against dominant society (i.e.,
street mentality). Interestingly, Rowe et al. (2004) have found that T is related
to antisocial behaviors only in boys with deviant peers, whereas it is related to
leadership in boys with non-deviant peers, supporting the hypothesis that high
T is associated with socially valued characteristics in prosocial environments.

Finally, socioeconomic influences can also modulate the T-behavior
pathway. Research has supported that T mainly relates to delinquency and
antisocial behavior in the lower socioeconomic classes, whereas it shows no
associations with antisocial behavior in the higher socioeconomic classes (Aromäki
et al., 1999; Dabbs and Morris, 1990; Mazur, 1995). It has been suggested and supported that T is more strongly related to competitive achievement motivation and social dominance in the higher socio-economic classes (Dabbs and Morris, 1990). For example, T has been positively associated with socially desirable traits such as social dominance (Booth et al., 1989; Christiansen and Knussmann, 1987; Ehrenkranz et al., 1974; Lindman et al., 1987), leadership qualities (Rowe et al., 2004), fair bargaining behaviors (Eisenegger et al., 2010), social assertiveness (Lindman et al., 1987), and competitiveness (Booth et al., 1989), behaviors that are more likely to be observed in high T individuals from the higher socioeconomic classes.
Socioeconomic variables can strongly impact on psychological processes. For example, different studies have found that lower socioeconomic status was related to a higher incidence of hostile attributional biases in children (Schultz and Shaw, 2003; Weiss et al., 1992). As an explanation, the authors assert that the higher levels of subjective stress and lower levels of support and resources experienced by parents in lower socioeconomic statuses can increase harsh or impatient caregiving thereby increasing the risk for hostility and anger in offspring (Schultz and Shaw, 2003). For example, socioeconomic status predicted maternal depression, which was directly related to biased social information-processing patterns and conduct problems in children (Schultz and Shaw, 2003). See figure 5.7 for an overview of the interactions between T and environment and how these interactions may influence the emergence of prosocial or antisocial personality patterns.
CHAPTER 6
FUTURE DIRECTIONS AND CRITICAL COMMENTS
The Eternal Dance between Biology and Psychology
Now that I have attempted to elucidate in more detail the complex web of social and biological risk-factors that can interactively contribute to psychopathic development, it is important to take a critical look at the constructed hypotheses in this book. I have first discussed and re-structured the conceptualization of psychopathy into two continua (primary and secondary) and then made an attempt at clarifying the various causal mechanisms involved. However, there are still a number of questions that need to be answered before we gain a more complete understanding of both primary and secondary psychopathy.

To discuss how future research could benefit our understanding of the psychopathy construct and the different social, biological, and psychological processes that contribute to its etiology, I have divided this chapter into three separate parts; (1) The discussion of venues for research in order to improve the conceptualization and understanding of psychopathy as a clinical condition. (2) Discussion of the various problems that need to be overcome to gain a better understanding of how biology may contribute to psychopathology but also how these biological risks are also influenced by environmental factors. Here, I will also mention the ‘neglected’ system, namely the noradrenergic system, which is currently scarcely researched despite its paramount role in adequate stress responsivity, emotional processing, and autonomic reactivity. (3) In de final
section of this chapter I will also provide a critical commentary on contemporary ways of viewing the biology-psychology link and discuss what is still missing to understand the exact role of biological or genetic alterations in the development of complex clinical conditions such as psychopathy. In order to gain a greater understanding of clinical conditions we should start incorporating the role of identity in our socio-biological explanations.

### 6.1 Future Directions on the Conceptualization of Psychopathy

There are still a number of questions that need to be answered before we gain a more complete understanding of both primary and secondary psychopathy. We can divide these questions into three main categories; (1) clarifying sources of homogeneity and heterogeneity between psychopathic subsamples, (2) further elucidating biological/psychological risk and protective factors, (3) validating the relevance of primary and secondary psychopathy across ethnicity, culture, and gender.

First, there is a need to define the boundaries of the psychopathy construct by clarifying which features and traits are integral to primary and secondary psychopathy (i.e., emotional deficiency vs. emotional disturbance), which traits are more likely to emerge in individuals with such a personality pattern (e.g., instrumental vs. reactive antisociality), and which traits show heterogeneity (e.g., self-control vs. affect instability). Current debates focus mainly on whether adaptive features such as low neuroticism belong in the operationalization of psychopathy (see Patrick, 2006; Skeem et al., 2011), whether psychopaths are impulsive, hostile, and aggressive by definition (see Patrick, 2006; Poythress and Hall, 2011), and whether neurotic and fearful individuals should be eligible for the diagnosis of psychopathy (Skeem et al., 2011). I have already provided some answers to these questions in chapter 2. That is, one way of reconciling inconsistent data on the external correlates of psychopathy is to divide this heterogeneous group into more homogeneous clusters that show divergent etiological pathways and therefore also diverge regarding phenotypical expressions. Within this framework it is understandable that if primary and secondary psychopaths share the same diagnosis due to similar PCL-R profiles, that external correlates to neuroticism, hostility, and impulsivity would indeed show inconsistency because
these are precisely the constructs on which these groups have been found to diverge.

Another source of heated debate is whether antisociality, especially behavior that is punishable by law (i.e., criminality), is central to primary psychopathy or “consequential” to core features such as fearlessness (Hare and Neumann, 2010; Skeem and Cooke, 2010a, 2010b). For example, using structural equation modeling Cooke and Michie (2001) concluded that antisocial behavior is best viewed as a likely consequence of psychopathy rather than part of the inherent personality structure. Indeed, as put forward in this chapter 1, the PCL-R indexes a much more maladjusted and criminal individual than was initially intended by Cleckley (see also Skeem and Cooke, 2010a, 2010b). Furthermore, since the dominant tool to assess psychopathy, the PCL-R, includes both emotional detachment and social deviance, it is expected that included individuals would indeed show criminal behaviors (i.e., tautological error). As proposed in chapter 2, we should begin focusing more on primary psychopaths who show high factor 1, PPI-I, and boldness scores but vary regarding levels of social deviancy. In so doing we would be better able to index the entire range of possible psychopathic phenotypes rather than including only those who are persistently criminal or more generally disinhibited. Studies that compare primary psychopathic subgroups regarding psychological constructs (e.g., disinhibition, executive functioning, impulsivity, risk-taking, conscientiousness) are highly needed.

Second, we need to know which biological and psychological mechanisms may account for the variability observed within the primary and secondary psychopathic group more specifically. It is particularly important to examine whether the more adapted primary psychopaths show differences in neurobiology or mentality that protects them from developing antisocial and criminal behaviors (see Gao and Raine, 2010 for suggestions). Although I have discussed in detail the biological basis on which primary and secondary psychopathy might diverge in chapter 2 and 3, these hypotheses are still based on preliminary evidence and more research is direly needed. There is a particular urgency to uncover the biological and psychological mechanisms that might serve as risk or protective factors in the various psychopathic subsamples. This might greatly facilitate the development of new interventions aimed at reducing violence and antisocial behavior in primary psychopathy and increasing attachment, peace, and understanding in secondary psychopathy.

Third, contemporary explanations on the expression and etiology of psychopathy are exclusively extrapolated from North American and Western
European males. It is thus unclear how these findings would generalize to other ethnicities or cultures (Sullivan and Kosson, 2006). Hare (1991) also acknowledges that differences exist in the way psychopathy manifests across different ethnic and cultural groups and advises against the use of the PCL-R in non-validated samples (e.g., in Asian, South American, African countries). A first and foremost step would be validating the relevance of psychopathy instruments in those continents since the use of these instruments outside North America and Europe is limited and thus research regarding specific manifestations is currently very scarce. For example, one study found that Brazilian inmates showed much lower PCL-R scores than North American samples and rather than the cutoff score of 30, the researchers reported that psychopathy could be reliably identified using a cutoff score of only 23 (Morana et al., 2005). This finding in a Brazilian prison sample also attests to the somehow greater prevalence of psychopathic traits in the most individualized countries such as North America and Europe.

Thus, another point of importance is to clarify the reason behind the higher prevalence of psychopathic traits in North American and European offender samples compared to the rest of the world (Sullivan and Kosson, 2006). For example, among 499 Inuit Eskimo’s only one was identified as exhibiting personality features coherent with the Western construct of psychopathy, which is a prevalence of about 0.2% (Murphy, 1976). Furthermore, the prevalence of antisocial personality traits in different villages in Taiwan is around 0.3% (Hwu et al., 1989). In contrast, a classification of psychopathy may apply to about 0.6 – 1.2% of Western society (Coid et al., 2009, 2012). In other words, the anonymity, lack of social control, social inequality, emphasis on personal control, competitive atmosphere, and hierarchical structure of increasingly individualized societies might more readily incite psychopathic development at lower levels of genetic risk or that psychopaths are more likely to thrive in such a society (Lykken, 1995; Stout, 2006). Although the scientific community has primarily emphasized biological and psychological processes as an explanation for psychopathy, it would be interesting to know how cultural norms and values influence the development of psychopathic traits in biologically at-risk individuals (e.g., individualism vs. collectivism) (Stout, 2006). Thus, we want to know whether psychopathic traits thrive and develop more readily in certain societies as compared to others (e.g., collectivism vs. individualism, conflict vs. no-conflict zones). See Sullivan and Kosson (2006), Skeem et al. (2003a), and Stout (2006) for interesting reviews and discussions on the topic of psychopathy and ethnicity/culture.
Similarly, most of the research on psychopathy has been conducted in males and it is currently unclear whether these findings can be generalized to women. Preliminary studies have already indicated that similar to males, primary and secondary psychopathy can also be identified in females (Hicks et al., 2010). Female secondary psychopaths were also characterized by higher levels of negative emotionality and lower levels of behavioral constraint compared to the primary psychopathic females. Contrastingly, primary psychopathic females showed few distinguishing personality features compared to controls (i.e., female prisoners low on psychopathy) but were “prolific criminals especially regarding nonviolent crimes, and exhibited relatively few mental health problems despite substantial exposure to traumatic events” (abstract). Nonetheless, women are suggested to express psychopathy differently (i.e., histrionic/borderline in women versus narcissistic/antisocial in men) and psychopathic traits in women also show a different pattern of external correlations compared to men (Skeem et al., 2011; Sprague et al., 2012; Verona et al., 2012). For example, in addition to externalizing dynamics and other-directed aggression, females with psychopathic traits show higher levels of internalizing psychopathology, BPD traits, impulsivity, and inward-directed aggression, whereas males show a higher level of the narcissistic and ASPD traits of psychopathy (Blonigen et al., 2005; Cale and Lilienfeld, 2002; Sadegh et al., 2011; Tsang et al., 2015; Verona and Vitale, 2006; Verona et al., 2012; Wynn et al., 2012). More research is needed to clarify if primary and secondary forms of psychopathy manifest differently in females and whether the factor structure and external correlations of psychopathy instruments differs across gender (Skeem et al., 2011).

Taken together, psychopathy is currently still a hotly debated topic and there are still disagreements on its conceptualization and etiology. In this book I have tried to communicate the importance of differentiating primary and secondary psychopathy if we are to gain a greater understanding of these conditions. In addition, psychopathy as currently defined is a condition which is most prevalent in males from individualized countries and it is important to know whether these findings also generalize to women and to other parts of the world or that cultural and gender difference exist in the expression of psychopathic traits.
6.2 Future Directions on the Neurobiology of Psychopathy

**Testosterone**

The exact mechanisms driving the correlation between biology and psychology are largely unknown and it is therefore paramount to exhibit intellectual modesty about the fact or direction of causality (Miller, 2010). In the last decade there has arisen the ingrained belief that psychological events are driven by, and rooted in biological events, rather than the other way around (Miller, 2010). This belief has restricted us in our thinking and this is apparent in the vast amount of literature describing the “biological basis of…” or “neural substrate for…”, and only a subset of papers which discuss the influence of psychological processes on biological events.

In the case of testosterone (abbreviated as T), very little research has been done to determine how psychological events influence circulating levels of free and total T. Although it is generally regarded as a “background fact” that individuals differ constitutionally or naturally in their basal circulating T levels, it has been indicated in research that genetic factors explain approximately 40% of interindividual variation in T levels (Meilke et al., 1987). The remaining variation is explained by environmental factors, underscoring the importance of studying socially induced long lasting increases or decreases in T levels. Therefore, it is important to know whether certain psychological processes leading to low empathy also affect T production? For example, it has been known that T not only influences behavior, but that certain behaviors (aggression, sex, submission) and social circumstances (social stress, competitive imperatives, feelings of victory or defeat) also influences circulating T levels (Mazur and Booth, 1998; Archer, 2006). Since T is strongly activated by competition and social provocation, growing up in a competitive and socially stressful environment, where one has to be on-guard at all times for possible threats and counteract in an aggressive manner to self-protect, may induce both long-lasting changes in T levels and reactivity, synchronously increase threat reactivity, aggression, dominance, and dampen affective empathy, thereby explaining in part the found correlation between circulating T and these psychological and behavioral constructs. In a
similar vein, social stress, -isolation, and -uncertainty during pregnancy (which many women experience in our competitive society), can induce long lasting increases in T levels and thus T exposure to the fetus (Sayegh et al., 1990; Roelofs et al., 2010), but may also decrease maternal sensitivity to the infant postnatally, precluding a healthy vmPFC maturation and socio-emotional development and thereby impairing empathetic concern (Schore, 2001b). In other words, the negative effect of fetal T on empathetic qualities may be partly mediated by the level of stress and competition that the mother experiences during pregnancy.

Therefore, it is paramount to know whether different positive and negative social experiences, beyond winning and losing in competition, can induce both short-term and long lasting changes in circulating T levels? Another interesting approach would be longitudinal research in children that have been abused or have experienced trauma to see how the hormonal levels of these children are affected in the long-term. Also important is to determine how rejection, social discrimination, and living in low SES can influence T levels or the T-antisocial behavior relationship. These study designs would shed more light on the strength of influence T has on behavior and in how far it directly influences behavior or is being influenced itself by environmental, social, and psychological influences. Finally, another question relevant in this context is whether there are personality differences in children that have different endocrinological reactions to the same sort of experiences. Some children may react with long-lasting increases in T levels (in reaction to feeling challenged) and externalizing pathology, while other children faced with the same experiences may react with a decrease in T-levels (in reaction to feeling victimized and helpless) and internalizing pathology.

Second, although the organizational–activational hypothesis has been supported by a great body of research in animals, studies that examine the co-impact of both fetal and circulating T on behavioral measures are virtually nonexistent in the human literature, probably because of the difficulty of collecting both measures from the same person. It is of dire importance to uncover how fetal and circulating T co-influence neurobiology and ultimately behavior. Future studies may profit if they include both circulating T (preferably measured through blood draws) and fetal T exposure (preferably measured trough amniocentesis and followed-up at later ages) as independent and potentially interacting measures. In so doing, we might get a clearer picture on which profiles (high fetal T or not?/high circulating T or not?) may be related to the different male-biased clinical conditions such as ADHD, autism, antisocial personality, and psychopathy. These designs require comprehensive longitudinal research designs and are
therefore expensive and complex, but the payoff could outweigh the potential
costs when they provide clearer solutions for future preventive measures.

Finally, we find consistent associations between both fetal and circulating
T and different behavioral traits but research regarding the underlying mechanisms
is scarce. For example, we do know that T increases aggressive responding during
certain circumstances and in certain environments, but we still have a limited view
on which neurobiological events drive most of these associations. Of interest are T
interactions with neuropeptide functioning (oxytocinergic and vasopressinergic
circuitry), monoaminergic circuitry (norepinephrine, serotonin and dopamine),
and endocrinological functioning (HPA-axis, estrogen, progesterone, SHBG) in
the prediction of antisocial behavior and impulsivity. Additionally important
to know are T-induced changes in the reactivity and functionality of brain
regions that are involved in behavior and emotions such as the different parts
of the limbic system and vmPFC during decision making, response inhibition,
aversive experience, fear-conditioning, and executive functioning. Studies like
those of Mehta and Beer (2009), Van Wingen et al. (2010), and Van Honk et
al. (2011) are highly important to better understand how fetal and circulating
T co-influence biology and behavior. Regarding psychological factors it would
be useful to know whether T shows any interactions with social information
processing, attachment, or peer-group affiliation in the prediction of antisocial
behavior.

**Serotonin and dopamine**

First, all the serotonergic polymorphisms that have been discussed are common in
the general population meaning that the alleles that have been identified as being
“risk” markers are found in large portions of healthy individuals. For example,
although the results indicating remarkable parallels between \( l_A \)-homozygosity
of the 5HTTLPR and psychopathy are very convincing (Glenn, 2011a), one
must not dismiss that \( l_A \)-homozygosity characterizes nearly 30% of the general
population (e.g., Zalsman et al., 2006), whereas the added prevalence of primary
and secondary psychopathy is about 0.6-1.2% in the general population (Coid
et al., 2009). Another good example is the Val158Met SNP in the COMT gene,
which is often considered the main source of interindividual variation in COMT
activity. However, there are many sites within the COMT gene that contain
potential for SNPs and the specific allelic configurations at these different sites
are in a transmission disequilibrium with each other (i.e., haplotypes) (e.g., Belfer et al., 2013; Pap et al., 2012; Jugurnauth et al., 2011; Nackley et al., 2006; Tunbridge, 2010; Xu et al., 2011). Moreover, the power of finding significant differences between individuals is enhanced when considering high and low-expressing haplotypes rather than low and high expressing alleles with some studies reporting a 18 to 25 fold variation in COMT activity when considering haplotypes (Jugurnauth et al., 2011; Nackley et al., 2006; Xu et al., 2011). Therefore, SNP’s likely account for small variances of the interindividual variation in mRNA expression (Nackley et al., 2006, 2009). Furthermore, homozygosity for a single high expressing allele has little predictive utility because it may reside within multiple larger haplotypes related to differential expression patterns (see Nackley et al., 2006, 2009). Therefore, SNP’s are likely to have a small effect on neurophysiology and phenotypical expression and future research should instead focus on constellations of alleles within genes (haplotypes) and constellations of haplotypes between functionally interrelated genes and study factors that could modulate these gene x gene effects such as gender, social experiences, and substance abuse.

**Norepinephrine; “the neglected system”**

Studies on monoaminergic functionality in psychopathy have mainly focused on serotonergic and dopaminergic mechanisms. However, despite the close relationship between the noradrenergic system and different emotional processes (Stahl, 2008), there has been remarkably little research into this monoaminergic system in relation to psychopathic traits (Minzenberg and Siever, 2006). Due to this profound scarcity of information, the noradrenergic/adrenergic circuitry has not been discussed in part II. However, different researchers have already pointed at the possibility that noradrenergic mechanisms are involved in the etiology of the core characteristics of psychopathy (Blair, 2006a; Blair et al., 2005; Dishman et al., 1982; Galvin et al., 1991; Lidberg et al., 1978; Minzenberg and Siever, 2006; Rogeness et al., 1989a, 1989b, 1990a, 1990b; Zhang et al., 2005). Thus, the omission of noradrenergic/adrenergic genetics must not be misunderstood as indicating lower importance of these transmitters in the etiology of psychopathy and merely reflects the scarcity of data to warrant an in depth analysis. Nonetheless, based on existing research some new hypotheses might be deduced which might aid researchers in choosing future experimental designs.
First, activation of the locus coeruleus increases HPA-axis output through its direct interconnections with the paraventricular nucleus of the hypothalamus (i.e. reactive allostasis) (Herman and Cullinam, 1997). The reactive allostatic regulation to imminent threat (i.e. fear) is also crucially modulated by alpha1 and bèta-adrenoceptors in the amygdala (Morilak, 2007). Accordingly, the noradrenergic system, which originates in the locus coeruleus, is a strong modulator of the startle response (Stahl, 2008). Activation of noradrenergic transmission has an amplifying effect on the acoustic startle response, and lesions of the locus coeruleus significantly reduce startle reactivity (Adams and Geyer, 1981; Davies et al., 1984). Davis et al. (1979) report reductions in fear-potentiated startle in human subjects with the administration of propranolol (bèta-antagonist) and increases with both piperoxan (alpha1-agonist) and yohimbine (alpha2-antagonist), while leaving baseline startle unaffected. Furthermore, administration of clonidine (alpha2-agonist), in either the bed nucleus of the stria terminalis (BNST) or the lateral amygdala, dose-dependently blocks the acquisition and expression of fear-potentiated as well as light-enhanced startle in rats, without affecting baseline startle (Schweimer et al., 2005; Schulz et al., 2002).

Second, in addition to the direct amplifying effect of locus coeruleus activation on HPA-axis activity, noradrenergic neurotransmission in the BNST is also critically involved in regulating HPA-axis sensitivity to different psychological stressors and temporarily uncertain danger (i.e. predictive allostasis) (Morilak, 2007; Shields et al., 2008; Schweimer et al., 2005). Reactivity of the BNST to different stressors is mainly regulated by alpha2-adrenergic inhibitory influences and alpha1-adrenergic excitatory influences on glutamatergic neurotransmission within this structure (McElligott and Winder, 2008; Morilak, 2007; Shields et al., 2008; Schweimer et al., 2005). Higher allostatic regulation of the BNST, due to increased baseline glutamatergic neurotransmission, is directly related to heightened vigilance, baseline arousal, and anxiety in humans (Grillon, 2008a). In accordance, it has been found that the brains of patients with panic or generalized anxiety disorder have a significantly lower number of alpha2-adrenergic binding sites than control subjects (Cameron et al., 1990), thus likely having less baseline inhibitory tone over glutamatergic neurotransmission in the BNST. Bèta-antagonists such as betaxolol and metoprolol have also proven to reduce anxiety/fear symptoms in human subjects with generalized anxiety disorder and panic symptoms (Chaturvedi, 1985; Swartz, 1998), and it is suggested that increased bèta1-adrenergic signaling in the basolateral amygdala is
also involved in the etiology of these disorders (Nutt, 2001). These results indicate that noradrenergic signaling at excitatory adrenoceptors strongly modulates both reactive and predictive allostatic regulations to aversive, stressful, and threatening stimuli.

Third, noradrenergic projections originating in the locus coerulceus are critical pathways involved in the signaling of emotional valence information to PFC and amygdalar structures during stressful encounters and thus directly influence the intensity of emotional conditioning (Buffalari and Grace, 2007). For example, different studies have shown that noradrenergic functioning in the amygdala amplifies processing of fearful facial expressions (Kukolja et al., 2008). Noradrenergic antidepressants, such as reboxetine, dampen processing of fearful and angry facial expressions by reducing the amygdala responses to negative emotional facial expressions (Harmer et al., 2001, 2003; Norbury et al., 2007). Furthermore, administration of propranolol impairs selectively the processing of sad expressions (Harmer et al., 2001), and significantly reduces amygdala reactivity to fearful faces (Hurlemann et al., 2010). Nevertheless, despite influencing the emotional processing of affective facial expressions, norepinephrine modulations did not affect the emotional empathy response, demonstrating that conversely to serotonin and dopamine, norepinephrine is primarily implicated in threat responsivity but does not necessarily alter social sensitivity (Harrison et al., 2010). Dampened reactivity of the amygdala to direct threat due to noradrenergic dysregulation, might have a profound impact on the processing of emotional material (Blair et al., 2005). Accordingly, several studies have shown that in particular bèta-adrenergic activation of the basolateral amygdala is crucial in forming new aversive emotional associations such as during fear conditioning (Fu et al., 2008; LaLumiere et al., 2003; Roozendaal, 2007; Roozendaal et al., 2008). Therefore, administration of bèta-antagonists leads to a dampened amygdala reactivity to emotional stimuli and impairs the conditioning of that material (Lennartz et al., 1996; Roozendaal, 2007; Van Stegeren et al., 2005). In contrast, the alpha2-adrenoceptor system has inhibiting influences on basolateral amygdala reactivity (Buffalari and Grace, 2007). In accordance with this finding, administration of alpha2-agonists such as clonidine impairs aversive conditioning, while alpha2-antagonists enhance aversive conditioning (Roozendaal, 2007; Sirviö et al., 1992).

Finally, the noradrenergic system modulates the impact of punishment and the emotional value of a certain decision (Doya, 2007; Rogers et al., 2004). Research indicates that the bèta-adrenoceptors play an important role in
mediating the impact of aversive cues during decision-making. Administration of the selective bêta1-antagonist propranolol leads to attenuation of volunteers’ discrimination between the magnitude of possible losses in situations where the probability of winning is relatively low and the probability of suffering losses is relatively high (Rogers et al., 2004), which is highly parallel to the findings of impaired passive avoidance in psychopathic individuals (Newman and Schmitt, 1998).

Taken together, an excitatory balance of the adrenoceptors in the BNST (alpha1- > alpha2-adrenoceptors) and the basolateral amygdala (increased bêta-adrenoceptors) may contribute to heightened allostatic regulations in response to fear provoking stimuli (immediate/unexpected threat and physiological arousal). The opposite profile may thus be related to primary psychopathy (alpha2- > alpha1-adrenoceptors and decreased bêta-adrenoceptors in limbic structures). Decreased excitatory tone on limbic structures may also impair the processing of emotional stimuli and the assessment of probable risk, resulting in less emotional modification of behavior. Polymorphisms of noradrenergic genes that induce this specific profile may thus be related to psychopathy.

Furthermore, a focus on peripheral mechanisms (adrenoceptors) rather than central mechanisms (regulation of synaptic norepinephrine) may be more relevant to psychopathy since different studies have indicated that centrally mediated norepinephrine release is normal in psychopathic individuals but somehow does not engage peripheral mechanisms that mediate the ultimate physiological response to emotional stimuli (Dishman et al., 1982; Woodman, 1979a, 1979b). Also, epinephrine, which has also been found to be less responsive in psychopathy, primarily engages the peripheral bêta-adrenoceptors indicating that a reduction of specifically these receptors (especially the bêta1-adrenoceptor) could strongly affect physiological responsivity to affectively salient stimuli. An alternative hypothesis is that norepinephrine functionality and adrenoceptors densities are within average ranges but because of the low HPA-axis responsivity, phenylethanolamine-N-methyltransferase in the adrenal medulla is not sufficiently activated thus attenuating the conversion of norepinephrine into epinephrine and dampening physiological responsivity to affectively salient stimuli (Dishman et al., 1982).

Although there is a scarcity in research on the effect on noradrenergic polymorphisms on emotional responsivity, some preliminary results can be discussed. The bêta1-adrenoceptor gene, ADRB1, is located on chromosome 10 position q24-q26 (Belfer and Goldman, 2007). There are two common

Future directions
polymorphisms of ADRB1; Ser(49)Gly (with the Ser and Gly alleles being interchangeable) and Gly(389)Arg (with Gly and Arg being interchangeable). It has been shown in humans that a polymorphism of the ADRB1 is associated with lower resting heart rate in a large population of Chinese and Japanese individuals from nuclear families in whom the heritability of resting heart rate was 39.7% (Ranade et al., 2002). In addition, studies indicate that differential beta-adrenoceptors activity/sensitivity is related to both gender and race differences in cardiovascular stress reactivity (Girdler et al., 1993). For example, the Pima Indians, known for their low sympathetic nervous system reactivity to stressors, have lower beta-adrenergic sensitivity than Caucasians (Tataranni et al., 1998). Also, variations in ADRB1 polymorphisms have been associated with social phobia and extraversion, suggesting an impact on anxiety related traits (Stein et al., 2004).

These preliminary results coupled with the solid theoretical background of an important involvement of noradrenergic components on many of the basic emotional processes that are disturbed in psychopathy, indicates that noradrenergic polymorphisms could contribute to the etiology of psychopathy but this hypothesis has not yet been supported by empirical research. More research is needed to deduce confidently specific hypotheses about noradrenergic functioning in psychopathy.

Other genetic effects

A plethora of different genes that regulate neurobiological functions have been related to antisocial behaviors and associated endophenotypes but have not been discussed in this book. For example, genotypes that influence intrasynaptic monoaminergic levels more generally such as monoamine oxidase-A genotypes (Buckholtz and Meyer-Lindenberg, 2008; Fowler et al., 2009; Weder et al., 2009), regulate neuropeptide functioning such as vasopressinergic and oxytocinergic polymorphisms (Chakrabarti et al., 2009; Malik et al., 2012; Meyer-Lindenberg et al., 2009), alter functionality of second messenger systems such as protein kinase C gamma (PRKCG) (Schleapfer et al., 2007), modulate the activity of voltage-gated potassium channels such as KCNIP4 or voltage-gated calcium channels such as CACNA1C (Strohmaier et al., 2012; Weiβflog et al., 2013), impact on neural growth factors such as BDNF (Perea et al., 2012; Wagner et al., 2009), and alter the effects of sex-steroids (Chakrabarti et al., 2009), have
also been found to impact on various measures of emotional/stress responsivity, impulsivity, empathy, and antisocial/aggressive behaviors. Furthermore, other variables that are strongly influenced by genetics may also influence the route from genotype-to-phenotype such as intelligence (Johansson and Kerr, 2005). These potentially relevant genes have not been studied as extensively as monoaminergic polymorphisms but may in fact strongly modulate ultimate monoaminergic effects on physiology and behavior.

### 6.3 Critical Commentary:
**Understanding the Biology-Psychology Link**

A final and more general comment on biobehavioral research is that there is a growing imperative to differentiate between the specific effects of genes on biology and complicated psychological conditions. In doing research in this area on the border of biology and psychology, the complex relationship between these two qualitatively different processes needs more critical thinking. That is, biology and psychology are two fundamentally different processes, each operating on a separate level with different mechanisms which cannot simply be reduced to one and other. Mental events are “not the same thing as neural activity; phenomenological experience cannot be described in terms of ion flows, synaptic connections, and so forth” (Kosslyn and Koenig, 1992, pp.432; Miller, 2010). Therefore, different validity issues automatically arise when studying biological “underpinnings” of complex psychological constructs such as psychopathy. Since there has been no fully developed demonstration of how psychology and biology affect each other and which neural events drive rather than correlate with psychological events, validity of conclusions regarding the biological basis of these psychological constructs is inherently compromised (Miller, 2010).

Although in general, different brain structures, genes, and hormones perform the same molecular functions accross individuals, the unique expression of those processes through physiology, psychology, and behavior is determined by culture, socialization, situation, etc. For example, literally opposite results have been found with regard to the effect of specific serotonergic alleles on neural reactivity patterns in collectivistic versus individualistic cultures (e.g. Chiao and Blizinsky, 2010; Lee and Ham, 2008). It has been asserted that the effect of serotonergic genotypes such as 5HTTLPR on emotional processing may be
modulated by ethnic differences (Chiao and Blizinsky, 2010). This result also raises the question if environmental effects do not ultimately overshadow direct genetic mechanisms.

In addition to being psychological constructs in need of a psychological theory, most behaviors related to psychopathy, such as instrumental aggression, also have strong social determinants (e.g. low SES, alienation) and social meaning (increasing wealth and status). Biological explanations encompassing also psychological events should account for the complex relationship with the social environment. Otherwise, we ignore the complexity of human behavior when we try to reduce complex psychological constructs into localized neural activity patterns or response tendencies in reaction to very specific and isolated tasks. Therefore, many endocrinological influences on real-life human behavior and on psychopathological conditions, such as psychopathy, are probably weaker than we assume and are mediated by a host of social and psychological influences.

In essence, biology is the fundamental building block of learning but the unique and random content of that learning and its specific psychological expression is shaped through social experiences and influenced by many random situational factors. This means that it is literally impossible and epistemologically wrong to construct a specific theory on how very specific behaviors arise out of general and simplistic biological alterations (i.e., too high, too low, imbalanced, etc.). Although biology may influence how we process socio-emotional information and which unconscious motivational drives are more likely to control our behavior, the specific psychological themes of our conscious motivations and emotions are shaped by unique life experiences and are interpreted and act upon based on both cultural and social norms and direct situational parameters (i.e., our dynamic identity). Most human behaviors have strong social determinants (e.g., self-image, SES) and meaning (e.g., preserving self-esteem, increasing adaptiveness to an according worldview), also in the case of psychopathy and antisocial behavior. Therefore, reducing these intricate psychological patterns by means of biological explanations, such as neurophysiological processes and imbalances, blatantly ignores their intricate relationship with the intra- and inter-psychic atmosphere that dynamically changes throughout life.

According to Goldman (2012), genes distinctively influence the reaction range of an individual to environmental events of salience. Because environmental factors dynamically change throughout life and context, genes are not fixed attributes of behavior. If the environment is changed so that no one or everyone exhibits the behavior then heritability of the behavior will drop to zero. Indeed,
antisocial behaviors in maltreated children are increased in genetically at-risk subjects but only up to moderate levels of trauma exposure. Extreme levels of trauma appear to overshadow the effect of genotype (Weder et al., 2009). This is true because many heritable behaviors are contingent on exposure to some environmental factor “so that if the environment is not so varied as to expose some individuals the effect of the gene will not be visible” (pp. 82-83, Goldman, 2012).

Furthermore, since there has been no fully developed demonstration of how biology and psychology affect each other and which neural events drive rather than correlate with psychological events, validity of conclusions regarding the biological basis of these psychological constructs is inherently compromised. This is also the reason why it is advisable to use the word “genetic contributions to” rather than “role of genes in” or “genetic underpinnings of” and consistently refer primarily to effects on endophenotypes and only secondarily to psychopathy as one of many possible phenotypes that could flow forth from these emotional processing profiles. The endophenotypic approach is an intriguing way for examining the relationship between biology and psychology. This perspective acknowledges the fact that specific ways of processing information can bias towards a wide variety of behaviors so that the ultimate phenotypic outcomes are primarily determined by the unique way that experience shapes the crystallization of the processing profiles into stable and unique personality traits. However, the endophenotypic approach is also confined because empirical experiments such as measuring the effect of genes on very specific and isolated experimental task (i.e. amygdalar response to fearful stimuli) can never reflect the complexity of real-life demands on cognitive or emotional processing.

Finally, in the past several decades we have automatically assumed that DNA controls physiology and behavior but we are now also unraveling the fact that belief-systems and the social atmosphere one is exposed to may determine how and if certain genes will be transcribed and translated into protein material. Biological contributions to pathological behavior may thus only be expressed when there is an environmental demand (e.g., stress) to produce a specific protein (e.g., TPH) that cannot be met adequately because of a certain polymorphism that reduces its expression and efficiency. In this sense, although genetic factors may confer a risk towards certain processing profiles during allostatic states (e.g., emotional hypo- vs. hyperreactivity) environment is always the final determinant whether a specific genetic load will lead to serious psychopathology, especially criminality. Some environments may cause antisocial behavior with weak genetic
risks (e.g., profit based societies with high levels of competition and inequality between citizens such as in many African, North-, and South-American countries) whereas other countries may dampen most genetic risks to antisocial behavior (e.g., collective communities with minimal competition or inequality such as the Israeli Kibbutz society). Therefore, biological explanations encompassing also psychological events should be aware of the complex relationship with belief-systems, cultural values, unique life-events, and the social environment. In other words, the crucial link between biology and eventual behavior and psychology can only be understood individually, per person.

Similarly, while the placebo effect is a recognized phenomenon, there are not many scholars who stop to think what it actually means. It really states that we as humans can change our physiology simply by believing something to be true. Similarly, identity is formed when the associational traces of certain beliefs are repeatedly strengthened by environmental reinforcement that these eventually get established as neural highways through which information is filtered that is relevant to the self or Ego. In other words, since what you believe can influence how you feel it is logical to assume that belief systems may in fact change neural response patterns independent from socio-biological risk-factors. As long as we continue to focus on socio-biology at the cost of identity, serious mental disorders will always seem to be absolute and unchangeable because such socio-biological processes are often defined at an early age and quite stable over time. However, if we start to focus more on personal values, identity, and responsibility than we might appeal more strongly to the side of psychopathology that can be controlled through one’s beliefs and which is more amenable to treatment.

Taken together, explanations on how neurophysiological alterations through genetic mechanisms can contribute to psychopathology should be embedded in solid and predictive theoretical frameworks in order to progress from inferring circumstantial correlations to causal interpretations. At this point in neurobiological sciences, it is still unclear how genes that influence neurophysiology may specifically and causally contribute to psychological diseases rather than generally associate with a variety of conditions. An attempt has been made in this book to clarify some of these underlying mechanisms but much work needs to be done to empirically establish clear links.
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Throughout all ages, beginning in ancient times, there has been the widespread recognition that people exist who are conscienceless, unscrupulous, and deficient in morality. Different scholars and theologians have written about the subject even as early as the dawn of religion. Over the many centuries that followed, the philosophical and eventually scientific community began systematically describing these individuals according to their characteristic behaviors and personality styles. It has only been in the last century, especially the last couple of decades, that psychopathy was incepted as a term for corrupt minded individuals. Before the 20th century, the terms psychopath and psychopathic were used to denote a large variety of disordered personality styles and the related term moral insanity referred to disordered socio-emotional processes in general rather than morality as operationalized today.

During the mid 20th century Hervey Cleckley pioneered the field of psychopathy by operationalizing the characteristic features observed in such individuals. These criteria spanned the behavioral, cognitive, affective, and interpersonal domains. Cleckley described psychopaths as outwardly affable and charming individuals who make a convincing impression of being in good mental health. However, despite the “mask of sanity”, as Cleckley named it, these individuals are inwardly deficient of strong affective reactions to even the
most serious matters of life, leading them to behave in an utterly irresponsible, unreliable, egocentric, and reckless manner. His operationalization of psychopathy has survived over the many subsequent decades of empirical research and has strongly influenced our current understanding of the condition.

In a related attempt two decades later, William and Joan McCord also set out to clarify the boundaries of the psychopathy construct. In line with their forerunner, Cleckley, they emphasized emotional disturbances such as lovelessness and guiltlessness as being the central defining features of psychopathy. In contrast to Cleckley, however, they also included more malignant traits as being exemplary of the condition. They asserted that psychopathic individuals were not only deficient in emotion but more importantly, were severely impulsive, aggressive, and explosive. Furthermore, the McCords excluded adaptive traits such as low neuroticism and good “intelligence”. Also, writing on the etiological background of psychopathy, the McCords emphasized negative environments as being the prime factor that could incite such traits, in particular parental rejection, while ignoring possible genetic or biological effects. I have suggested that the McCord’ian conceptualization of psychopathy conflates both primary and secondary subtypes into one overarching category of callous, hedonistic, impulsive, and aggressive individuals.

During the first attempt at reliable classification and the introduction of the DSM in 1952, a new category was introduced, termed sociopathic personality disturbances. This initial diagnostic entity was largely consistent with the operationalization of Cleckley in that it also included latent personality traits (e.g., emotional immaturity, callousness, lack of loyalty, hedonism, lack of judgment). However, later editions of the DSM, starting with the DSM-III, parted from this original definition and influenced by the behavioristic Zeitgeist of the late 20th century decided to focus exclusively on concretely observable traits. This led to the introduction of the diagnostic category of antisocial personality disorder (ASPD). Undoubtedly, the initial goal of the DSM-III task force was to strive for reliability within the diagnosis since the history of psychopathy was known to be unclear and checkered. However, the diagnostic criteria for ASPD have been repeatedly criticized as being too broad and non-specific. Different scholars and scientists in the field of psychopathy passionately contended that the DSM-III and later also the DSM-IV focused too much on outward behavior and blatantly neglected the underlying personality dispositions.

Although it seemed that the DSM-5 was going correct these wrongs, the American Psychological Association (APA) Board of Trustees decided at
the last moment that continuity with current clinical practice would be lost if the diagnostic criteria were abruptly changed. The board therefore disproved of revisions for any of the personality disorders. Nonetheless, a new diagnostic model for the classification of ASPD is still retained in an appendix-like section III as an “emergent model”, currently waiting to be validated by empirical research to merit replacement of the old diagnostic criteria. Preliminary findings have indicated that the DSM-5 Section III criteria may particularly index secondary forms of psychopathy rather than primary variants. Indeed, apart from two main criteria, all the included items show negligible and some even show negative correlations to features integral to Cleckley’s psychopathy such as boldness and fearless dominance.

Trying to find a way to reliably identify psychopathic subjects for his research projects, and dissatisfied with the instruments that were available at the time, Robert Hare used the initial insights of Cleckley to construct a diagnostic tool for psychopathy. His efforts eventually resulted in the development of the PCL-R which was later also translated in an instrument for psychiatric patients and community subjects (PCL-SV) and one for youngsters (PCL-YV). These tools designed by Hare have ever since been the dominant measures to assess psychopathy. Although most criminals are eligible for the diagnosis of ASPD as diagnosed by the DSM, only a small subset can also be diagnosed as exhibiting psychopathy when adhering to the more stringent criteria of the PCL-R. Further analyses with the PCL-R revealed that its items actually cohered around two separate but related factors. Factor 1 is suggested to index the core personality traits of psychopathy and includes traits such as cunning manipulation, grandiosity, and superficial charms, while factor 2 assesses a more global antisociality construct not unique to psychopathy.

Indeed, the PCL-R items were originally extrapolated from samples of incarcerated criminals and therefore focus more on the socially deviant and criminal side of psychopathy compared to the initial conceptualization of Cleckley. Furthermore, whereas Cleckley included different indicators of positive adjustment as being characteristic features of psychopathy, these indicators are absent from the PCL-R. In other words, the PCL-R indexes a more deviant and maladjusted pattern of psychopathy than intended by Cleckley. Similar to the McCord’s conceptualization, the PCL-R conflates features characteristic to both primary and secondary psychopathy into one checklist. Finally, the fact that the PCL-R does not include any items pertaining to low neuroticism and fearlessness has led different researchers to question its validity in assessing
primary psychopathy.

Responding to the critique expressed at the PCL instruments for being less useful or valid in non-criminal community samples, Scott Lilienfeld and his colleague Brian Andrews developed the PPI to facilitate research in community samples. The PPI is an empirically constructed self-report questionnaire that indexes latent personality traits pertaining to both the affective and interpersonal features of primary psychopathy (stress immunity, social potency, and fearlessness) as well as global behavioral deviancy more closely related to secondary psychopathy. In contrast to the PCL-R, the PPI was initially developed in a community sample and its aim was not to design an item set that cohered around an unitary construct but to best capture a number of personality traits that were deemed relevant to psychopathy by different scholars in the field. To reduce its reading level and remove culturally laden or psychometrically problematic items, the PPI was later revised (PPI-R).

In response to factor analysis, it was determined that the PPI items could be clustered into two main factors similar to the PCL-R. The factor of fearless dominance (PPI-I) includes traits such as fearlessness, stress immunity, and social potency and most closely resembles the Cleckley’s conceptualization of primary psychopathy. Conversely, the orthogonal factor of impulsive antisociality (PPI-II) mainly includes items that index personality traits as observed in antisocial individuals more generally such as Machiavellian egocentrism, carefree nonplanfulness, impulsive non-conformity, and blame externalization, and more closely indexes secondary forms of psychopathy. However, the use of self-report measures in psychopathic populations has some notable disadvantages since psychopaths are characteristically deceitful, lacking of insight into their own pathology, and have little experience with constructs such as guilt or empathy, and are thus more likely to give inaccurate responses.

In order to provide a basis for reconciling and accommodating alternative accounts of psychopathy, Christopher Patrick, Don Fowles and Robert Krueger developed the Triarchic model of psychopathy in 2009. The main premise of the Triarchic model is that psychopathy encompasses three distinct phenotypic constructs: disinhibition, which reflects a general propensity toward problems of impulse control; boldness, which is defined as the nexus of social dominance, emotional resiliency, and venturesomeness; and meanness, which is defined as aggressive resource seeking without regard for others. These phenotypic constructs are later also operationalized through the self-report questionnaire Triarchic Psychopathy Measure (TriPM) that is published in 2010. Because of its
recent development (published in 2009), the TriPM has not yet been sufficiently examined and additional validation studies are still needed to determine in what degree these domains assess different subtypes of psychopathy and differentiate such individuals from narcissistically disturbed or antisocial patients.

Chapter 2 - Towards A New Continuum of Primary and Secondary Psychopathy
A Matter of Deficiency versus Disturbance

Throughout the 20th century, different scholars and researchers have argued that individuals with psychopathic tendencies can be differentiated on the basis of both etiological (i.e., constitutional vs. environmentally mediated) and personological differences (i.e., fearless and buoyant vs. anxious and neurotic).

At the same time that Cleckley released his seminal work, Ben Karpman introduced the notion that psychopaths are a heterogeneous group. He argued that scholars should separate those in whom the psychopathic pathology is considered to be idiopathic, and thus constitutionally predisposed, from those in whom these traits are symptomatic and reflective of a coping response to a harsh or abusive childhood. In response to cluster analysis of a prison population, Blackburn validated this initial proposition by Karpman and reported that outwardly similar psychopathic individuals could be differentiated on the basis of neuroticism. Blackburn made the general distinction between primary and secondary psychopathy and in later studies confirmed that primary variants were more likely to be characterized by low levels of harm avoidance, anxiety, and child abuse, whereas the secondary psychopaths showed high scores on each of these measures.

Since Blackburn’s initial inception, different theorist have tried to explain the etiological disparities between these psychopathic conditions. Both Fowles and Lykken elaborated on the initial distinction by Blackburn, and proposed that primary psychopathy is underpinned by a hyporesponsive fight-flight system (low fear) and low levels of BIS thereby resulting in attenuated appraisal and low avoidance of danger, risk, novelty, and otherwise aversive events, whereas secondary psychopathy evolves out of an unusually active BAS which increases the risk of impulsive responding to reward-anticipatory cues. In contrast to these researchers, Porter explained that secondary psychopathy is equally affectionless as the primary variants due to the dissociation of emotion from cognition, which
serves as a coping response to deal with traumatic and painful experiences.

Over the following decades, further empirical evidence arose that suggested that primary and secondary psychopathy are indeed separate clinical entities. Despite overlapping traits (i.e., callousness, antisociality, deceitfulness), these conditions were found to differ widely regarding a variety of psychological domains (fearfulness, impulsivity, hostility), biological processes (PFC functioning, limbic response patterns, endocrinological profiles), and corresponding etiological pathways. Different cluster-analytic studies with the PCL-YV in adolescent offenders, PCL-R in adult criminals, and the PCL-SV in community samples have accordingly supported that individuals identified as psychopathic can be further segregated into separate, more homogeneous groups resembling Blackburn’s primary and secondary variants. The primary variants, regardless of legal status or age, are consistently reported to be more emotionally stable, fearless, and self-assured while secondary groups are more impetuous, neurotic, and generally show more severe psychopathology, social maladjustment, and externalizing symptomatology. Nonetheless, some studies report that secondary psychopathic inmates may have a greater potential for growth and improvement following psychological therapy.

In response to the available literature, it can be plausibly stated that primary psychopathy arises out of a constitutionally based hyporesponsivity of bottom-up emotional input (impaired reactive allostasis) thereby precluding a healthy physiological response to emotionally salient events and hindering the proper integration of affect into a developing model of morality. Morality is hollow of emotional content and moral and ethical transgressions, while understood, are not felt. This particular affective and moral profile is likely mediated through an unresponsive right-hemisphere limbic-circuitry during socio-emotional events (i.e., emotional hyporesponsivity) and can develop into both adaptive and maladaptive behavioral patterns (i.e., controlled and disinhibited subtypes) dependent on social experience, the degree of genetic risk (moderate or high), and other factors that disturb PFC maturation and functionality. Indeed, there might also exist a separate class of individuals who have been born with the same emotional deficiency as their pathological counterparts but who, due to different protective factors, have become properly socialized and thus adjusted to society in a healthy and constructive manner.

In contrast, despite that secondary psychopathy is also associated with some genetic risks (e.g., irritability, hyperactivity, reward sensitivity), these risks only result in psychopathic development if other destructive factors are
also present. The most important etiological triggers in secondary psychopathy include relational trauma (i.e., abandonment, separation), neglect, and abuse during childhood. Such experiences increase hostile attributional biases and disturb the healthy development of vmPFC regions that mediate top-down regulation/appraisal of affective and motivational signals (i.e., emotional disturbance). This particular neural profile has been related to disordered affective appraisals of future possibilities and a dysregulation of behavioral tendencies and emotional reactions, and might thus increase the risk for a host of both externalizing and internalizing symptoms. Some secondary psychopaths may primarily express the emotional detachment characteristic of this group and mainly show a hedonistic and impetuous pursuit of short-term reward (i.e., detached secondary psychopathy) while others may be primarily characterized by a severe dysregulation of affect and thus display higher levels of hostility and reactive aggression (i.e., unstable secondary psychopathy).

Chapter 3 - Serotonergic Risks towards Emotional Pathology

Everything is About Balance

The purpose of this chapter was to uncover through systematic review and structural analysis of the literature the potential serotonergic mechanisms underlying the emotional pathology associated with either primary or secondary psychopathy. Several hypotheses have been constructed on the potential role of the serotonergic circuitry in mental health more generally, and in the etiology primary or secondary psychopathy more specifically.

The primary role of serotonin in both mind and body is the maintenance of a homeostatic operating range in physiological processes necessary for optimal growth, development, and well-being of psychological, emotional, cardiac, and metabolic processes. Although most of us prefer the feeling of comfort and tranquility that accompanies this homeostatic state, without transient disruptions to this internal balance in response to salient events, physiological processes would become disconnected from external events.

Therefore, serotonergic genotypes that stabilize the intra-/intersynaptic serotonergic homeostasis to a non-optimally strong state and result in a stabilized regulatory balance of postsynaptic serotonin receptors in fronto-limbic structures, will naturally dampen the strength (i.e., allostatic regulations) and duration (i.e., homeostatic disruptions) of internal physiological resonations to salient
events and therefore contribute to emotional deficiency as observed in primary psychopathy. Such a physiological system is highly self-regulatory and thus decreases the need for social attachments to regulate internal states, contributes to the etiology of socio-emotional detachment, and slows down punishment/empathy-driven conscience development irrespective of social experiences.

Furthermore, these genotype effects on emotion and behavior could be explained through the role of serotonin in the development of physiological regulation throughout life. It has been found that serotonin during critical phases in early life programs the characteristic serotonergic response later in life and thus determines in part emotional regulation and responsivity throughout life (Ahmari et al., 2009; Hariri and Holmes, 2006; Holmes, 2008; Nordquist and Oreland, 2010; Ohta et al., 2014; Rok- Bujko et al., 2012; Rood et al., 2014). Serotonergic genotypes that strongly improve both short- and long-term stability of serotonergic homeostasis in the brain during critical developmental phases (i.e., faster and more efficient serotonergic synthesis; G-allele of TPH2, combined with a stronger re-uptake; the lA-allele of 5HTTLPR, and increased stability of 5HT1A receptor densities during prolonged neurotransmission; C-allele of HTR1A), boost healthy neural development and improve serotonergic responsivity during adulthood which strengthens physiological regulation.

In extreme cases, multiple serotonin regulating genotypes could effectively dampen homeostatic disruptions/allostatic regulations below the threshold needed to respond adequately to aversive emotional events such as threat, punishment, and the suffering of others. These processes subsequently dampen the child’s need to learn social means for the regulation of internal states, empathic responding to distress cues, or the child’s motivation to avoid social discord that can result in punishment, shame, and guilt. Interactively, these processes could delay or hinder conscience development and interacting with other biological (i.e., dopamine, testosterone) and environmental risk factors (i.e., neglect, abuse, victimization, deviant peers, low SES), increase the risk for primary psychopathy and modulate its specific expression (i.e., disinhibited or controlled).

Conversely, early childhood abuse/trauma, social rejection/exclusion, or other stressful life events that result in long-term allostatic states, are likely to have greater detrimental effects on the intra-/intersynaptic serotonin homeostasis and regulatory receptor balances in individuals with serotonergic “plasticity” genotypes (i.e., low stability/high flexibility) thereby concomitantly resulting in sensitized homeostatic disruptions during stressful states and deregulating.
allostatic regulations in response to salient stimuli (i.e., emotional dysregulation) and ultimately increasing the risk for impulsivity, fear, depression, and aggression as observed in secondary psychopathy.

The contribution of these interactive effects on serious personality disorders such as secondary psychopathy may be explained through the impact of these genotypes on neurodevelopment during critical phases in utero and early childhood. Dysregulation of serotonergic homeostasis in the developing brain can desensitize the central serotonergic response throughout life (trait-like) and contribute to disturbed brain development (Ansorge et al., 2008; Whitaker-Azmitia, 2001, 2010). For example, stressful or traumatic life events boost serotonergic neurotransmission and thus require the serotonergic system to adapt by modulating synthesis, transport, degradation, and receptivity so that a healthy baseline functioning can be maintained. In individuals with the less efficient versions of the different serotonin regulating components (e.g., lower TPH and 5HTT expression), adaptations may be less efficient thus resulting in neuro-maldevelopment when this allostatic state ultimately exceeds intrasynaptic energy resources.

We might say that these serotonergic plasticity genes increase the natural resonation of the individual with idiosyncratic social experiences and thus naturally increase the impact of these experiences on neurodevelopment and behavior. The development of self-regulation is then strongly shaped by social experiences during the first years of life resulting in a strong emotional resilience when treated sensitively but also increasing the risk for psychopathology when abused or traumatized (Homberg and Lesch, 2011). Specific socio-psychological themes that develop in response to idiosyncratic experiences with the environment during late childhood and adolescence may then subsequently determine how this emotional dysregulation is uniquely expressed throughout life. For example, narcissistic, borderline, and antisocial personality traits such as dampened empathy, hostility, and heightened aggression may then develop particularly in response to neglectful experiences that induce socio-emotional detachment, frustrating/anger-inducing social experiences that increase the risk of hostile attributional biases, and positive reinforcement by deviant family members/peers which establishes antisocial behavior as part of one's identity.
Chapter 4 - Dopaminergic Risks towards an Antisocial Lifestyle
When Wanting Overrules Having

The purpose of this chapter was to uncover through systematic review and structural analysis of the literature the dopaminergic mechanisms at work in the etiology of different subtypes of primary psychopathy. Several hypotheses have been constructed on the potential role of the meso-cortico-limbic DA circuitry in the etiology of controlled and disinhibited subtypes of psychopathy. In addition, it has been argued that these DA risk profiles should not be considered in isolation and that, in order to understand how DA might contribute to psychopathic features, future studies should also include measures of serotonergic functioning since serotonin can crucially modify the relationship between DA functioning and emerging phenotypes.

In light of the findings regarding the mesolimbic DA system, it is hypothesized that primary psychopathy, regardless of subtype, is associated with higher levels of tonic and population activity of striatal DA neurons. However, disinhibited forms of psychopathy could relate to a more deregulated state of mesolimbic DA activity that hinders normative PFC development and increases the risk for impetuous forms of risk-taking. Pathologically heightened mesolimbic DA activity strengthens limbic coupling between the hippocampus, amygdala, and VTA-striatum and impedes subsequently maturing structures such as the PFC from taking strong control over striatal DA activity, thereby resulting in lower fronto-striatal coupling, impairing behavioral flexibility, and boosting impetuous and reckless responding to cues predictive of reward (reward hyperfocus, impaired response modulation, impetuous risk-taking). Controlled psychopathic personalities on the other hand, are expected to show moderate elevations and more optimal PFC maturation trajectories enabling them to curtail strong motivational urges, and strategize their hedonistic exploits in a more calculated, foresighted, and controlled manner (deliberate risk-taking to maximize reward).

Regarding mesolimbic DA components and the genes that code for them, higher TH expression accompanied by D2-receptor subsensitivity increases the level of DA turnover and synaptic activity in mesolimbic projections while preventing strong homeostatic autoregulations. Primary psychopaths, regardless of subtype, are likely to show higher TH and lower D2-receptor expression, which, under normal circumstances promotes a high stable DA functioning. However, in the context of additional risk factors, this genetic profile may
substantially increase the risk for dysfunctional impulsivity, impetuous risk-taking, and persistent criminality. For example, lower DAT densities can sensitize homeostatic deregulations in response to both acute and prolonged DA neurotransmission which might result in heightened synaptic DA activity, especially when autoinhibitory control is impaired (D2S subsensitivity). In other words, the combined presence of high tonic DA release rates and low DAT and D2S expression might more readily lead to hyperdopaminergic states, whereas the adequate counterbalancing of higher tonic DA release by moderately elevated DAT expression could stabilize DA functioning at more optimal levels. Therefore, moderately higher DAT densities could specifically relate to controlled psychopathy whereas lower DAT densities may form an additional risk-factor for criminal and aggressive behaviors in individuals with D2-receptor subsensitivity and high DA activity and thus increase the risk for disinhibited psychopathy.

Furthermore, regarding the mesocortical DA system, the reviewed data demonstrates that disinhibited psychopathic individuals are likely characterized by an impaired DA-driven stabilization or labilization of PFC neural circuits. Simply put; a lower DA functionality in the PFC. This profile can incite higher obsessivity and hyperfocus on immediate and strong reinforcements and impair cognitive flexibility when confronted with non-reward or punishment. Conversely, controlled psychopathic subtypes likely show higher levels of PFC DA mediated cognitive stability and flexibility during goal-pursuit and thus engage more adaptively in long-term pursuits (higher persistence and conscientiousness) and change ongoing behavioral strategies more adaptively when contingencies change or peripheral cues signal such a possibility (better response modulation).

One etiological risk-factor that might bias psychopathic development towards a disinhibited profile could be a non-optimal increase in the COMT-driven degradation of synaptic DA which naturally reduces overflow of synaptic DA during tonic release rates and attenuates the concomitant stimulation of extrasynaptic D1-receptors. Long-term understimulation of extrasynaptic D1-receptors can prompt a compensatory upregulation of these receptors thereby skewing the D1-to-D2-type ratio in the PFC and fronto-striatal pathways. Sensitization of D1-receptors would then evoke stronger task-relevant focus and vigor but only towards immediate incentive-laden goals since weaker signals pertaining to long-term goals do not escape the synaptic cleft to engage D1-receptors and stabilize goal-pursuit. The negative effect of this D1-receptor sensitization is particularly strong if D2-type receptors (D2L and D4) are downregulated thereby further skewing the delicate receptor balance and
interactively impairing the appropriate appraisal and attentional orientation to an unexpected change in contingencies (lower flexibility/perseveration towards immediate rewards despite repeated negative feedback) (Loos et al., 2010; Pardey et al., 2013; Winstanley et al., 2006b).

Important to note, however, is that although higher tonic DA functioning in PFC-amygdala circuitry (as associated with Met-homozygosity) could serve as a protective factor in the development of disinhibition and criminality in psychopathic personalities, its final effect on phenotypical expression is strongly modulated by environmental risk or protective factors (e.g. Baumann et al., 2013). These genotypes may only increase the chance of a good outcome in good environments and might protect against less severe risk factors such as low socio-economic status but do not necessarily decrease the risk of a bad outcome when exposed to more severe risk-factors such as trauma, addiction, and abuse. That is, in response to childhood physical/sexual abuse or long-term substance dependence, psychopaths with high activity PFC DA systems are equally likely to develop criminal behaviors and could even be more organized/cunning, hostile, and aggressive because of higher levels of executive functioning, higher social and stress sensitivity, better social cognition, and higher levels of outward-directed aggression (serial killers and sadistic pedophiles may be extreme examples).

It is crucial that these hypotheses are tested in future empirical research to firmly establish their validity so that we may begin implementing the found results into clinical practice. Uncovering the biological contributions to the etiology of primary psychopathy will greatly facilitate the development of specialized pharmacological therapy. The neurobiological processes that contribute to the etiology of primary psychopathy are just beginning to be uncovered and are potentially viable for understanding some of the major pathologies associated with this condition, an easy target for the design of psychotropic medications, and thus an important direction of future research.

**Chapter 5 - The Role of Testosterone**

*A Real Man is Shaped by his Environment*

In the recent years testosterone (T) has received considerable interest as a potential etiological contributor to the development of male-biased clinical conditions such as antisocial behavior and psychopathy. T is a male gonadal hormone and affects brain and behavior throughout the lifespan, beginning in
An influential model that has gained much attention and support is the organizational/activational hypothesis of T. It specifically states that exposure to T during fetal development organizes the maturation of the physiological system and brain to react to a surge of T throughout life in a masculinized manner. It is therefore imperative that researchers study the interaction of fetal and circulating T since their effects on behavior are interdependent.

To examine how T is related to psychopathic development, we must first operationalize these traits and clarify their underlying endophenotypic pathways. As discussed in part 1 of this book, a differentiation is often made between the core psychopathic traits which are partly a product of fearlessness and callousness (low empathy), and the life-course persistent antisocial behavior, which arises more generally out of a lack of self-control/-regulation (impulsivity) and is strongly related to aggression and violence.

First, both fetal and circulating T have shown inconsistent associations to core psychopathic traits when studied directly, often finding weak, non-significant, and sometimes even negative correlations. When further examined whether T might be a risk-factor in the etiology of associated endophenotypes, it can be concluded that T is closely involved in the development of empathy related problems but not so much fearlessness, which is likely mediated through other risk-factors that affect emotional processing. The effect of T on empathy is mediated through different neurobiological steps; T reduces the ability of the emotionally laden limbic system to communicate with the more rational and decision-making PFC thereby effectively disconnecting emotion from cognition. Therefore, while T does in fact increase the emotional reaction to an empathy eliciting stimuli such as a fearful face, it also decreases the ability of the PFC to pick up on these signals, appraise them, and use them to affect behavior. These results are also supported by the findings of a lesser sensitive oxytocinergic system in men, which may also partly be programmed through higher levels of fetal and circulating T.

Second, a comprehensive review of the literature indicates that T is consistently and positively related to antisocial behaviors throughout the lifespan. Also, the endophenotypes underlying life-course persistent antisocial behavior including impulsivity and aggression have both been related to T exposure. First, regarding impulsivity, T has been found to increase DA reward sensitivity thereby boosting risk-taking and novelty-seeking. However, whether pathological impulsivity arises depends strongly on how well the individual is able to control and curtail inherent drives toward hedonism. Especially individuals with
additional risk-factors that compromise healthy PFC, serotonin, and HPA-axis functioning may show increased levels of impulsivity when combined with high T, whereas in otherwise healthy individuals, the T-induced reward sensitivity may contribute to vigor, persistence, and more deliberate forms of risk-taking and novelty-seeking rather than dysfunctional impulsivity.

Third, T may particularly boost intermale aggression by increasing vasopressinergic, limbic, and dopaminergic reactivity to social challenge, thereby inducing a competitive, vigorous, and sometimes aggressive response which mainly serves to acquire or maintain a certain social status. In addition, T can also influence different forms of pathological aggression mainly through its dampening effect on fronto-limbic connectivity. Because T reduces top-down PFC mediated regulation of limbic-generated emotion but also bottom-up emotional input into the PFC it may increase the risk for both emotional dysregulation but also the risk for instrumental and utilitarian decision-making, ultimately increasing the risk for both reactive and instrumental aggression. However, similar to its influence on impulsivity, these T induced endophenotypes are likely to be modulatory rather than necessary and the effect of T on aggression is particularly pronounced in individuals who exhibit emotional pathologies such as emotional disturbances (in reactive aggression) and deficiency (in instrumental aggression). Again in individuals with a healthy development and loving, sensitive, and prosocial environment, these T induced endophenotypes may also evoke socially admirable traits such as assertiveness, parochial altruism, and competitiveness.

Also interestingly, the correlation between T and antisocial behavior varies considerably throughout the lifespan, being lowest in childhood, somewhat higher during adolescence, and in adulthood either increasing in strength in antisocial samples or decreasing back to childhood levels in community samples. A socio-psycho-biological explanation may explain the differing correlations between T and antisocial behavior during different life phases. Critical psychological and biological development phases occur parallel to early childhood and adolescence. When these psychological and biological transitions are promoted by positive social experiences, and positive mental models of the world, the healthy maturation of brain circuitry involved in impulse-control and empathy could inhibit T influences over antisocial behavior during adulthood and maybe even direct high T individuals towards increased prosocial and socially admirable behaviors. Alternatively, when healthy biological maturation during these critical phases is thwarted by negative social experiences, the resulting disturbances in psychological and neurobiological functioning could augment the effect of T on
antisocial behavior.

For example, insecure attachment relationships with caregivers and social rejection by peers (negative social experiences) may lead to chronically high levels of dysfunctional social stress (i.e., social distress > social eustress). High levels of prolonged social stress can result in; HPA-axis deregulation thereby modulating approach-withdrawal behaviors, oxytocinergic deregulation thereby impacting on basic social sensitivity, and serotonergic deregulation thereby decreasing healthy impulse control. In addition, imbalances in neurochemical pathways brought about by high levels of chronic social stress can disturb healthy maturation of the prefrontal cortices, in particular during critical development phases such as the first three years of life. However, serotonergic, HPA-axis, and oxytocinergic deregulations are likely to be the result of an interaction between these social risk factors and specific genetic predispositions (e.g., MAOA, 5HTT).

Concerning socio-psychological development, the link between T and antisocial behavior may also be mediated by social information-processing patterns that arise from accumulated social experiences. First, when raised by abusive/neglectful caregivers, rejected by peers and teachers, and living in impoverished low SES environments, children may develop social information-processing patterns biased towards social threat hypersensitivity and a strong fight/flight response. I have argued that high T individuals are more likely to develop these hostile attributional biases because of the increased social threat sensitivity and more likely to react on them with a “fight” response such as aggressive dominance. Second, rejected youth are also at a greater risk to affiliate with deviant peers who reinforce shared activities such as delinquent and aggressive acts. Since T is strongly associated with achieving and maintaining a high social status, these youngsters learn to gain this status by perpetuating delinquent acts and maintain it through aggressive dominance. In short, individuals who have in addition to high T levels, also other biological and social risk factors, are at greatest risk for developing life-course persistent antisocial behavior and have more severe antisocial behaviors during adolescence. In addition, antisocial behaviors during the life-span are also likely to alienate others, cause further rejection and victimization, and lead to lead to many legal and social problems, thereby creating a vicious circle.

However, children with high T levels but who have had a healthy and enjoyable socio-emotional development (i.e., positive social experiences) and have no constitutional predisposition towards neurochemical dysfunctioning, have the lowest risk of developing life-course persistent antisocial behavior.
These individuals may have difficulties in impulse-control during the identity forming years in adolescence, especially when not properly supervised by caregivers, but these behaviors are likely to wane in adulthood. Low genetic load towards antisocial behavior coupled with balanced social stress (i.e., eustress > distress) caused by positive social experiences may help to regulate serotonergic and HPA-axis functioning throughout life and serve as a strong protective factor against antisocial behavior. Positive social experiences may also serve as a protective factor against antisocial behavior through protective psychological processes such as secure and trustworthy mental models of the world. Moreover, since T has been implicated in social functioning in general, with other factors modulating its pathway to either antisocial or prosocial behavior, these positive social experiences in high T individuals can lead to desirable social characteristics such as leadership qualities, competitive achievement motivation, fair bargaining behaviors, and social assertiveness.

Therefore, in individuals with healthy maturation and functioning of serotonin, HPA-axis, and the PFC, and/or with positive social experiences such as high SES, love, and acceptance, T may increase deliberate risk-taking and dampen social sensitivity but may not necessarily lead to pathological levels of callousness or dysfunctional impulsivity. Conversely, in individuals with maturational deficits and dysfunctioning of these neural systems and/or who have been exposed to negative social experiences such as low SES, abuse, and rejection, T may aggravate empathy deficits and risk-taking behaviors, thereby effectively contributing to the etiology of antisocial behavior. T might thus act as a modulatory variable and only increase the risk for callousness and reward driven antisocial behavior in the context of other biological and environmental risk factors.

Similarly, while T may aggravate the psychopathic condition and lead to higher levels of violence and deviancy, it may only have this negative effect in individuals with additional, more primary risk-factors towards psychopathic development. In individuals with serotonin deficiency and a deregulated HPA-axis reactivity leading to a basal emotional disturbance, T may especially increase the risk for secondary psychopathic and reactive aggressive phenotypes while in those with serotonin hyperstability and HPA-axis hyporesponsivity leading to a basal emotional deficiency, T may increase the risk for primary psychopathic and instrumental aggressive phenotypes.
Hoofdstuk 1 - Ontmaskeren van de Ongrijpbare Psychopaat
De Veelbewogen Geschiedenis van het Psychopathie Construct

Door de eeuwen heen, beginnend bij de aanvang van de westerse kalender, is er een wijdverbreide erkenning dat er mensen bestaan die van nature gewetenloos zijn. Verschillende geleerden en theologen hebben tijdloze stukken bijgedragen aan het onderwerp van moraliteit die net zo ver terug dateren als het ontstaan van huidige religies. Door de vele eeuwen die volgden hebben filosofen en uiteindelijk wetenschappers getracht deze individuen systematisch te bestuderen en de karakteristieke persoonlijkheidsstijlen in kaart te brengen. Het is echter pas in de laatste eeuw, zelfs in de laatste paar decennia, dat de term psychopathie verwijst naar corrupte en gewetenloze personen. Voor de 20ste eeuw werden de termen psychopathie en psychopathisch gebruikt om een grote verscheidenheid aan gestoorde persoonlijkheden te duiden.

Deze bestaande onduidelijkheden over de betekenis van psychopathie veranderde in 1941 toen Hervey Cleckley 16 karakteristieke persoonlijkheidseigenschappen identificeerde die volgens hem de prototypische psychopaat weerspiegelen. Cleckley beschreef de prototypische psychopaat als een charmante en vriendelijke individu die in eerste instantie een positieve en gezonde indruk maakt. Echter, ondanks deze “mask of sanity” (masker van gezondheid), zoals Cleckley het noemde, zijn psychopaten gevoelsarme individuen met afwezige emotionele reacties, zelfs ten opzichte van de meest serieuze zaken.
Nederlandse Samenvatting

Deze deficiëntie van interne emotionele reacties stelt psychopathische mensen in staat om met gemak en zonder wroeging of spijt zich (herhaaldelijk) op een zeer onverantwoordelijke, egoïstische, roekeloze en onbetrouwbare wijze te gedragen, ongeacht of de slachtoffers van hun gedrag vreemden of familie zijn. Cleckley’s systematische conceptualisatie van psychopathie heeft de test van tijd doorstaan en werd keer op keer bevestigd in empirisch onderzoek. Cleckley heeft daarom daaropvolgende onderzoek en onze kijk op deze stoornis sterk beïnvloed en wordt vaak beschreven als de “vader van het psychopathie construct”.

Ongeveer twee decennia later introduceerde William en Joan McCord hun eigen conceptualisatie van psychopathie met de intentie dit begrip verder te begrenzen en beter te definiëren. In lijn met hun voorganger, Cleckley, benadrukten de McCords de emotionele verstoringen zoals liefdeloosheid en een gebrek aan schuldgevoelens als kernkenmerken voor de psychopathische stoornis. Echter, in scherp contrast met Cleckley, benadrukten de McCords ook andere, meer kwaadaardige trekken. Ze beargumenteerden dat psychopathische individuen niet alleen deficiënt zijn in hun emotionele reacties maar dat ze daarnaast ook zeer impulsief, agressief en zelfs explosief gewelddadig kunnen zijn in hun gedrag. Ook laten de McCords enkele adaptieve trekken weg die aanwezig zijn in Cleckley’s lijst zoals lage mate neuroticisme en goede “intelligentie”. Bovendien, wanneer ze schrijven over de factoren die bijdragen aan de ontwikkeling van psychopathie, benadrukten de McCords omgevingsfactoren als zijnde primaire risicofactoren, met name ouderlijke afwijzing, en negeerden ze genetische of biologische factoren. Ze zagen biologische factoren, zoals afwijkingen in de ontwikkeling van de hersenen, als secundair. In dit proefschrift wordt beargumenteerd dat in de McCord’iaanse conceptualisatie zowel primaire als secundaire psychopathie worden samengevoegd in een overkoepelde diagnostische categorie van ongevoelige, hedonistische, impulsieve en agressieve individuen. Daarentegen heeft de Cleckley’aanse conceptualisatie met name betrekking op de primaire variant.

Gedurende de eerste poging om psychische stoornissen betrouwbaar te classificeren, en de daarmee samenhangende introductie van de DSM in 1952, werd er een nieuwe diagnostische categorie geïntroduceerd, namelijk de sociopathische persoonlijkheidsstoornis. Deze categorie is grotendeels consistent met de operationalisatie van Cleckley omdat deze ook latente persoonlijkheidsstrekken omvat (bijv. emotionele onrijpheid, ongevoeligheid, afwezigheid van loyaliteit, hedonisme en gebrekkelig vermogen tot inzicht). Desalniettemin zouden de latere edities van de DSM, beginnend met de DSM-III deze focus op
Hoofdstuk 1 Samenvatting

persoonlijkheidstrekken laten vallen. Mede onder invloed van de tijdgeest van de jaren 60, wanneer de behaviorisme een sterke opkomst maakt, besluit de DSM comité om nieuwe criteria voornamelijk te baseren op observeerbaar gedrag. Dit leidt tot de creatie van een nieuwe diagnostische categorie genaamd de antisociale persoonlijkheidsstoornis (APS). Het eigenlijke doel van de DSM comité is zonder meer geweest om de betrouwbaarheid van classificatie te vergroten omdat er veel onduidelijkheden bestonden in de geschiedenis van het psychopathie construct. Het argument was dat observeerbaar gedrag veel betrouwbaarder is vast te stellen dan niet te observeren en dieperliggende persoonlijkheidstrekken. Echter, sinds de introductie van de DSM-III is er een continue stroom van kritiek geuit op deze nieuwe diagnostische categorie omdat de criteria zo overkoepelend en breed zijn dat niet alleen psychopaten worden geclasseerd, maar eenieder die de wet heeft overtreden en daarnaast impulsief, onbetrouwbaar en agressief is geweest. Verschillende auteurs weigeren de diagnostische categorie van APS in de DSM-III en de daaropvolgende edities zoals de DSM-IV te gebruiken als synoniem voor psychopathie en beargumenten passievol dat deze diagnose teveel focust op observeerbaar gedrag en ten onrechte de onderliggende persoonlijkheidstrekken negeert. De DSM-5 heeft hier geen verandering in gebracht. Voorlopige resultaten hebben uitgewezen dat de nieuwe criteria van de DSM-5 met name de secundaire psychopathische stoornis in kaart brengen. De primaire variant is dus tot op hedendaags niet correct geoperationaliseerd in de meest gebruikte diagnostische handboek, de DSM.

In de jaren 80 ontwikkelde Robert Hare of basis van de lijst van Cleckley een nieuwe instrument om de meetbetrouwbaarheid van het psychopathie construct te verbeteren. Zijn inzet leidde uiteindelijk tot de ontwikkeling van de Psychopathy Checklist-Revised (PCL-R) die vooral wordt gebruikt om de mate van psychopathie vast te stellen in criminelle en forensische populaties. Later wordt de PCL-R vertaald in een psychopathie instrument voor psychiatrische patiënten en gezonde personen (PCL-SV) en eent voor jongeren (PCL-YV). Deze PCL instrumenten worden sinds hun ontwikkeling gezien als state-of-the-art instrumenten om psychopathie te classificeren, dit echter ten koste van andere, ook veelbelovende instrumenten die daardoor minder gebruikt worden. De criteria van de PCL-R om psychopathie te kunnen vaststellen zijn vele malen strenger dan de criteria van de DSM voor de classificatie van APS. Als gevolg voldoet slechts een klein percentage van de gevangenis populatie aan de classificatie van psychopathie (15-25%) terwijl de meeste criminelen in aanmerking komen voor de diagnose van APS (>75%). Verdere analyses met de
Nederlandse Samenvatting

item set van de PCL-R onthullen dat deze criteria kunnen worden opgedeeld in twee algemene factoren. Het is meermalen aangetoond dat factor 1 de kern persoonlijkheidstrekkens in kaart brengt die geassocieerd zijn met psychopathie zoals berekenende manipulatie, affectieve stoornissen, narcisme en oppervlakkige charmes, terwijl factor 2 op een wat meer algemenere manier het antisociale gedrag in kaart brengt die niet perse uniek is voor psychopathie maar ook voorkomt in andere psychische stoornissen.

Omdat de PCL-R items zijn opgesteld door middel van onderzoek met opgesloten criminelen hebben deze, in vergelijking met de originele conceptualisatie van Cleckley, veel meer betrekking op de antisociale en sociaal afwijkende gedragingen van psychopathie. Daarnaast is het zo dat Cleckley's lijst ook een aantal items bevat die betrekking hebben op de wat meer adaptieve kant van psychopathie terwijl de PCL-R deze positieve indicatoren negeert. In andere woorden; de PCL-R definieert psychopathie als een veel gestoordere en criminellere stoornis dan Cleckley. De PCL-R bevat items die betrekking hebben op zowel primaire and secundaire varianten van psychopathie, vergelijkbaar met de McCord’iaanse conceptualisatie. Het feit dat de PCL-R geen enkele item bevat die betrekking heeft op de lage neuroticisme of lage angstgevoeligheid, welke keer op keer geobserveerd is in primaire psychopathie, wordt dan ook door veel onderzoekers en geleerden gezien als een cruciale tekortkoming.

Als antwoord op de herhaalde kritiek op de PCL-R, namelijk dat het niet de lage angstgevoeligheid meet en dat de validiteit of bruikbaarheid twijfelachtig is in minder gestoorde populaties zoals gezonde burgers, ontwikkelden Scott Lilienfeld en zijn collega Brian Andrews de Psychopathic Personality Inventory (PPI). Hiermee trachten ze onderzoek te bevorderen in de normale populatie. De PPI is een empirisch geconstrueerde vragenlijst die latente psychopathische persoonlijkheidstrekkens in kaart brengt die betrekking hebben op zowel de sociale en emotionele afwijkingen van primaire psychopathie (bijv. stress immuniteit, sociale invloed, en angstloosheid). Tevens wordt de antisociale gedragsproblematiek die geassocieerd is met zowel primaire als secundaire psychopathie ook gemeten. De belangrijkste verschillen met de PCL-R is dat de PPI ontwikkeld is in de normale burger populatie in plaats van criminelen. Voorts streefden de onderzoekers er niet naar een item set te ontwikkelen die was georganiseerd rondom een unitaire construct maar om een aantal psychopathische persoonlijkheidstrekkens zo goed mogelijk in kaart te brengen ongeacht of deze trekken met elkaar samenhingen. Om het leesniveau te verlagen, psychometrische problemen op te lossen en cultureel beladen items
te wijzigen word later een revisie van de PPI ontwikkelt, namelijk de PPI-R.

Factor analyse met de PPI items heeft uitgewezen dat ook deze weer georganiseerd kunnen worden onder twee overkoepelende factoren, net zoals de PCL-R. De eerste factor, genaamd angstloze dominantie (PPI-I) omvat persoonlijkheidskenmerken zoals angstloosheid, stress immuniteit, en sociale invloed. Deze eerste factor komt grotendeels overeen met de conceptualisatie van primaire psychopathie zoals geformuleerd door Cleckley. Daarentegen, de orthogonale factor genaamd impulsieve antisocialiteit (PPI-II) bevat voornamelijk kenmerken die geobserveerd worden in antisociale individuen in het algemeen zoals Machiavelliaanse egocentrisme, zorgeloze onverantwoordelijkheid, impulsieve non-conformiteit en het externaliseren van schuld. Deze tweede factor hangt met name samen met secundaire psychopathie.

Ondanks de vele voordelen van de PPI ten opzichte van de PCL-R zijn er ook een aantal zwaktepunten. Psychopathische individuen zijn erom bekend dat ze liegen, weinig inzicht hebben in hun eigen functioneren en onervaren zijn met sociale emoties zoals schaamte en empathie en zullen daardoor ook een grotere kans lopen inaccuraat te beantwoorden wanneer ze naar zulke ervaringen worden gevraagd. De validiteit van zelf-rapportage vragenlijsten is dan ook twijfelachtig bij zulke manipulatieve individuen.

Met als doel de verschillende alternatieve theorieën en conceptualisaties over psychopathie onder één dak te brengen, ontwikkelden Christopher Patrick, Don Fowles en Robert Krueger de Triarchic model van psychopathie in 2009. Het uitgangspunt van de Triarchic model is dat psychopathie drie verschillende fenotypische expressies kent die in verschillende mate aanwezig zijn in psychopathische individuen. (1) Disinhibtie reflecteert de algemene tendentie tot problemen in de impulscontrole; (2) vrijmoedigheid is gedefinieerd als de schakel tussen sociale dominantie, emotionele weerbaarheid, en avontuurlijkheid; en (3) gemeenheid is gedefinieerd als de tendentie om op een agressieve manier de eigen behoeften te bevredigen zonder rekening te houden met de gevoelens van anderen. Deze fenotypische constructen zijn later in 2010 ook geoperationaliseerd door middel van een zelf-rapportage vragenlijst; de Triarchic Psychopathy Measure (TriPM). Doordat deze vragenlijst pas recentelijk is ontwikkeld is deze nog niet voldoende onderzocht om er uitspraken over te doen. Meer onderzoek is nodig om te duidelijk in kaart te brengen in hoeverre deze drie fenotypische constructen samenhangen met de verschillende psychopathische varianten en in hoeverre ze psychopathie diagnostisch differentiëren van narcistische en antisociale patiënten.
Hoofdstuk 2 – Richting een Nieuwe Continuüm van Primaire en Secundaire Psychopathie

Een Kwestie van Deficiëntie versus Verstoring

Gedurende de twintigste eeuw hebben verschillende onderzoekers beargumenteerd dat de grotere groep psychopathische individuen verder onderscheiden kunnen worden in subcategorieën op basis van zowel ontwikkelingsachtergrond (sterkere rol genen vs. omgeving) als persoonlijkheidszaken (angstloos en relaxed vs. reactief en neurotisch).

Op hetzelfde moment dat Cleckley zijn belangrijke werk publiceerde, introduceerde Ben Karpman de notie dat er binnen de groep psychopaten verschillende persoonlijkheden bestaan die allen aangeduid kunnen worden als psychopathisch wat betreft gedrag en immoraliteit maar toch verschillen van elkaar op cruciale aspecten. Hij beargumenteerde dat men een onderscheid moet maken tussen individuen bij wie de psychopathische aandoening idiopathisch is en dus met name bepaald door genetische achtergrond, en individuen bij wie deze pathologie symptomatisch is en dus tot stand is gekomen door destructieve omgevingsinvloeden.

Een aantal decennia later valideerde Blackburn de argumenten van Karpman door middel van cluster analyse in een gevangenisdemonstratie. Hij rapporteerde dat psychopathische individuen verder gedifferentieerd kunnen worden op basis van neuroticisme. Blackburn maakte de distinctie tussen primaire en secundaire psychopathie en bevestigde in door middel van clusteranalyse dat primaire varianten voornamelijk gekenmerkt worden door een lage niveau van vermijding van gevaarlijke situaties, angstloosheid en vaak ook niet mishandeld zijn als kinderen. De secundaire varianten daarentegen vertoonden op ieder van deze maatstaven een hoge score en werden daarnaast gekenmerkt door vroegkinderlijke mishandeling, verwaarlozing en misbruik.

Sinds Blackburn dit onderscheid heeft gemaakt, zijn er verschillende theoretici geweest die hebben geprobeerd te verklaren hoe deze psychopathische varianten van elkaar verschillen, zowel wat betreft ontwikkelingsachtergrond als persoonlijkheid. Fowles en Lykken argumenteerden dat primaire psychopathie veroorzaakt zou worden door een onderactieve vecht-vlucht systeem (lage angst) en lage “gedrags-inhibitie systeem” niveaus welke samen kunnen leiden tot een verminderde inschatting en vermijding van gevaar, risico, straf en andere beangstigende situaties. In tegenstelling hiermee ontstaat secundaire psychopathie voornamelijk door een overactieve “gedrags-activatie systeem”
Hoofdstuk 2 Samenvatting

waardoor de persoon sneller geneigd is impulsief te reageren op belonings- of bedreigingssignalen. Daarentegen beargumenteerde Porter dat de secundaire psychopaat net zo angstloos en affectief vervlakt is als de primaire variant door de dissociatie van emotie en cognitie, en dus net zo laag in neuroticisme.

In de loop van de volgende decennia ontstond er verder empirisch bewijs dat primaire en secundaire psychopathie inderdaad aparte klinische entiteiten zijn. Ondanks overlap in kenmerken (ongevoeligheid, antisociaal gedrag, bedrog) werd keer op keer gerapporteerd dat primaire en secundaire psychopathie sterk verschillen met betrekking tot een verscheidenheid van psychologische domeinen (angst, impulsiviteit, vijandigheid), biologische processen (PFC functioneren, limbische reactie patronen, endocrinologische profielen) en de bijbehorende ontwikkelingspaden. Verschillende cluster-analytische studies met de PCL-YV bij adolescente delinquenten, PCL-R bij volwassen criminelen, en de PCL-SV in de gezonde populaties hebben dienovereenkomstig ondersteund dat individuen geïdentificeerd als psychopathisch verder kunnen worden onderscheiden in afzonderlijke groepen. De primaire varianten, ongeacht de juridische status of leeftijd, hebben een hogere emotioneel stabiliteit, zijn angstloos en zijn daarnaast ook zelfverzekerd terwijl secundaire groepen in het algemeen ernstigere psychopathologie, hogere niveaus van angst en depressie, meer geweld en sterker afwijkend gedrag vertonen. Tevens melden sommige studies dat secundaire psychopathische gevangenen een groter potentie hebben voor groei en ontwikkeling en een betere response op therapie.

Gezien de beschikbare literatuur kan aannemelijk worden gemaakt dat primaire psychopathie voor een groot deel voortvloeit uit een genetisch gebaseerde hyporeactiviteit van emotionele processen (verminderde reactieve allostasis) welke een gezonde fysiologische reactie op sociale en emotionele gebeurtenissen belemmert en daarmee ook verhinderd dat emotie adequaat wordt geïntegreerd in een ontwikkelende model van moraliteit. Doordat moraliteit niet gekleurd word door emoties, worden morele en ethische overtredingen wel begrepen als “fout” maar deze intellectuele analyses gaan verder niet gekoppeld met een diepere en fysiologisch gebaseerde gevoel van schuld, spijt of schaamte (nervens, zweten, hartslag activatie etc.). Dit bijzondere affectieve en morele deficiëntie wordt in het brein weerspiegeld als een hyporeactiviteit van het limbische circuit tijdens socio-emotionele gebeurtenissen of tijdens het maken of uitvoeren van morele beslissingen. De lage reactiviteit van het limbische circuit is voornamelijk geobserveerd in de rechterhersenhelft welke vooral betrokken is bij de intuïtieve en onbewuste emotionele processen. Desalniettemin, ondanks dat dit bijzondere
Nederlandse Samenvatting

affectieve profiel per definitie lijdt tot sommige primaire psychopathische patronen zoals angstloosheid, onthechting van anderen, narcisme, en oppervlakkige sociale emoties is ook gebleken dat niet al deze individuen antisociaal, impulsief of crimineel zijn. Terwijl er inderdaad veel primaire psychopaten impulsief en gewelddadig zijn (gedisinhibeerde subtypes), zijn er ook veel die berekenend, gecontroleerd en planmatig leven (gecontroleerde subtypes). Of er zich adaptieve of maladaptieve gedragspatronen ontwikkelen tijdens de levensloop hangt af van opvoeding, omgeving, de mate van genetische risico (matig of hoog), en andere factoren die de rijping en functionaliteit van de hersenen verstoren. Als laatste zou er ook een aparte klasse van personen kunnen bestaan die zijn geboren met dezelfde emotionele tekortkomingen als hun pathologische tegenhangers, maar die, als gevolg van verschillende beschermende factoren, op de juiste wijze gesocialiseerd worden en dus aangepast zijn aan de samenleving op een redelijk gezonde en constructieve wijze.

Ondanks dat secundaire psychopathie ook geassocieerd is met een aantal genetische risico's (bv prikkelbaarheid, hyperactiviteit, gevoeligheid voor beloning) is de connectie tussen deze risico's en het uiteindelijke profiel veel minder direct. Dat wil zeggen dat omgevingsvariabelen een meer cruciale rol hebben in de ontwikkeling van secundaire ten opzichte van primaire psychopathie. De belangrijkste etiologische triggers in secundaire psychopathie omvatten relationele trauma (verlating), verwaarlozing, mishandeling en misbruik in de vroege kindertijd (1-3 jaar). Zulke ervaringen hebben een scala aan negatieve effecten op zowel de biologische rijping van de hersenen als de sociaal en emotionele ontwikkeling van het kind. Bijvoorbeeld, deze stressvolle gebeurtenissen kunnen de gezonde ontwikkeling van de ventromediale prefrontale cortex (vmPFC) verstoren en daarmee de dus ook de top-down begrip, evaluatie en controle van emoties en motivaties. Daarnaast kunnen zulke destructieve ervaringen ook een invloed hebben op de sociaal cognitieve ontwikkeling van kinderen en leiden tot een vijandige attributiestijl. Een afwijkend vmPFC neuraal profiel gekoppeld aan verstoorde cognitieve taxaties kan leiden tot een deregulatie van zowel emotionele als motivationele processen en daarmee de kans vergroten op zowel internaliserende als externaliserende psychopathologie. Terwijl sommige secundaire psychopaten voornamelijk gekenmerkt worden door de dissociatie van cognitie en emotie en daardoor ongevoelig, hedonistisch en impulsief zijn (onthechte subtypen) worden anderen vooral gekenmerkt door een ernstige ontregeling van emoties en daardoor onstabieler, vijandiger en vaak ook agressiever zijn (instabiele subtypen).
Hoofdstuk 3 – Serotonerge Bijdragen aan Emotionele Pathologie
Alles Draait om Balans

In dit hoofdstuk wordt de functie van serotonine in het centrale zenuwstelsel en brein besproken en daaruit zijn verschillende hypotheses gededuceerd die betrekking hebben op de ontwikkeling van psychopathie. Kort samengevat wordt beargumenteerd dat serotonine een belangrijke rol vervult bij het bewaken en dynamisch reguleren van de interne homeostase zodat het binnen bepaalde biologisch relevante en gezondheid bevorderende waarden blijft. De efficiëntie en stabiliteit waarmee serotonine in staat is om deze interne fysiologische balans te reguleren is direct van invloed op onze weerbaarheid en ons vermogen om emoties te reguleren tijdens stressvolle of bedreigende situaties. Zowel een te sterke als te zwakke serotonerge regulatie van fysiologische fluctuaties en de daarmee geassocieerde non-optimaal sterke of respectievelijk non-optimaal zwakke balans in psychofysiologische of neurofysiologische processen kan door middel van verschillende mechanismen leiden tot problemen in de sociaal emotionele ontwikkeling.

Serotonerge genotypen die de synaptische serotonerge homeostase stabiliseren tot een non-optimaal sterke staat en een stabiel evenwicht van regulatieve postsynaptische serotonine receptoren teweegbrengen (d.w.z. sneller en efficiënter serotonerge productie, betere recycling door efficiëntere heropname en een verhoogde stabiliteit van 5HT1A en 5HT2A receptor expressie), kunnen op een additieve of synergistische wijze de sterkte en duur van interne fysiologische resonanties op belangrijke gebeurtenissen dempen en zo bijdragen aan de emotionele deficiëntie die wordt waargenomen bij primaire psychopathie. Omdat een hyperstabiele serotonine homeostase leidt tot een fysiologisch systeem dat zichzelf makkelijk kan reguleren vermindert het automatisch de behoefte aan externe regulators, zoals sociale steun, en draagt het zodoende bij aan een basale sociale onthechting en een vertraagde straf of empathie gedreven gewetensontwikkeling.

Deel van deze gevolgen in emoties en gedrag worden verklaard door de rol van serotonine bij de vroegkinderlijke ontwikkeling van fysiologische zelfregulatie vermogens. Gebleken is dat de mate van stress, aandacht, liefde en andere sociale invloeden tijdens kritieke vroegkinderlijke fasen een programmerende invloed kan hebben op de serotonerge response later in het leven en daarmee dus ook voor een deel de emotionele regulatie en responsiviteit kan beïnvloeden (Ahmari

Een alternatieve ontwikkeling richting psychopathie, in dit geval secundaire psychopathie, is geassocieerd met een te labiele homeostase van het serotonerge systeem. Verschillende stressoren zoals vroegkinderlijke misbruik, verwaarlozing, trauma, afwijzing en sociale isolatie kunnen een nadelig effect hebben op de levenslange functioneren van het serotonerge systeem en dit nadelige effect is met name zichtbaar in individuen die geboren zijn met een aantal serotonine “plasticiteit” genotypen. Door deze plasticiteit in serotonerge werking leiden stressoren sneller tot een homeostatische disbalans en ook sneller tot stress-gerelateerde pathologie zoals depressie, angst, prikkelbaarheid, agressie, slaapproblemen etc. Echter, als deze homeostatische disbalans vroeg in het leven plaatsvindt, in een periode dat het serotonerge systeem nog ontwikkelende is, kan dit leiden tot verandering in de ontwikkeling van dit serotonerge systeem en beïnvloedt het de emotieregulatie in de volwassenheid. Deze mensen hebben hun gehele leven lang problemen met het reguleren van hun emoties en wanneer dit gekoppeld gaat met een vijandig wereldbeeld, paranoia en agressieve tendenties kan dit leiden tot antisociaal en agressief gedrag en in ernstigere gevallen tot een secundair psychopathisch persoonlijkheidsontwikkeling.
De bijdrage van zulke complexe socio-psycho-biologische processen op de ontwikkeling van persoonlijkheidsstoornissen zoals secundaire psychopathie kan voornamelijk worden verklaard door de impact van deze genotypen op de neurologische ontwikkeling tijdens kritieke fasen in de baarmoeder en de vroege kindertijd. Ontregeling van serotonerge homeostase tijdens de ontwikkeling van de hersenen kan de centrale serotonerge respons gedurende het hele leven verstoren en deze negatieve effecten zijn met name sterk in individuen met genen die de serotonerge homeostase labiliseren (Ansorge et al, 2008; Whitaker-Azmitia, 2001, 2010). Dat komt omdat stressvolle of traumatische gebeurtenissen de serotonerge neurotransmissie stimuleren en dus vereisen dat het serotonerge systeem zich aanpast door synthese, transport, afbraak en ontvankelijkheid te moduleren zodat een gezonde basale werking gehandhaafd kan blijven. In personen met de minder efficiënte versies van de verschillende serotonine regulerende elementen (bijvoorbeeld lagere TPH en 5HTT expressie), zijn deze dynamische aanpassingen minder efficiënt en kunnen uiteindelijk resulteren in neuro-ontwikkelingsstoornissen. Of met andere woorden, als er meer serotonine nodig is dan dat er aanwezig is.

We zouden kunnen zeggen dat deze serotonerge plasticiteit genen de natuurlijke resonantie tussen het individu en zijn omgeving verhogen en daarmee ook de impact van stressvolle ervaringen op de neurologische ontwikkeling en gedrag. Bepaalde sociaal-psychologische thema’s die zich ontwikkelen in reactie op belangrijke ervaringen met de omgeving tijdens de late kindertijd en adolescentie kunnen dan vervolgens bepalen hoe deze emotionele ontregeling wordt uitgedrukt door het leven. Narcistische, borderline en antisociale persoonlijkheidstrekken zoals een verstoorde empathie, vijandigheid en agressie kunnen dan in het bijzonder ontwikkelen als reactie op negatieve sociale ervaringen die de hechting verstoren, frustrerende/woede-inducerende sociale ervaringen die leiden tot een vijandig wereldbeeld en positieve bekrachtiging van antisociaal gedrag door antisociale familieleden of vrienden die zulke gedrag verankerden als deel van de identiteit.

**Hoofdstuk 4 Dopaminerge Risico’s richting een Antisociale Levensstijl**

*Wanneer Hebben niet meer Genoeg is*

In dit hoofdstuk is geprobeerd door middel van systematische review en structurele analyse van de literatuur de dopaminerge mechanismen te achterhalen die
bijdragen aan de etiologie van verschillende subtypes van primaire psychopathie. Er zijn verschillende hypothesen afgeleid over de mogelijke rol van mesocortico-limbische dopamine (DA) circuits in de etiologie van gecontroleerde en gedisinhibeerde subtypen van psychopathie. Daarnaast is er betoogd dat deze DA risicoprofielen niet geanalyseerd moeten worden in isolement en dat, om te begrijpen hoe DA kan bijdragen tot psychopathische kenmerken, toekomstige studies ook de interactieve effecten moeten bestuderen van DA en andere neurobiologische systemen, zoals serotonine, op de ontwikkeling van psychopathie en andere mentale stoornissen.

Gezien de bevindingen tot nu toe kan worden gededuceerd dat primaire psychopathie, ongeacht de subtype, geassocieerd is met een hogere tonische en populatie activiteit van het mesolimbische DA systeem, met name de DA neuronen die projecteren naar de striatum. Desalniettemin is er beargumenteerd dat de gedisinhibeerde primaire subtypen, namelijk de primaire psychopaten die ernstige vormen van impulsiviteit en agressie vertonen, waarschijnlijk een meer pathologische verhoging van deze activiteit laten zien dan gecontroleerde primaire varianten bij welke de DA verhoging nog binnen de grenzen van normatieve variatie ligt. Een pathologisch verhoogde activiteit van het mesolimbische DA systeem belemmert een gezonde ontwikkeling van de PFC en verhoogt daarmee de risico voor kortzichtigheid, hedonisme en het daaraan gekoppelde impulsieve, onverantwoordelijke en risico-nemende gedrag. Dat komt deels omdat een verhoogde mesolimbische DA activiteit de neurale koppeling tussen de verschillende limbische structuren versterkt, en daarmee de sensitiviteit richting beloningen en bedreigingen, maar tegelijkertijd de neurale koppeling tussen de PFC en dit limbische circuit verzwakt, en daarmee de bewuste controle over deze behoeften, driften en emoties. Dit leidt vervolgens tot een verminderde flexibiliteit van het gedrag wanneer geconfronteerd met feedback over gemaakte fouten, verminderde vermijding van risico en gevaar, felle agressieve reactie op bedreiging en een sterk verhoogde hyperactiviteit en aandacht naar korte-termijn beloningen. In contrast tot deze gedisinhibeerde varianten vertonen de gecontroleerde primaire psychopaten een wat matigere verhoging van de mesolimbische DA activiteit die een gezonde rijping van de PFC en de daaropvolgende controle over het gedrag niet in de weg staat en dus zijn deze individuen beter in staat hun gedrag strategisch te controleren, te leren van hun fouten en berekenender te werk te gaan. Gecontroleerde varianten nemen ook risico’s maar deze zijn beter doordacht en minder impulsief dan het risico-nemende gedrag van de gedisinhibeerde varianten.
Op genetisch-moleculair niveau is er beargumenteerd dat een hogere activiteit van het mesolimbische DA systeem voornamelijk wordt bevordert door genotypen die leiden tot een hogere activiteit van het enzym tyrosine hydroxylase (TH) en een lagere expressie van D2-receptoren in fronto-limbische structuren. Dit moleculaire profiel leidt tot een hogere DA omzet en afgifte in de synaptische kleef maar vermindert tegelijkertijd ook de feedback inhibitie van de geactiveerde neuron en kan daardoor bijdragen aan een continu verhoogde activiteit van het DA systeem. In het kader van deze proposities is gehypothetiseerd dat primaire psychopathie, ongeacht subtype, samenhangt met een verhoogde TH en een verlaagde D2-receptor expressie, welke in de afwezigheid van andere risicofactoren een hoge stabiele DA functioneren bevordert. Echter, wanneer gekoppeld met bijkomende risicofactoren kan dit genetische profiel de neiging tot dysfunctionele impulsiteviteit, overhaast risico-nemend gedrag en aanhoudende criminaliteit vergroten.

Een van deze bijkomende risicofactoren is een lagere expressie van de dopamine transporter (DAT) in het brein. De DAT dient ter regulatie van synaptische DA niveaus en dus kan een lagere expressie ervan leiden tot een disregulatie in het DA systeem, vooral in de context van verminderde autoinhibitoire controle (lagere D2-receptor sensitiviteit). Met andere woorden, de gecombineerde afwezigheid van zowel D2-receptoren als de DAT kan leiden tot een disregulatie van het DA systeem in response op verhoogde neurotransmissie en kan dus sneller leiden tot een hyperdopaminerger toestand. Daarentegen, een sterke tegenwicht op hogere tonische DA afgifte door middel van een goed functionerende DAT stabiliseert het DA systeem op optimale niveaus van activiteit. Daarom wordt gecontroleerde psychopathie in verband gebracht met een betere DAT functionaliteit terwijl lagere DAT dichtheden een extra risicofactor voor crimineel en agressief gedrag bij personen met D2-receptor subsensitiviteit en een verhoogde DA werking en daarom voornamelijk wordt gekoppeld aan gedisinhibeerde varianten van psychopathie.

Met betrekking tot het mesocortical DA systeem kan worden geconcludeerd uit de wetenschappelijke literatuur dat gedisinhibeerde psychopathie waarschijnlijk samenhangt met een verminderde DA-gedreven stabiliteit en labiliteit van PFC neurale circuits. Simpel gezegd; een lagere DA functionaliteit in de PFC. Dit mesocorticale DA profiel verhoogt het risico op kortzichtigheid en tast daarnaast het vermogen aan om het eigen gedrag te evalueren en aan te passen wanneer men geconfronteerd wordt met straf of de afwezigheid van verwachtte consequenties. Het gedrag is kortzichtig en
obsessief. Fouten worden herhaaldelijk gemaakt zonder tekenen van inzicht. Daarentegen worden gecontroleerde psychopathische subtypes waarschijnlijk gekenmerkt door een hogere niveau van DA functionaliteit in de PFC en dus een betere stabiliteit en flexibiliteit van het gedrag tijdens doelgericht gedrag. Gecontroleerde psychopaten zijn dus beter in staat zich te blijven concentreren en te werken richting lange-termijn doelen (stabiliteit; hogere persistentie en nauwgezetheid) maar ook om hun gedrag adaptief aan te passen als reactie op onvoorziene situaties of wanneer de situatie erom vraagt (flexibiliteit; betere response modulatie).

Een etiologische risicofactor die de kans vergroot op zo een PFC DA profiel en daarmee de risico op een gedisinhiberde ontwikkeling is een niet-optimale verhoging van de COMT gedreven afbraak van synaptische DA in de PFC. Deze verhoogde afbraak zorgt ervoor dat DA minder snel de synaptische kleef verlaat en leidt daardoor tot een lagere stimulatie van extrasynaptische D1-receptoren, met name tijdens de zwakkere tonische activiteit patronen. Als deze receptoren echter te weinig gestimuleerd worden dan ontstaat er een compensatoire verhoging van hun expressie in de PFC en is het gevolg een niet-optimale verhouding van D1 tot D2 receptoren. Deze verhouding is voornamelijk vertekend in individuen met een verlaagde D2-receptor expressie zoals bij primaire psychopathie. Dit verhoogde D1-receptor profiel kan dan leiden tot een sterkere doelgerichte focus maar alleen richting korte-termijn beloningen omdat de zwakkere signalen die behoren aan de lange-termijn beloningen niet in staat zijn DA dusdanig te activeren dat het de gelijktijdige afbraak door COMT overstijgt, de synaptische kleef verlaat en de extrasynaptische D1-receptoren stimuleert. Dit negatieve effect van een verhoogde COMT maar ook D1-receptor expressie is bijzonder zichtbaar wanneer daarnaast de D2-receptoren, die normaalgesproken neurale tegenwicht bieden aan de D1-receptoren, een verlaagde expressie vertonen. Een verhoogde expressie van D1 ten opzichte van D2-receptoren in de PFC leidt dan tot een sterke doelgerichte focus op korte-termijn doelen en een verminderde flexibiliteit van dit doelgerichte gedrag ondanks herhaaldelijk negatieve feedback. Echter, belangrijk om op te merken is dat hoewel een betere DA functioneren in PFC-amygdala circuits als een beschermende factor kan dienen tegen de ontwikkeling van ontremming en criminaliteit in psychopathische persoonlijkheden en het uiteindelijke effect wordt sterk gemoduleerd door de opvoeding. Deze genotypen bevorderen een positieve en minder criminele ontwikkeling alleen in goede omgevingen en misschien beschermen ze daarnaast tegen minder ernstige risicofactoren, zoals een lage sociaal-economische status,
maar ze verminderen niet het risico op een slechte uitkomst wanneer blootgesteld aan meer ernstige risicofactoren zoals mishandeling, misbruik, trauma en verslaving. Psychopaten met een goede DA functionaliteit in de PFC die zijn blootgesteld aan fysiek of seksueel misbruik of langdurige drugverslaving zullen dan misschien wel minder impulsief zijn maar niet perse minder crimineel of agressief. Sterker nog, door hun betere planvermogen, hogere gevoeligheid voor sociale signalen, betere sociale cognitie en betere controle over hun gedrag zijn deze psychopaten vaak juist sluwder, vijandiger en agressiever (seriemoordenaars en sadistische pedofielen zijn de ernstigere varianten uit deze groep).

Het is cruciaal dat deze hypothesen worden getest in toekomstig empirisch onderzoek zodat we de validiteit kunnen bepalen en daadwerkelijk kunnen beginnen met de implementatie van de gevonden resultaten in de klinische praktijk. De blootlegging en begrip van dit soort neurobiologische bijdragen aan de etiologie van psychopathie zal onze zoektocht naar een succesvolle farmacologische of therapeutische ingreep sterk faciliteren. De neurobiologische, en dan met name de monoaminerge processen die bijdragen aan het ontstaan van primaire psychopathie worden steeds beter in kaart gebracht, bieden goede verklaringen voor het ontstaan van verschillende psychopathische persoonlijkheidstrekken, zijn een gemakkelijk doelwit om te manipuleren met psychotrope medicatie en om deze redenen een belangrijke richting voor toekomstig onderzoek.

**Hoofdstuk 5 De Rol van Testosteron**

*Een Echte Man wordt Geschapen door zijn Omgeving*

In de laatste jaren is er een grote belangstelling ontwikkeld voor testosteron (T) als een mogelijke etiologische bijdrage aan de ontwikkeling van psychopathologische beelden die vaker voorkomen bij mannen zoals antisociaal gedrag en psychopathie. T is een mannelijke gonadale hormoon en beïnvloedt de hersenen en het gedrag gedurende de levensduur, beginnend in de baarmoeder. Een belangrijk model dat veel aandacht en onderbouwing heeft gekregen is de organisatorische/activerende hypothese van T. Het benadrukt voornamelijk dat blootstelling aan T tijdens de foetale ontwikkeling de rijping van het fysiologische systeem en de hersenen op zo een manier organiseert dat het organisme op een mannelijkere manier reageert op een stijging van T later in het leven. Het is daarom noodzakelijk dat onderzoekers de interactieve effect van foetale en circulerende T op gedrag en
fysiologie bestuderen omdat de effecten van elkaar afhankelijk zijn.

Om te onderzoeken hoe T kan bijdragen aan de ontwikkeling van psychopathie moeten de geassocieerde persoonlijkheidszorgen eerst worden geoperationaliseerd en de endofenotypische ontwikkelingspaden tot deze trekken worden verduidelijkt. Zoals besproken in deel 1 van dit boek, wordt er vaak een onderscheid gemaakt tussen de kern psychopathische trekken, die deels het gevolg zijn van een aangeboren angstloosheid, en de life-course-persistent antisociaal gedrag, die in het algemeen ontstaat uit een gebrek aan zelfbeheersing/-regulering (impulsiviteit) en sterk gerelateerd is aan agressie en geweld.

Ten eerste laten zowel foetale als circulerende T niveaus een inconsistent samenhang zien met kern psychopathische trekken wanneer deze direct onderzocht worden. Vaak worden er zwakke, niet-significante en soms zelfs negatieve correlaties gevonden. Wanneer men echter onderzoekt of T samenhangt met de endofenotypes onderliggend aan de ontwikkeling van deze psychopathische kernvariabelen dan kan geconcludeerd worden dat T significant negatieve correlaties vertoont met empathie maar niet met angst, welke voornamelijk wordt bepaald door de genetische aanleg tot emotionele verwerking. Het negatieve effect van T op empathie wordt gemedieerd door verschillende neurobiologische processen. T het vermogen van het emotioneel beladen limbische systeem om te communiceren met de meer rationele en besluitvormende PFC en ontkoppelt het daardoor emotie van cognitie. Dat betekent dat terwijl T de limbische reactie verhoogt op een empathische stimulus, zoals een angstige gezichtsuitdrukking, verminderd het tegelijkertijd het vermogen van de PFC om deze emotionele signalen op te pikken, te beoordelen en ze te gebruiken om verder gedrag te beïnvloeden. Daarnaast worden deze resultaten ondersteund door bevindingen die wijzen op een minder gevoelige oxytocinerge systeem bij mannen die gedeeltelijk geprogrammeerd zouden kunnen worden door de invloed van T op de ontwikkeling van hersenen.

Ten tweede geeft een uitgebreid overzicht van de literatuur aan dat T consequent en positief gerelateerd is aan antisociaal gedrag gedurende de levensduur. Ook vertonen de endofenotypes die onderliggend zijn aan life-course persistent antisociaal gedrag, zoals impulsiviteit en agressie, consequent een positieve correlatie met T niveaus. Bijvoorbeeld met betrekking tot impulsiviteit is gevonden dat T de dopamine gedreven beloningsgevoeligheid verhoogt en daardoor risico-nemend gedrag en novelty-seeking vermeerderd. Of het daadwerkelijk leidt tot pathologische impulsiviteit is sterk afhankelijk
Hoofdstuk 5 Samenvatting

van het vermogen van het individu om zijn hedonistische driften in bedwang te houden. Voornamelijk bij individuen met extra risicofactoren die de PFC, serotonine en HPA-as werking beschadigen kan de T-geïnduceerde beloning gevoeligheid leiden tot pathologische impulsiviteit. Daarentegen kunnen dezelfde T verhogingen bij gezonde individuen bijdragen aan krachtigheid, persistentie en meer adaptieve uitingen van risico-nemend gedrag en novelty-seeking in plaats van disfunctionele impulsiviteit.


Het valt daarnaast op dat de correlatie tussen T en antisociaal gedrag aanzienlijk varieert door het leven heen. Deze correlatie is het laagst tijdens de kindertijd, iets hoger tijdens de adolescentie en fluctueert dan tijdens de volwassenheid afhankelijk van de sociale ontwikkeling. In volwassenen met verschillende risicofactoren stijgt de positieve correlatie verder terwijl het in gezonde volwassenen een daling vertoont naar het niveau van de kindertijd. Een socio-psycho-biologische verklaring kan verheldering bieden over de verschillende correlaties tussen T en antisociaal gedrag afhankelijk van de leeftijd. Kritische psychologische en biologische ontwikkelingsfasen vinden plaats gedurende de vroege kindertijd en adolescentie. Wanneer deze psychologische en biologische overgangen worden bevorderd door positieve sociale ervaringen, leidt dit tot een
gezonde ontwikkeling van de hersencircuits die betrokken zijn bij empathie en impulscontrole en wordt de risico op T gedreven antisociaal gedrag kleiner en kan zoals hiervoor besproken een hoge T niveau zelfs de ontwikkeling van prosociaal gedrag bevorderen. Echter, wanneer gezonde biologische rijping tijdens deze kritieke fasen wordt verhinderd door negatieve sociale ervaringen, kunnen de daaruit voortvloeiende verstoringen in het psychologische en neurobiologische functioneren het effect van T op antisociaal gedrag vergroten.

Bijvoorbeeld, een onveilige hechting met de opvoeders of sociale afwijzing door leeftijdgenoten (negatieve sociale ervaringen) leidt tot chronisch hoge niveaus van disfunctionele sociale stress. Een chronisch hoog niveau van sociale stress kan op ten duur leiden tot een deregulatie van de HPA-as met als gevolg verstoringen in motivationeel gedrag, in het oxytocinerge systeem met als gevolg verstoringen in sociale sensitiviteit/cognitie en in het serotonerge systeem met als gevolg een gebrekke zelfregulatie en impulscontrole. Daarnaast kunnen onevenwichtigheden in deze neurochemische systemen ook de gezonde groei van de PFC verstoren, in het bijzonder tijdens kritieke ontwikkelingsfasen, zoals tijdens de eerste drie levensjaren. Echter, deregulering van deze serotonerge, HPA-as en oxytocinerve systemen is waarschijnlijk het gevolg van een wisselwerking tussen deze sociale risicofactoren en een genetische aanleg tot neurobiologische plasticiteit.

Daarnaast kunnen sociale informatie-verwerkingspatronen, die ontwikkelen in respons op herhaalde ervaringen met de omgeving, ook deels de relatie tussen T en antisociaal gedrag verklaaren. Ten eerste, zullen kinderen die zijn verwaarloos of mishandeld door opvoeders, afgewezen of gepest door leeftijdgenoten en/of zijn opgegroeid in de lagere sociaal-economische klassen sneller een vertekend beeld ontwikkelen van de wereld. Zulke kinderen ontwikkelen vaak wantrouwende verwachtingspatronen jegens anderen, ook wel vijandige attributiestyle genoemd, en kunnen daardoor gevoeliger en agressiever reageren op ambigue sociale signalen. Hoge T individuen zijn sneller geneigd een vijandige attributiestyle te ontwikkelen vanwege hun verhoogde sociale gevoeligheid en sneller geneigd agressief reageren op zulke attributies vanwege hun de tendentie fel, confronterend en dominant te reageren op conflicten en uitdagingen. Ten tweede lopen afgewezen jongeren meer risico om zich aan te sluiten bij deviante leeftijdgenoten die gezamenlijke antisociale activiteiten, zoals delinquent en agressief gedrag, belonen en daarmee bekrachtigen door middel van status. Aangezien T sterk geassocieerd is met het willen bereiken en behouden van een hoge sociale status, zullen hoge T jongeren in zulke kringen
Hoofdstuk 5 Samenvatting

meer gemotiveerd zijn deze status te verkrijgen ongeacht of dat moet door middel van crimineel en agressief gedrag. Kortom, personen die naast een hoge T waarde ook bloot zijn gesteld aan andere biologische en sociale risicofactoren lopen het grootste risico voor het ontwikkelen van life-course persistent antisociaal gedrag. Bovendien heeft antisociaal gedrag ook negatieve consequenties die het gedrag en de vijandige attributiestijl in stand houden, zoals het vervreemden van het sociale netwerk, afwijzing en veroordeling door de maatschappij en een hoop sociale en juridische problemen.

Daarentegen zullen kinderen met hoge T niveaus maar die een gezonde en plezierige sociaal-emotionele ontwikkeling genoten hebben en geen genetische predispositie tot neurochemische disfunctioneren hebben, een veel lager risico lopen op het ontwikkelen van life-course persistent antisociaal gedrag. Deze individuen kunnen misschien enige problemen ervaren in hun impulscontrole tijdens de pubertijd, voornamelijk wanneer niet genoeg begrenst door opvoeders, maar dit gedrag is sneller van voorbijgaande aard en minder snel geneigd door te zetten tot in de volwassenheid. Een lage genetische lading richting antisociaal gedrag gekoppeld met een normatieve of gebalanceerde niveau van sociale stress reguleert belangrijke hersensystemen, zoals de HPA-as en serotoninere systeem, die als beschermende factoren kunnen dienen tegen het ontwikkelen van antisocialiteit. Positieve sociale ervaring kunnen ook beschermend werken doordat deze een gezonde sociaal-psychologische ontwikkeling bevorderen en leiden tot een betrouwbaar en veilig wereldbeeld. Omdat een hoge T niveau op een wat algemenere manier de gevoeligheid van het individu op zijn sociale omgeving verhoogt en andere variabelen bepalen of deze ontwikkeling prosociaal of antisociaal is, is beargumenteerd dat T in positieve omgevingen ook sociaal bewonderenswaardige eigenschappen kan bevorderen zoals leiderschap kwaliteiten, competitiviteit, eerlijkheid in onderhandelingen en sociale assertiviteit.

Net zoals T een modulerende in plaats van directe effect heeft op de sociale ontwikkeling kan T alleen de psychopathische stoornis verergeren en leiden tot hogere niveaus van geweld en criminaliteit als er al sprake is van andere en meer primaire en directe risicofactoren richting dit gedrag. Individuen die worden gekarakteriseerd door een emotionele verstoring, zoals geassocieerd met serotonine-deficiëntie en een gedereguleerde HPA-as activiteit, kan T met name de risico vergroten op reactieve agressiviteit en secundaire vormen van psychopathie terwijl in individuen met een basale emotionele deficiëntie, zoals geassocieerd met serotoninere hyperstabiliteit en een lage HPA-as reactiviteit, kan
Nederlandse Samenvatting

T het risico voor primaire psychopathie en instrumentale agressiviteit verhogen.
What is psychopathy? How is it possible for such detached and immoral individuals to outwardly appear just as normal, if not more well-adjusted than the average person? What makes psychopaths different from normal criminals and the general population at large? How are these differences reflected in biology and psychology? Moreover, how do biological, social, and psychological risk-factor interact to contribute to such a conscienceless and predatory personality profile?

These were the questions that initially drove me to start my journey into the depths of the psychopathic mind. This journey accelerated back in 2005 when I first read *Personality Disorders in Modern Life* by Theodore Millon and his colleagues. The amazing talent of Dr. Millon to describe the most complex workings of the human mind in such readily understandable language helped me to gain a more holistic and comprehensive understanding of personality development. Unfortunately, this great man of science has recently deceased in January 2014 at the age of 85 before I could meet him. I want to sincerely thank him for his great work. Other authors that strongly shaped my thinking on the subject and who I cannot thank enough are John Bowlby, Otto Kernberg, Robert Hare, Hervey Cleckley, David Lykken, Allan Schore, James Blair, Joaquin Fuster, Jack van Honk, Aaron Beck, Reid Meloy, Robert Sapolsky, Jay Schulkin, and Stephen Stahl.

My interest in psychopathy and associated personality features eventually propelled me to work in the forensic sector. For my Master’s thesis, I decided to conduct empirical research on the neuropsychological correlates...
of the Psychopathy Checklist-Revised (PCL-R) in a large forensic clinic. Then in 2009, I was motivated by my professor, Jan Derksen to start a PhD under his guidance. Although I had never considered the possibility before, the prospect of further investigating the psychopathic condition resonated with my core interests in the human mind. Truly understanding the psychological antecedents of violent and immoral behavior, and investigating how brain abnormalities might contribute to such acts, had become my passion. Little did I know back then that the road ahead was more bumpy, arduous, and confusing than I could have ever imagined. The personality profiles ascribed to psychopathy and the literature regarding associated psychological and neurobiological profiles is wrought with many inconsistencies, nuances, paradoxes, exceptions, and seemingly incompatible data that makes for a challenging task for those who wish to construct a scientifically coherent and holistic theory on its causal etiology, rather than identify biological or psychological risk factors.

This thesis on the etiology of psychopathy is the result of many years of dedicated full-time work, which I could not have achieved were it not for my parents Aynur and Halil Yildirim who were always thoughtful and considerate of my ongoing work. Thanks dad for your tremendous help with the references! Special thanks also to my sister Yağmur Yildirim who believed in me and helped me to stay focused on my main goals. She is, and has always been, one of my best friends en my trusted confidant. I further thank my friends Justin Soemoredjo, Nana Cardna, Demian Kreemers, Gregor van den Bosch, Jorrit van Deur, and Tarik Brummelaar, who helped me to forget my work and have fun. Also special thanks to my close friend Beyhan Güngörmez for supporting me all the way through, always giving me the courage to continue. And Désiré Palmen, thank you for our many interesting talks, but also for being the first one to actually read the entire book and give me feedback. It was invaluable. Last but not least, I want to thank Jan Derksen who believed in me from the get-go and who always made time whenever I needed his help or advice. The creativity, persistence, and discipline I showed during these years had certainly not been possible were it not for the many instances that they helped me regulate the apparently inescapable conative and affective fluctuations inherent to such a task, and through love incited my passions and ambitions that kept me going. I sincerely thank you all,

Bariş Onur Yildirim,
Nijmegen, Netherlands, 2015
My name is Bariş Onur Yıldırım and I was born in 1984 in Istanbul, Turkey. Because of the political ideas of my parents we were forced to flee to the Netherlands in 1985, where we live, study, and work ever since. I have completed high school with a main interest in the fields of mathematics, physics, and chemistry. After high school, however, I became increasingly involved and interested in human behavior and physiology, which led me to choose Psychology, and later Clinical Psychology and Psychopharmacology as my master at the Radboud University of Nijmegen. I finished cum laude and continued to work as a psychologist for several years and in different institutions but eventually turned to research and development as my main passion and interest. I am currently employed at the pharmaceutical branch of Johnson & Johnson, called Janssen Pharmaceutica, in Beerse (Belgium), where I help design new pharmaceutical treatments for a variety of mental disorders, including depression, Alzheimer’s disease, schizophrenia, and anxiety disorders.

**Research**

My research interests are on the field of clinical psychology and neurobiology. In these areas I examine the potential role and interaction of biology and environment in shaping intricate mental disorders such as psychopathy and antisocial/borderline, depression, and schizophrenia, but also behavioral patterns.
such as delinquency, violence, aggression, impulsivity, anxiety, and empathy more specifically. I spend particular focus on the genetics, prenatal risk factors, hormones, and other biological risk factors and try to disentangle how these factors interact with social experiences in shaping behavior. The method employed for this thesis is qualitative meta-analysis which entails the systematic review and structural analysis of the literature regarding the different facets of a certain relationship (e.g., dopamine and impulsivity) in order to identify consistent correlations, evaluate possible causal mechanisms, and eventually, commence new theories. By constantly switching from a thorough review of causal mechanisms on the level of socio-biology to a more general understanding of the functional relevance of those mechanisms for psychology, I have constructed several holistic theories on the etiology of mental disorders as rooted in a matrix of interdependent biological, environmental, and psychological influences. The ambition is to integrate theory and research from neurobiological and psychological sciences in order to place this work in a broader conceptual framework and promote synergy across fields.

Goals and Ambitions

My goal is to introduce new methods for early and adequate diagnosis of, and pharmaceutical and psychotherapeutic treatment of a variety of mental disorders.

Experience

- Post Doc Traineeship/Manager Neuroscience R&D (Johnson&Johnson)
- Trainer Psychotherapy (Radboud University)
- Assistant Teacher Clinical Psychology (Radboud University)
- PhD. Student (Radboud University)
- Psychologist in Addiction Clinic (CARE zorg)
- Psychologist/ EMDR therapist in an Intercultural Setting (iPsy)
- Interim Researcher (Forensic Psychiatric Clinic Oldenkotte)
- Section Psychologist (Forensic Psychiatric Clinic Oldenkotte)
- Spokesperson/Negotiator/Social Worker for a Juvenile Center for Adolescent Delinquents from a Disadvantaged Neighborhood
List of Publications


Upcoming Publications


Books

*What Makes A Psychopath: Neurodevelopmental Pathways to Immoral and Antisocial Behavior.*

A 700 page book that introduces and comprehensively discusses various novel perspectives on the conceptualization and etiology of psychopathy. *Finished, expected publication date; 2016-2017.*