Sina Radke



Acting social

Neuroendocrine and clinical modulations of approach and decision behavior

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Acting social

Neuroendocrine and clinical modulations of approach and decision behavior

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Sina Radke

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Promotor

Prof. dr. R. P. C. Kessels

Copromotor

Dr. E. R. A. de Bruijn

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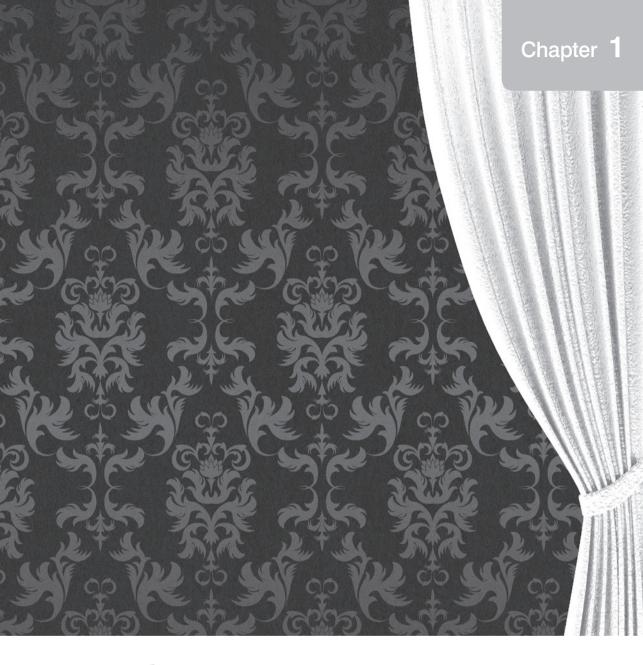
Prof. dr. M. Ullsperger Prof. dr. C. K. W. de Dreu (UvA)

Dr. A. G. Sanfey

Table of Contents

Chapter 1	Introduction	7		
Chapter 2	Acting on anger Psychological Science, 2013, 24(8), 1573-1575	21		
Chapter 3	Regulating approach in preparation	35		
Chapter 4	Ready to go! in preparation			
Chapter 5	In action or inaction? under review			
Chapter 6	There's something about a fair split PLoS ONE, 2012, 7(2), e31491	75		
Chapter 7	The other side of the coin Frontiers in Human Neuroscience, 2012, 6, 193			
Chapter 8	Unfair offers, unfair offenders? Frontiers in Human Neuroscience, 2013, 7, 406	105		
Chapter 9	Facing unfairness Psychiatry Research, 2013, 201, 438-443	121		
Chapter 10	Summary and Discussion	137		
	References	153		
Appendix	Publications	173		
	Curriculum Vitae	175		
	Nederlandse samenvatting	177		
	Deutsche Zusammenfassung	181		
	Acknowledgements	185		
	Donders Graduate School for Cognitive Neuroscience Series	187		





Introduction

Humans almost constantly engage in social behaviors. We interact with family members, friends, colleagues, and strangers on a daily basis and often in highly complex, changing social environments. Efficient regulation of social behaviors is vital for both our psychological well-being and our fitness (Darwin, 1859). Along these lines, appropriate expression of social approach behaviors, e.g., mating and bonding, ensures propagation of a species. In addition, commonly shared social standards. e.g., dividing food and duties, strengthen group cohesion. Motivational processes like these benefit survival in both lower and higher organisms, but particularly human social interactions are vastly intricate. To handle this complexity, we adapt our behavior to different interaction partners and situations as well as to different roles and standards that come along with them. For example, we might dominate our colleagues at work and respond sensitively and caringly to the needs of our children. In contrast, other individuals in the same situation might behave even in an entirely different manner than we do. This thesis will investigate internal and external factors that modulate two categories of social behavior, i.e., social approach behavior and social decision-making. As internal factors, both biological and psychological influences will be examined by looking at the impact of i) 'social' hormones, i.e., oxytocin and testosterone, which prime a wide range of social behaviors across species, and ii) traits and dispositions in subclinical manifestations as well as their more extreme forms - psychiatric disorders. With regard to external modulations, the focus lies on the social elements of the interaction, such as characteristics of interaction partners, e.g., their emotional expression or intention.

Social approach

Engaging in social interactions, i.e., social approach, traditionally involves physical contact, such as during mating or bonding. The motivational tendency to get close to others is derived from the emotional evaluation of stimuli, i.e., objects or other persons. Usually, positive or desirable stimuli elicit approach tendencies, whereas negative or threatening stimuli trigger avoidance (Chen & Bargh, 1999). These action tendencies manifest in many of our daily behaviors, for instance when we draw loved ones to us for a hug or when we shove someone who attacks and might harm us. Examples like these hint at the association of motivational tendencies with body movements, which has already been proposed by Darwin (1872, p. 64): "if we eagerly wish an object to move in any direction, we can hardly avoid moving our bodies in the same direction, although we may be perfectly aware that this can have no influence". Since then, the idea of motivationally congruent motor responses has received empirical support, with approach being linked to pulling objects closer to oneself, while avoidance is linked to pushing them away (Chen & Bargh, 1999; Duckworth,

Bargh, Garcia, & Chaiken, 2002; Solarz, 1960). To assess approach-avoidance behavior in experimental settings, participants often pull a joystick towards or push it away from their body. The joystick movement causes participants' arm to move likewise, i.e., to flex (approach) and to extend (avoidance). Reaction time (RT) differences between the two movement directions are taken as an indication of individual dominant behavioral tendencies. A well-established social task variant is the Approach-Avoidance Task (Roelofs, Minelli, Mars, van Peer, & Toni, 2009; Roelofs et al., 2010; Rotteveel & Phaf, 2004), which relies on facial expressions as stimuli. Healthy participants typically show an approach tendency in response to happy faces and an avoidance tendency in response to angry faces. Conversely, altered approach-avoidance tendencies can be identified on both a clinical and an empirical level in populations associated with inflexibilities and impairments in interpersonal behavior, e.g., socially anxious or psychopathic individuals (Heuer, Rinck, & Becker, 2007; Roelofs, et al., 2010; Von Borries et al., 2012).

In contrast to the rigidity evident in psychopathological states, healthy individuals display remarkable flexibility in regulating initial tendencies, which renders a 1-to-1 mapping between valence and motivational direction difficult. Basic biological mechanisms, e.g., the influence of hormones such as cortisol, may shape the expression of social motivational behavior (van Peer et al., 2007; van Peer, Spinhoven, van Dijk, & Roelofs, 2009). In addition, more psychologically elaborate strategies such as goal-setting are likely to modulate our initial reactions to emotional stimuli (Elliot & Covington, 2001). After all, observable approach behavior towards negative stimuli might be a means to an end and serve different purposes, e.g., approaching someone sad in order to provide comfort (Seidel, Habel, Kirschner, Gur, & Derntl, 2010) or approaching fearful stimuli in order to overcome one's fear (as in exposure therapy). Similarly, impulse control is particularly indicative when avoiding directly rewarding stimuli, for instance caloric or sexual temptations that compete with abstract, long-term goals such as maintaining a stable weight or relationship.

Previous neuroimaging studies have established the involvement of a prefrontal region, the anterior prefrontal cortex, during counterintuitive responses, i.e., when approaching angry and avoiding happy faces during the Approach-Avoidance Task (Volman, Roelofs, Koch, Verhagen, & Toni, 2011; Volman, Toni, Verhagen, & Roelofs, 2011; Volman et al., 2013). In the study of Volman, Roelofs et al. (2011), inhibition of this area entailed not only more errors, but also increased activity in the amygdala, a brain structure that prompts automatic behavioral responses (Quirk & Gehlert, 2003). Moreover, in a male sample, higher endogenous testosterone levels were associated with 1) decreased activity of the anterior prefrontal cortex and 2) reduced connectivity between the anterior prefrontal cortex and the amygdala when action tendencies needed to be regulated (Volman, Toni, et al., 2011). Taken together, these findings highlight the crucial role of the anterior prefrontal cortex and point to potential

hormonal influences in social motivational behavior. However, the causal impact of testosterone and other hormones relevant for social approach behavior, e.g., oxytocin, has not been addressed in human research until now.

Social decision-making

When engaging with others, we often decide between different options or courses of action – for instance, whether we will literally get engaged with our partner and share the rest of our lives with each other. These decisions take place in a social context, meaning that our choices affect not only ourselves, but also other individuals, whom we take into account. Along with them, their needs, intentions or wishes influence our decisions to a great extent, especially when they conflict with our own interests. As a result, various concerns and standards are weighed and negotiated, ranging from simple situations, such as allocating household chores when moving in together, to complex peace negotiations between several nations. Despite their simplicity, economic paradigms provide reliable formal accounts of strategic interactions that converge with actual behavior (Camerer, 2003).

A game representing the last step in many bargaining contexts is the Ultimatum Game (Güth, Schmittberger, & Schwarze, 1982). Here, two players interact in dividing a stake, with the first player, i.e., the proposer, making a take-it-or-leave-it-offer. Subsequently, the other player, i.e., the responder, decides whether to 'take' (accept) or 'leave' (reject) it. If the responder accepts, the split is implemented as proposed; in the case of rejection, neither player receives anything. Importantly, the game ends in either case; there is no further interaction. Besides, the players usually remain anonymous in order to capture the most stable individual preferences. In experimental settings, this means usually that the game is played via a computer-interface where the relevant information is provided throughout all stages of the game.

In the Ultimatum Game, proposers typically offer around half of the stake, generally leading to acceptance and mutual financial benefit. In contrast, if only one-fifth is offered, rejection considerably increases to about 50% and rises even more as offers become more unfair. In other words, responders prefer to end up with nothing rather than being treated unfair. This phenomenon is relatively stable across cultures and stake sizes (Camerer, 2003), hinting at underlying concerns that go beyond maximizing one's own payoff. Preferences for an equal sharing of resources, alongside with a dislike for unequal outcomes, are evident in non-human primates and young children as well (Blake & McAuliffe, 2011; Brosnan et al., 2010; Takagishi, Kameshima, Schug, Koizumi, & Yamagishi, 2010).

Yet, in human negotiations, social preferences comprise not only the (un)fairness based on the distribution. Instead, we also ponder – often in our daydreams – about

different options both in the past and in the future as well as their potential consequences, for example how would we live now if we had rented a small apartment instead of buying this house or what would I do if I win in the lottery next Saturday. Additionally, we consider the motivations and intentions of others e.g., our decision to share a house or our lottery win with our partner might depend on his/her interest being truthful and affectionate versus being devoted entirely to our possessions and wealth.

A variant of the Ultimatum Game has been developed to assess these more elaborate considerations when taking the role of responders in fairness decisions. In this modified version, the proposer chooses from a fixed set of two allocations, which establishes the 'context' in which an offer is selected. Unfair proposals that are identical in terms of payoff (one-fifth of the stake for the responder) are paired with different alternatives. Since not much conflict or negotiation can be expected to arise from a fair 50:50 offer, reactions to unfair offers form the main research interest. Essentially, this is driven by the question "what makes an offer unfair?" Indeed, responders behave differently depending on the options that had initially been available, but were not chosen: Unfair offers are most often rejected when the alternative was an equal split (Falk, Fehr, & Fischbacher, 2003; Güroğlu, van den Bos, & Crone, 2009; Sutter, 2007).

However, it remains open whether this manipulation actually assesses higher-order social reasoning (Falk, et al., 2003; Güroğlu, et al., 2009) or straightforward outcome comparisons (Brandts & Sola, 2001; Sandbu, 2007). Moreover, previous research points to the importance of intentionality in social decision-making as unfair offers are rejected more often when playing against a human than against a computer (Blount, 1995; Rilling, Sanfey, Aronson, Nystrom, & Cohen, 2004; Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003; van't Wout, Kahn, Sanfey, & Aleman, 2006). Still, these higher social inferences have hardly been methodologically disentangled from outcome-based judgments. In addition, although inequity aversion is a robust phenomenon, the strength of social preferences varies between individuals and situational constraints (Camerer, 2003; Fehr, 2009). Taken together, fairness considerations appear to be sensitive to a wide scope of factors, ranging from outcome- and socially relevant information to interindividual differences. This clearly necessitates systematic empirical investigations on different aspects of fairness considerations in several populations. Fundamental research in healthy samples can contribute to providing a solid basis for examining psychological states that have been associated with impairments in decision-making, e.g., individuals suffering from psychiatric disorders.

Individual variations in social behavior

'Social' hormones

The hormone, i.e., endocrine, system is a main communication system of our body that regulates homeostasis. Being essential for homeostasis and survival, many social, particularly reproductive, behaviors are influenced by hormones. Research in non-human animals has established the role of peptide hormones, such as vasopressin and oxytocin, in parental as well as partner bonding. Steroid hormones, especially cortisol and testosterone, have been implicated in responses to stress and social challenges. Since four empirical chapters of this thesis will examine the role of oxytocin or testosterone in social behavior, a brief biological framework for these studies will follow.

Oxytocin is composed of nine amino acids and synthesized in the mammalian hypothalamus. Being a neuropeptide, it is not only released into the bloodstream by the posterior pituitary gland, but via axonal projections, it also functions as a neurotransmitter with targets in several brain regions, such as the amygdala (Insel & Shapiro, 1992; Veinante & Freund-Mercier, 1997). Peripheral and central oxytocin can be regulated independently (Neumann, Ludwig, Engelmann, Pittman, & Landgraf, 1993). In human psychological research, the latter form the main interest, with emerging evidence on the involvement of oxytocin in various aspects of social cognition. Major attention has been drawn to improvements on complex behaviors implying prosociality, e.g., trust, cooperation, and 'mind-reading' (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008; Domes, Heinrichs, Michel, Berger, & Herpertz, 2007; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005; Mikolaiczak et al., 2010; Mikolajczak, Pinon, Lane, de Timary, & Luminet, 2010; Zak, Stanton, & Ahmadi, 2007). From an information processing view, it has been argued that oxytocin intensifies the salience of social stimuli, as reflected in an increased sensitivity to biological motion (Keri & Benedek, 2009) and a shift towards processing (positive) social stimuli (Gamer, Zurowski, & Büchel, 2010; Guastella, Mitchell, & Dadds, 2008; Guastella, Mitchell, & Mathews, 2008; Rimmele, Hediger, Heinrichs, & Klaver, 2009). Both of these perspectives on the oxytonergic modulation of human behavior are sustained by studies that reveal attenuated responses to stress and threat as well as (social) anxiety after oxytocin administration (Bartz, Zaki, Bolger, & Ochsner, 2011; Ditzen et al., 2009; Heinrichs & Domes, 2008; Heinrichs et al., 2006; Norman et al., 2010). Therefore, it has also been suggested that oxytocin, instead of selectively enhancing social-cognitive functions, acts on underlying motivational factors, for instance by anxiolysis (Churchland & Winkielman, 2012; see also Kemp & Guastella, 2010a; Kemp & Guastella, 2010b). Furthermore, it downregulates stress reactivity, e.g., by decreasing cortisol levels (Ditzen, et al., 2009; Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Quirin, Kuhl, & Duesing, 2010). As psychophysiological indicators of autonomic responses are also modulated by oxytocin, e.g., increased

heart rate variability (Gamer & Büchel, 2012; Kemp et al., 2012; Norman et al., 2011), oxytocin might facilitate social engagement and approach-related behaviors partially through peripheral influences. Yet, some recent studies indicate that the initially promising 'prosocial' findings are restricted to members of one's own group and might even reverse into 'antisocial' tendencies when dealing with outsiders (Bartz, et al., 2011; De Dreu, 2012; De Dreu et al., 2010; De Dreu, Greer, Van Kleef, Shalvi, & Handgraaf, 2011a; Shamay-Tsoory et al., 2009). Moreover, the effects of oxytocin depend on subclinical and clinical dispositions (Alvares, Chen, Balleine, Hickie, & Guastella, 2012; Bartz, et al., 2011; Bartz et al., 2010; Guastella, Howard, Dadds, Mitchell, & Carson, 2009; Guastella & MacLeod, 2012; Kret & De Dreu, 2013; Luminet, Grynberg, Ruzette, & Mikolajczak, 2011; Norman, et al., 2011; Quirin, et al., 2010), so that further investigation is warranted, especially for inferences on oxytocin's therapeutic potential.

The steroid hormone testosterone is mainly secreted in the testes and ovaries. In the brain, it binds to androgen receptors in the amygdala and the prefrontal cortex (Sarkey, Azcoitia, Garcia-Segura, Garcia-Ovejero, & DonCarlos, 2008). Additional cerebral effects can be obtained via estrogen receptors after testosterone has been converted to estradiol (Cornil, Ball, & Balthazart, 2006). Similarly to oxytocin, testosterone reduces stress and fear (Hermans et al., 2007; Hermans, Putman, Baas, Koppeschaar, & van Honk, 2006; McCall & Singer, 2012; van Honk, Peper, & Schutter, 2005) and has been implicated in social approach behavior, yet particularly in the context of aggression (Bos, Panksepp, Bluthe, & van Honk, 2012; Hermans, Ramsey, & van Honk, 2008; Montova, Terburg, Bos, & van Honk, 2012). However, rather than increasing dominance behaviors indiscriminately, testosterone modulates the perception of social challenges and enables subsequent adaptive responses (Wingfield, Hegner, Dufty, Alfred, & Ball, 1990). Along these lines, depending on the social environment, this may give rise to aggressive on the one hand and to prosocial behavior on the other hand (Eisenegger, Naef, Snozzi, Heinrichs, & Fehr, 2009; van Honk, Montoya, Bos, van Vugt, & Terburg, 2011; van Honk, Terburg, & Bos, 2011; Wibral, Dohmen, Klingmuller, Weber, & Falk, 2012). Furthermore, the effects of testosterone differ with respect to individual factors such as dominance motivation and prenatal exposure to androgens (Mehta & Josephs, 2011; Montoya et al., 2013; Schultheiss et al., 2005; van Honk et al., 2011). Testosterone also interacts with cortisol, which is evident by an enhanced proneness to socially aggressive behavior of individuals with high testosterone and low endogenous cortisol (Carre & Mehta, 2011; Denson, Mehta, & Ho Tan, 2013; Mehta & Josephs, 2010; Montoya, et al., 2012).

Taken together, this highlights the fundamental role of personal variability in social endocrinology and points to the interplay between basic biological processes and psychological dispositions, which will be addressed in this thesis as well (e.g., **chapter 2**).

Disturbances of social behavior

Studying psychopathological states associated with deficits in social behavior is essential for a better understanding of dysfunctional behavior as well as for developing and tailoring treatment. Moreover, new insights can provide a more thorough picture of the mechanisms underlying social behavior in healthy individuals. Although disturbances in social interactions are more or less common in all psychiatric conditions, some disorders are of particular relevance with respect to social motivational behavior.

For instance, social anxiety is characterized by a substantial, intense fear of social situations that involve being evaluated by others (American Psychiatric Association, 2000). Patients with social anxiety disorder are hypervigilant to cues signaling social threat, i.e., angry facial expressions, or social attention, i.e., facial expressions with direct gaze. An increased self-focus, particularly during social threat and other situations experienced as stressful (Hofmann, 2007; Ingram, 1990), is likely to uphold negative self-beliefs. Besides, their anxiety is sustained by safety behaviors, i.e., avoidance, thereby establishing a positive feedback loop that hinders fear extinction (Hofmann, 2007). Severe avoidance tendencies have been captured empirically with the Approach-Avoidance Task in highly socially anxious individuals (Heuer, et al., 2007; Roelofs, et al., 2010), highly avoidant individuals (van Peer, et al., 2007; van Peer, et al., 2009) and patients with social anxiety disorder (Roelofs et al., 2009).

Opposing motivational tendencies are illustrated by the antisocial lifestyles of individuals with psychopathy. Psychopathy has also been described as 'social predation', which points to their use of instrumental behavior in social situations (Glenn & Raine, 2009). In offenders with psychopathy, instrumental behavior can manifest in aggression and serious violent crimes. This – destructive – expression of social approach goes in hand with little consideration or empathy for their victims (Hare, 2003). Crucially, individuals with psychopathy neither display a reactivity to distress cues (R. J. Blair, Mitchell, & Blair, 2005) nor avoidance tendencies that are usually evoked by angry faces (Von Borries, et al., 2012). In addition, the study by Von Borries et al. showed that the absence of the inclination to react to social threat with avoidance was related to self-reported instrumental aggression and (a lack of) personal distress when observing another's negative experiences. Therefore, individuals with psychopathy might perceive interpersonal signals of threat and distress as an opportunity for reward when pursuing personal goals. Although the prevalence of instrumental aggression in psychopathy suggests a strong goal-directedness in their behavior towards others, research is scarce in this population on interactions in which their decisions and actions have actual consequences for themselves and for others.

Whereas individuals with psychopathy primarily rely on instrumental behavior (expressed as aggression) in their social interactions, avoiding instrumental behavior

in response to distress is a common symptom of depression (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). The dominance of recurrent negative thoughts and negative mood is associated with a reduced motivation to initiate action. Approach deficits, i.e., reduced energy and social withdrawal, are accompanied with inflexibilities in (social) information processing, e.g., biases for sad facial expressions and negative attributes (Gotlib, Krasnoperova, Yue, & Joormann, 2004; Leppanen, 2006). Given that impairments pervade basic attentional and cognitive functions (Beck, 2008; Gotlib, et al., 2004) as well as complex behaviors, such as decision-making (Cella, Dymond, & Cooper, 2010), it remains important to investigate different expressions of altered social behavior and the underlying mechanisms in patients with depression.

Experimental methods relevant for this thesis

Correlational studies have given rise to first insights into the interplay between hormones and behavior, for instance in the relationships between oxytocin and maternal care (Feldman, Weller, Zagoory-Sharon, & Levine, 2007; Galbally, Lewis, Ijzendoorn, & Permezel, 2011) as well as between testosterone and criminal behavior (Dabbs Jr, Carr, Frady, & Riad, 1995; Dabbs Jr, Ruback, Frady, Hopper, & Sgoutas, 1988). Nevertheless, for causal inferences, experiments that involve administration of hormones are indispensable.

Oxytocin administration

As oxytocin is a rather large, hydrophilic molecule (McEwen, 2004), peripherally (e.g., intravenously) administered oxytocin cannot penetrate the blood-brain-barrier and thus not exert its centrally-mediated effects in physiologically significant amounts (Ermisch et al., 1985). An alternative route for administering substances to the central nervous system via the nasal cavity has been established as a promising approach for neuropeptides, particularly since Born et al.'s (2002) seminal report. Here, increased levels of vasopressin were obtained in cerebrospinal fluid after intranasal administration within 80 minutes. Many studies followed relying on the same technique for delivering oxytocin, a peptide closely related to vasopressin, into the brain by means of a nasal spray. It is assumed that oxytocin passes through intracellular junctions of the olfactory epithelium and diffuses into the cerebrospinal fluid surrounding the olfactory bulb. Subsequently, it diffuses into the brain's extracellular space and reaches target regions such as the amygdala where it exerts its central effects (Landgraf & Neumann, 2004). Effects on social behaviors have commonly been found after 45 to 90 minutes post-administration (e.g., Domes, Heinrichs, Michel, et al., 2007; Gamer & Büchel, 2012; Kosfeld, et al., 2005; Schulze et al., 2011), but recent studies successfully endorsed even longer experimental durations (Ellenbogen, Linnen, Grumet, Cardoso, & Joober, 2012; Huffmeijer et al., 2012) or shorter onsets (e.g., De Dreu, 2011; Kret & De Dreu, 2013). While a dosage of 24 IU is handled in most studies, other quantities have also been used (e.g., Huffmeijer, et al., 2012; Zak, et al., 2007). Yet, the exact pharmacokinetic and pharmacodynamic properties of oxytocin remain to be investigated. Besides, Born et al. (2002) did not assess any behavioral effects following peptide administration, although the main outcome measures in human oxytocin research constitute changes in behavior.

Testosterone administration

In contrast to neuropeptides, steroid hormones such as testosterone are lipophilic, which enables them to diffuse across biomembranes, among which the blood-brain-barrier. It can therefore enter the brain directly (Runinow & Schmidt, 1996), where it targets androgen receptors in the amygdala and the prefrontal cortex (Sarkey, et al., 2008). Administering testosterone under the tongue, i.e., sublingually, entails immediate absorption into the bloodstream, evident in a sharp increase in plasma testosterone 15 minutes post-administration. Behavioral and physiological effects are measureable approximately 4 to 6 hours after testosterone intake (Tuiten et al., 2000), which has been verified by various investigations of social-emotional behaviors in young females (Bos, Hermans, Montoya, Ramsey, & van Honk, 2010; Bos, Hermans, Ramsey, & van Honk, 2012; Bos, Terburg, & van Honk, 2010; Hermans et al., 2010; Hermans, Putman, Baas, et al., 2006; Hermans, Putman, & van Honk, 2006).

Neuroimaging

Functional magnetic resonance imaging (fMRI) is a non-invasive imaging method that allows for drawing conclusions about the neural activity under certain experimental conditions. Enhanced neural activity is associated with enhanced use of oxygen and glucose, thereby increasing regional cerebral blood flow, and decreasing the amount of oxygenated hemoglobin. Due to the different magnetic properties of deoxygenated und oxygenated blood, changes in oxygen concentration can be captured as blood-oxygenated-level dependent (BOLD) signals. Stronger blood flow thus leads to stronger signals. The relation between neural activity and the BOLD-signal has been validated for neuroscientific research (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). The BOLD-response being rather weak for single measurements, multiple trials are necessary and subsequently averaged. Before making group inferences, data need to be preprocessed, for instance by standardizing individuals' brains into a common reference space. As body movements and verbal responses are likely to entail artifacts, responses in the scanner usually occur manually, i.e., by pressing buttons or in the case of the studies reported in this thesis via a joystick placed on the abdomen of participants.

Aim of this thesis

The present thesis investigates internal and external factors that modulate two categories of social behavior, i.e., social approach and social decision-making. Social approach is assessed with a behavioral and an fMRI-adapted variant of the Approach-Avoidance Task, and social decision-making is captured by modified versions of the Ultimatum Game. These two research angles each comprise four empirical chapters and will be addressed separately in succession. The first chapter of each section presents an experimental introduction to the research field, followed by investigations on (neuro-)endocrine and clinical modulations of social behavior. An outline of each chapter and its research question is given below.

First, **chapter 2** puts findings from animal research on the anxiolytic properties of oxytocin to test in a human sample. The study examines whether oxytocin facilitates social approach behavior in humans and in how far effects are modulated by individual differences in social anxiety. A distinction is made between different emotional expressions and gaze directions in order to determine whether oxytocin increases the salience of social information or approach-related behaviors in general.

Based on these results, a follow-up neuroimaging study with an adapted task version was conducted (**chapter 3**) to examine the neural mechanisms of social approach-avoidance tendencies after oxytocin administration. A similar methodological approach is taken in **chapter 4**, which addresses the causal role of testosterone in social approach behavior and the neural regulation thereof.

The influence of depression on social approach-avoidance tendencies is illustrated in **chapter 5**. Here, patients diagnosed with major depression are compared to a healthy control group in their reactions to happy and angry expressions with direct and averted gaze.

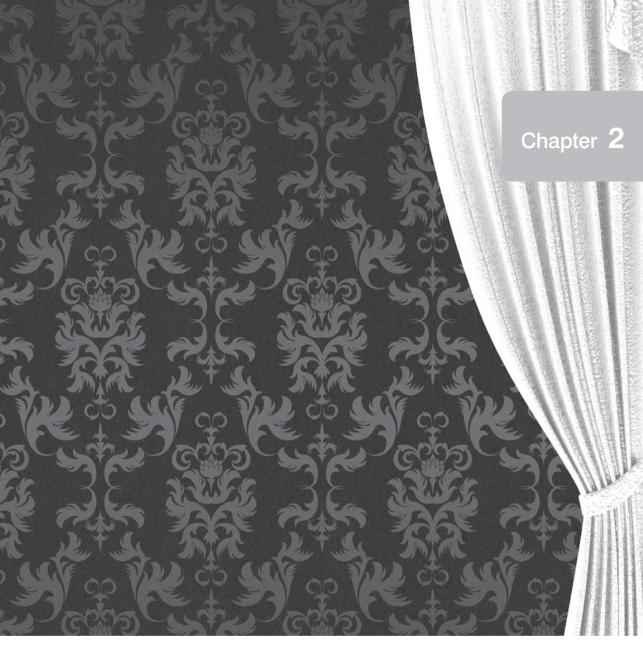
The aim of the first chapter on social decision-making (**chapter 6**) is to disentangle intention- and context-based fairness considerations. Specifically, the role of intentionality on responder behavior in a modified Ultimatum Game is analyzed. Both proposers' degree of control over the selection of offers and the context pertaining to the outcomes of offers proposers can choose from are manipulated.

Oxytocin has been implicated not only in social approach, but also in complex prosocial behaviors such as trust and generosity. In **chapter 7**, the effects of oxytocin administration on (pro-)social decisions that involve fairness norms are investigated in an Ultimatum Game. Additionally, to assess generosity, a Dictator Game is conducted.

The following two chapters portray fairness considerations in populations that have been associated with impairments in decision-making, i.e., offenders with psychopathy (**chapter 8**) and patients with major depression (**chapter 9**). In addition, **chapter 9** examines the impact of emotional facial expressions that accompany unfair offers on rejection patterns in healthy and depressed individuals.

Finally, the main findings are summarized and discussed in **chapter 10**. Further, this chapter will address methodological and clinical implications as well as future perspectives.





Acting on anger

Abstract

Oxytocin attenuates responses to stress and threat (e.g., by fostering social approach in animals), but direct investigations of whether the hormone also facilitates approach-related social behaviors in humans are lacking. To assess approach-avoidance tendencies, we had participants respond to images of happy and angry faces with direct or averted gaze by either pulling a joystick toward themselves (approach) or pushing it away from themselves (avoidance). When given a placebo, participants' action tendencies were typical, with happy faces eliciting approach responses and angry faces eliciting avoidance responses. However, 24 IU of oxytocin moderated these tendencies, with the inclination to approach angry faces with direct gaze being negatively related to social anxiety. The results demonstrate that oxytocin facilitates approach in humans in response to social threat, which verifies its anxiolytic potential. Moreover, they underscore the moderating role of dispositional factors reported in endocrine research and their therapeutic implications.

Based on:

Radke, S., Roelofs, K. & De Bruijn, E.R.A. (2013). Acting on anger: Social anxiety modulates approach-avoidance tendencies after oxytocin administration. *Psychological Science*, 24(8), 1573–1578.

Introduction

The growing interest in the therapeutic potential of the neuropeptide oxytocin stems from its role in attenuating anxiety (Heinrichs, et al., 2003) and promoting complex prosocial behaviors, such as trust and empathy (Domes, Heinrichs, Michel, et al., 2007: Kosfeld, et al., 2005). However, translation of these findings into the appendix applications for disorders associated with social impairments, such as social anxiety disorders, warrants further investigation, especially because some recent studies report antisocial rather than prosocial effects (Bartz, et al., 2011). Because social deficits often affect social motivational behavior, and many clinical interventions aim to modify behavior, knowledge of the influence of oxytocin on social approach-avoidance tendencies is highly important. Moreover, because in both preclinical and clinical research, oxytocin effects tend to be moderated by dispositional and situational factors (Alvares, et al., 2012; Bartz, et al., 2011; Bartz, et al., 2010; Guastella, et al., 2009), insight into the underlying mechanisms is essential to determine for whom and in which contexts meaningful therapeutic benefits from oxytocin can be anticipated. Accordingly, in the present study, we investigated whether oxytocin influences basic social approach-avoidance tendencies and whether its effects are modulated by individual differences in social anxiety.

Approach and avoidance are the fundamental behavioral responses associated, respectively, with appetitive and aversive motivation (Chen & Bargh, 1999; Roelofs, Minelli, et al., 2009); pleasant or positive cues typically trigger approach behavior and threatening or negative stimuli typically trigger avoidant behavior (Chen & Bargh, 1999). These automatic action tendencies can be assessed using reaction-time (RT) paradigms such as the Approach-Avoidance Task (AAT; Roelofs, et al., 2010; Rotteveel & Phaf, 2004), in which participants react to facial expressions by pulling a joystick toward (approach) or pushing it away from (avoidance) themselves. Participants typically show an approach tendency to happy faces and an avoidance tendency to angry faces.

On the assumption that improved processing of social information will facilitate social approach behavior and interpersonal communication, human oxytocin research has focused on the processing of facial expressions. It is argued that oxytocin intensifies the salience of social stimuli, manifest in an increase in gaze shifts toward the eye region of faces (Guastella, Mitchell, & Dadds, 2008) and in emotion recognition (Domes, Heinrichs, Michel, et al., 2007). The valence specificity of these effects being unresolved (Fischer-Shofty, Shamay-Tsoory, Harari, & Levkovitz, 2010; Marsh, Yu, Pine, & Blair, 2010; Schulze, et al., 2011), the question remains whether changes in recognizing facial emotions are rooted in an intensified salience perception or in a stronger motivation to approach social interactions.

Oxytocin fosters social approach behavior in animals (Ross & Young, 2009). Yet, despite the need for experiments to involve "a behavioral measure of approach and avoidance behavior" (Gamer & Büchel, 2012, p. 91), human studies to date have mainly focused on the recognition of facial emotions. To bridge the gap between emotion detection and action, and to determine whether oxytocin increases the salience of social information (Kemp & Guastella, 2010b) or the motivation to seek social interactions (enhancing prosocial, approach-related behaviors), we employed the AAT and manipulated the direction of stimuli's eye gaze – a subtle but highly relevant indicator of social salience in humans (Petrovic, Kalisch, Singer, & Dolan, 2008).

Direct gaze is a strong imperative, signaling the start of an interaction and prompting the recipient to react (Adams & Kleck, 2005), whereas averted gaze does not incorporate such motivational affordances (Roelofs, et al., 2010). A general increase in the motivation to seek social interactions would promote approach in response to all facial expressions; however, the social salience hypothesis predicts a differentiation between gaze directions and emotions. Given its anxiolytic properties (Heinrichs, et al., 2003), we expected oxytocin to reduce avoidance or possibly even induce approach responses only to salient, threatening social cues (i.e., angry faces with direct gaze). Moreover, as the effects of oxytocin can be moderated by dispositional anxiety (Alvares, et al., 2012; Bartz, et al., 2010; Guastella, et al., 2009), we also investigated whether social anxiety modulated oxytocin-induced effects.

Methods

Participants

Twenty-four healthy male students (M age = 21.46 years, SD = 1.93) participated voluntarily and were financially compensated. None reported a current or past neurological or endocrine disease, medication use, or drug or alcohol abuse. Exclusion criteria included being below the age of 18 or above the age of 30, smoking more than five cigarettes a day, participating in another pharmacological study or donating blood within 2 months prior to the study, and having fever, the common cold, or allergic rhinitis ("hay fever") on test days. Participants abstained from caffeine, alcohol, and nicotine for 24 h before, and from eating and drinking (except water) for 2 h before, substance administration.

All participants gave their written informed consent. Procedures were in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of the Radboud University Nijmegen Medical Centre.

Procedure

The study was conducted following a randomized, placebo-controlled, double-blind, within-subjects design and using a standardized procedure (for pharmacological details, see the Supplemental Material). Participants were tested in two sessions: Prior to the first session, we administered 24 IU of oxytocin (Syntocinon; Novartis, Basel, Switzerland), and prior to the second session, we administered a saline solution; both were given intranasally. During each session, participants performed several tasks approximately 40 min after substance administration, a time window derived from earlier oxytocin studies (Domes, Heinrichs, Michel, et al., 2007; Gamer & Büchel, 2012; Kosfeld, et al., 2005). As the order of the tasks was counterbalanced between subjects, one half started the AAT approximately 45 min after substance administration and the other half approximately 65 min after substance administration (see the Supplemental Material).

AAT

To perform the AAT, participants needed to respond as quickly and as accurately as possible to the emotional expression of face cues by pulling a joystick toward themselves (approach) or pushing it away from themselves (avoidance). The stimuli consisted of three expressions (angry, happy, neutral) with either a direct or averted gaze (for additional information on the stimuli, see the Supplemental Material).

A total of 384 experimental trials were randomly presented in six blocks (3 emotions \times 2 responses). Participants were instructed to respond with approach movements to one emotion and with avoidance movements to the other (approach happy faces-avoid angry faces, approach happy faces-avoid neutral faces, approach angry faces-avoid happy faces, approach neutral faces-avoid happy faces, approach neutral faces-avoid angry faces). The order of the blocks was counterbalanced. Each block was preceded by 16 practice trials. RTs were recorded at four different joystick angles (7°, 14°, 21°, and 30°). For all analyses, the time between stimulus onset and the maximum joystick displacement was used.

Liebowitz Social Anxiety Scale.

The Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987) was used to assess fear and avoidance in 24 social situations. Respondents rated on a 4-point scale how anxious they would feel in the specified situation and how often they would avoid it.

Statistical analyses

Following a standard procedure (Roelofs, et al., 2010), we excluded trials with RTs less than 150 ms and greater than 1,000 ms (5.5% of all trials) from analysis. Median RTs were calculated for correct responses for each level of the four experimental

factors: Substance (oxytocin, placebo), Emotion (angry, happy), Gaze (direct, averted), and Movement (approach, avoid). As in previous AAT analyses (Roelofs, Minelli, et al., 2009), we contrasted the RTs for angry and happy faces with direct gaze using a repeated measures analysis of variance (ANOVA) with Substance, Emotion, and Movement as within-subjects factors.

To investigate the motivational direction of the effects and to correct for individual velocity differences, we obtained AAT effect scores by subtracting the individual median RTs for joystick pulls from the individual median RTs for joystick pushes; negative values reflected a relative avoidance tendency, and positive values reflected a relative approach tendency (Heuer, et al., 2007; Roelofs, et al., 2010). The effect scores were entered into a repeated measures analysis of covariance (ANCOVA; Substance × Emotion) with the LSAS score as a covariate to determine the moderating effect of social anxiety.

Results

The repeated measures ANOVA on the RTs for angry and happy faces with direct gaze showed a significant main effect of Emotion, F(1, 23) = 52.10, p < .001, partial $\eta^2 = .69$, and a significant Substance × Emotion × Movement interaction, F(1, 23) = 6.96, p = .015, partial $\eta^2 = .23$. None of the other main effects or interactions were significant (Fs < 1.06, ps > .32).

The main effect of emotion was due to faster reactions to happy faces ($M = 638.06 \, \text{ms}$, SD = 72.30) than to angry faces ($M = 680.27 \, \text{ms}$, SD = 63.26). Separate analyses of joystick pulls and pushes revealed a significant Substance \times Emotion interaction for pulls (approach), F(1, 23) = 8.23, p = .009, $Partial \, \eta^2 = .26$, but not for pushes (avoidance), F(1, 23) = 1.02, P = .32, $Partial \, \eta^2 = .04$.

The interaction between Substance, Emotion, and Movement was qualified by an Emotion \times Movement interaction in the placebo condition, F (1, 23) = 4.31, p = .049, partial p = .16, which was not significant after oxytocin administration, F (1, 23) = 1.03, p = .32, partial p = .04. The AAT effect scores (Figure 2.1) illustrate this expected pattern of approach for happy faces (M = 12.02, SD = 52.01) and avoidance for angry faces (M = -17.00, SD = 47.88) in the placebo condition. As predicted, after oxytocin administration, the AAT effect scores for angry and happy faces were not significantly different (M = 8.15, SD = 41.07, and M = -4.88, SD = 42.94, respectively).

Social anxiety effects

The repeated measures ANCOVA on AAT effect scores with social anxiety as a covariate showed a main effect of Substance, F (1, 22) = 6.84, p = .016, partial

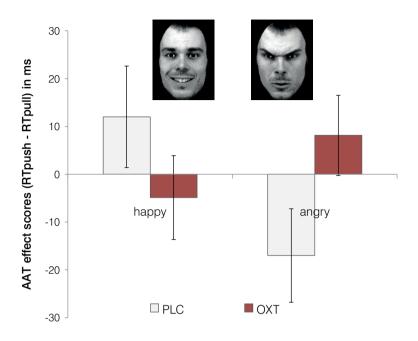


Figure 2.1. Mean effect score on the AAT for direct-gaze stimuli as a function of emotion type and drug condition (PLC = placebo; OXT = oxytocin). Effect scores were obtained by subtracting reaction times for pull movements from reaction times for push movements. Negative effect scores indicate avoidance tendencies, whereas positive effect scores indicate approach tendencies. Error bars represent standard errors. Also shown are sample angry and happy faces obtained from the Karolinska Directed Emotional Faces database (Lundqvist, Flykt, & Öhman, 1998; Identity AM29) and reproduced with permission from the copyright holders.

 $\eta^2=.24$, and interaction effects for Substance and Social Anxiety, F (1, 22) = 7.42, p=.012, partial $\eta^2=.25$, Substance and Emotion, F (1, 22) = 11.20, p=.003, partial $\eta^2=.34$, and, most critically, Substance, Emotion, and Social Anxiety, F (1, 22) = 4.84, p=.039, partial $\eta^2=.18$. The main effect of Social Anxiety was not significant (p=.24), and neither were the effect of emotion and the Emotion \times Social Anxiety interaction (Fs<.35, ps>.56).

The significant interactions were driven by a substance effect in reaction to angry faces, F (1, 22) = 13.11, p =.002, partial η^2 = .37, which was additionally modulated by social anxiety (i.e., a Substance × Social Anxiety interaction), F (1, 22) = 9.03, p = .007, partial η^2 = .29. Under oxytocin, approach toward angry faces increased, whereas responses to happy faces showed no substance effect, F (1, 22) = .28, p = .60, partial η^2 = .01, nor a Substance × Social Anxiety interaction, F (1, 22) = .30, p = .59, partial η^2 = .01.

Social anxiety associations were further explored using correlation analyses between social anxiety and individual AAT effect scores for emotional faces. There was a significant negative correlation for angry faces after oxytocin administration, r=-.58, p=.003 (Figure 2.2), which was absent after placebo administration, r=.30, p=.16. For happy faces, action tendencies were not associated with social anxiety after either oxytocin administration, r=-.23, p=.28, or placebo administration, r=-.10, p=.65. Accordingly, oxytocin increased approach behavior for angry faces with direct gaze specifically in participants scoring low on social anxiety.

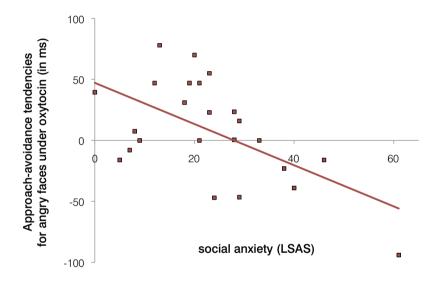


Figure 2.2. Scatter plot (with best-fitting regression line) showing effect scores on the AAT for angry faces with direct gaze after oxytocin administration as a function of social anxiety. Effect scores were obtained by subtracting reaction times for pull movements from reaction times for push movements. Social anxiety was measured using the LSAS (Liebowitz, 1987).

Averted gaze and neutral faces

Averted-gaze stimuli yielded no substance-related effects. Detailed analyses of averted-gaze stimuli and RTs for neutral faces are provided in the Supplemental Material.

Discussion

Our investigations into the influence of oxytocin on social motivational behavior in human subjects yielded three major findings. After placebo administration, participants displayed typical behavior on the AAT - approach tendencies for happy faces and avoidance tendencies for angry faces – replicating previous findings (Roelofs, et al., 2010; Rotteveel & Phaf, 2004; Volman, Toni, et al., 2011). Oxytocin altered approach-avoidance behavior for direct-gaze cues, which confirmed our hypothesis. It increased approach toward angry faces with direct gaze in participants with low levels of social anxiety.

Our results corroborate previous studies showing that oxytocin attenuates anxiety and stress (Heinrichs, et al., 2003), for example, by decreasing aversion to angry faces (Evans, Shergill, & Averbeck, 2010) and arousal to human threat stimuli (Norman, et al., 2010). But do oxytocin's anxiolytic properties foster prosocial, approach-related behaviors or enhance the salience of social information (Kemp & Guastella, 2010b)? Our findings favor salience modulation as the underlying mechanism and do not support the prosocial-approach account (universally enhanced approach). They corroborate earlier findings differentiating the salience of social cues (i.e., the direction of eye gaze and valence) but also point to the importance of dispositional factors.

Crucially, the inclination under oxytocin to approach signals of social threat or dominance, i.e., angry faces with direct gaze (Adams & Kleck, 2005; Roelofs, et al., 2010: Terburg, Aarts. & van Honk, 2012), was negatively related to social anxiety. which highlights the fundamental role of personal variability in social endocrinology (Mehta & Josephs, 2011; van Honk, Montoya, et al., 2011; van Peer, et al., 2009) and oxytocin research in particular (Bartz, et al., 2011; Guastella & MacLeod, 2012). As to dispositional anxiety, findings are inconsistent, showing more beneficial effects of oxytocin for participants with low rather than high attachment anxiety (Bartz, et al., 2010) but also for individuals with high trait anxiety (Alvares, et al., 2012) and social anxiety disorder when administered alongside exposure therapy (Guastella, et al., 2009). A crucial difference between these seemingly opposing results lies in the social focus of the dependent measures used, namely, features of the attachment bond between subjects and their parents (Bartz, et al., 2010) versus cognitive self-perceptions about one's speech performance (Alvares, et al., 2012; Guastella, et al., 2009). Whereas the latter is essentially self-centered, the former involves the perception of interaction partners, which renders it more similar to the current study. Consistent with the absence of reductions in anxiety or symptom severity as such (Guastella, et al., 2009) in individuals with severe social anxiety, our results showed that oxytocin may not provide sufficient anxiolytic properties to improve their social functioning (Hoge, Pollack, Kaufman, Zak, & Simon, 2008). Similarly, a differential

sensitivity to external oxytocin might underlie our findings, as the approach/avoid-ance-social anxiety association was evident only under oxytocin. It is also debatable whether in individuals with high social anxiety, anxiety reduction would induce approach to social threat. Given that oxytocin effects are most likely dependent on an individual's social repertoire and context, appetitive tendencies might first develop in quiescent, safe environments or when social support is provided as an external stress buffer (Heinrichs, et al., 2003). Regarding its therapeutic potential, it is thus essential to establish which personal and situational factors will facilitate or counteract the beneficial effects of oxytocin.

Moreover, it remains to be investigated how far oxytocin-induced perceptual changes of angry faces complement the approach inclination. Recent data on gaze endurance suggests that unconscious, reflexive biological mechanisms trigger testosterone-induced dominance when individuals are confronted with social threat stimuli (Terburg, et al., 2012). Eye movements and endocrine assessments could then improve the understanding of automatic reactions, such as interactions of oxytocin and cortisol (Heinrichs, et al., 2003), that might underlie anxiolysis.

In sum, our study is the first to establish that in humans, oxytocin facilitates approach behavior in response to social threat, most likely by reducing anxiety. But what is the affective and adaptive value of approaching social threat? In animals, both affiliative (tend-and-befriend) and aggressive (fight-or-flight) tendencies have been associated with oxytocin (Campbell, 2008; Ross & Young, 2009), which renders it an important regulator of different expressions of social approach behavior. As dispositional characteristics such as anxiety further modulate the neuroendocrine priming of prepotent responses, tuning motivational behavior to intra- and interpersonal dynamics may prove to be important in optimizing flexibility and adaptiveness in social interactions.

Supplementary Materials

Pharmacological materials and procedure

Participants self-administered oxytocin (Syntocinon; Novartis) and a saline solution via a nasal spray with three puffs per nostril (each with 4IU oxytocin, i.e., a dose of 24IU). Apart from the active substance, the exipient ingredients of Syntocinon were propyl parahydroxybenzoate (E216; 0.4mg/ml), methyl parahydroxybenzoate (E218; 0.2mg/ml), chlorobutanol hemihydrate, disodium phosphate, citric acid, sodiumchloride, sorbitol 70%, glycerol and purified water. The saline solution (Pharmachemie B.V.) contained 8mg sodiumchloride per ml as well as benzalkonium chloride (0.1mg/ml) and purified water.

The two testing sessions were separated by 14 days and scheduled for weekdays, starting at 10 a.m. In order to avoid any bias due to potential differences in scent between the oxytocin and the saline spray, the experimenter was not present during substance administration. An independent assistant blind to the experimental hypotheses supervised the procedure and left immediately after substance administration. Participants were not able to detect the correct order of substance administration above chance level (M = 47.83%; t(22) = -.204, p = .84). Including the order of tasks as a between-subject factor in the analyses did neither alter the results from the rm ANOVA on RTs (i.e., the effect of Emotion and the Substance x Emotion x Movement interaction remained significant) nor the results from the ANCOVA on AAT effect scores with social anxiety as a covariate (i.e., the effect of Substance and the interaction effects involving Substance remained significant). The most critical p-values were p = .20 for Movement x Order in the ANOVA on RTs, and p = .84 for Substance x Order the ANCOVA on AAT effect scores, respectively.

One participant reported having had a nosebleed in the evening after one session (in which placebo was administered). This was classified as a mild adverse event with unknown relation to the substance as he indicated experiencing nosebleeds occasionally.

Stimulus Materials

For the AAT, pictures of three facial expressions (angry, happy and neutral) from eight actors (four men and four women) were selected from Ekman & Friesen (1976) and from Karolinska Directed Emotional Faces (Lundqvist, Flykt, & Öhman, 1998) and used as direct gaze stimuli (Figure 2.1 provides examples). In order to obtain stimuli with averted gaze, the eye pupils were cut-out and pasted either at the right or left side of the eye. Left and right gaze were pooled together as one level of the factor gaze, i.e., averted gaze. This procedure resulted in a set of 48 stimuli in total.

Stimuli were presented in black and white on a computer screen with a resolution of 1024 x 768 pixels. Participants had to respond by using a joystick of the type

Logitech Attack 3, which was placed between them and the computer screen. Each trial was self-paced and started with a blank screen. The joystick being in the resting (upward) position, participants pressed the fire button, which initiated the stimulus presentation in the center of the screen. Participants responded to the emotional expression by pushing the joystick away from or pulling it towards their body. The joystick movement implied that participants' arm moved likewise and caused the stimulus to shrink or grow in size. It disappeared when the minimum, respectively the maximum size was reached (initial size and minimal and maximal size of the stimuli in visual degrees were: 9.5°x13°; 3.5°x4.5°; and 15.5°x20°). During practice trials, the stimulus remained visible after an erroneous response (allowing participants to practice until the response was correct).

Supplementary Results

Averted gaze

The rm ANOVA for the RTs (Substance [oxytocin, placebo] x Emotion [angry, happy] x Movement [pull, push]) showed a significant main effect of Emotion, F (1, 23) = 21.70, p < .001, partial q² = .49, and a significant Emotion x Movement interaction, F (1, 23) = 9.44, p = .005, partial q² = .29. All other effects were not significant (Fs < 1.94, ps > .12); in particular, the 3-way interaction of Substance x Emotion x Movement was, F (1, 23) = 1.94, p = .18, partial q² = .08.

The main effect of Emotion was due to faster reactions in response to happy faces ($M=639.47~{\rm ms}, SD=79.50$) than to angry faces ($M=675.30~{\rm ms}, SD=65.15$). The Emotion x Movement interaction was qualified by an effect of movement for angry faces, F (1, 23) = 13.02, p=.001, partial $\eta^2=.36$, with faster RTs for push movements ($M=663.89~{\rm ms}, SD=64.02$) than pull movements ($M=686.71~{\rm ms}, SD=66.30$). This illustrates an avoidance bias for angry faces with averted gaze. For happy faces, there was no such difference, F (1, 23) = .09, p=.77, partial $\eta^2<.01~(M_{push}=640.77~{\rm ms}, SD_{push}=77.10~{\rm and}~M_{pull}=638.17~{\rm ms}, SD_{pull}=81.90$).

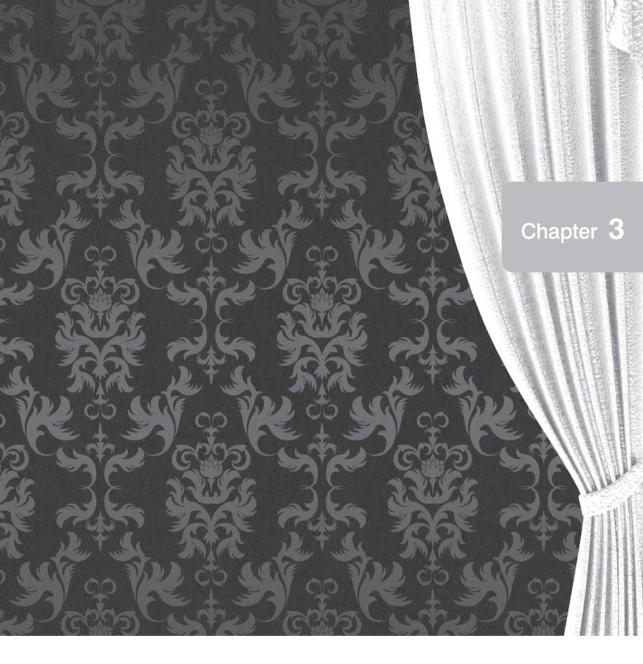
Effects of social anxiety

In the rm ANCOVA on AAT effect scores (Substance [oxytocin, placebo] x Emotion [happy, angry]) with Social Anxiety as a covariate, there were no significant effects (Fs < 1.84, ps > .19). Similarly, Social Anxiety did not correlate with AAT effect scores after oxytocin administration, $r_{angry} < .01, p_{angry} = .97$ and $r_{happy} = .05, p_{happy} = .84$, nor after placebo, $r_{angry} = -.04, p_{angry} = .84$, and $r_{happy} < -.01, p_{happy} = .99$.

Neutral faces

RTs in response neutral faces fell in-between the RTs to happy and angry faces for both direct and averted gaze stimuli. For direct gaze stimuli, reactions to neutral faces ($M=664.13~{\rm ms},~SD=69.59$) were significantly slower than responses to happy faces ($M=639.47~{\rm ms},~SD=79.50;~p<.001$) and significantly faster than responses to angry faces ($M=675.30~{\rm ms},~SD=65.15;~p=.007$). For averted gaze stimuli, RTs to neutral faces ($M=670.92~{\rm ms},~SD=78.12$) differed analogously from those to happy faces ($M=639.47~{\rm ms},~SD=79.50;~p<.001$), but were not significantly different from those to angry faces ($M=675.30~{\rm ms},~SD=65.15$).





Regulating approach

Abstract

Oxytocin regulates various psychosocial functions, e.g., by modulating amygdala reactivity to socioemotional stimuli. Although it has been suggested that oxytocin facilitates approach-related processing, particularly in environments perceived as safe, it has not been investigated until now whether oxytocin actually increases amygdala responses when approaching expressions of social safety, i.e., happy faces, along with decreasing amyodala responses when approaching social threat signals, i.e., angry faces. The current administration study tested this hypothesis in a placebo-controlled, randomized, double-blind, between-subjects design while 52 healthy males underwent fMRI during a social approach-avoidance task. Most importantly, during social approach, oxytocin increased amygdala activation for signals of social safety and decreased it for signals of social threat. These results suggest that oxytocin enhances the capacity for social approach via the amygdala and support a classification of socioemotional stimuli based on motivational direction rather than pure valence. They also give first insights into the neuroendocrine mechanisms that promote social engagement, which might have important implications for psychiatric disorders.

Based on:

Radke, S., Volman, I., Kokal, I., Toni, I., Roelofs, K., & De Bruijn, E. R. A. (in prep). Neural regulation of social approach-avoidance behavior after oxytocin administration.

Introduction

A growing body of studies demonstrated the central role of oxytocin in the regulation of social processes in humans (for a review see Guastella & MacLeod, 2012). Its influence on psychosocial functions is likely to be mediated via the amygdala, a brain structure rich in oxytocin receptors (Huber, Veinante, & Stoop, 2005; Veinante & Freund-Mercier, 1997). As the amygdala is involved in threat detection (for reviews see Davis & Whalen. 2001: Sergerie, Chochol, & Armony, 2008), it is not surprising that in males, exogenous oxytocin reduces activation to threatening scenes and faces in this region (Domes et al., 2007; Gamer, et al., 2010; Kirsch et al., 2005; Petrovic, et al., 2008). Together with heightened amyodala responses to happy facial expressions after oxytocin administration (Gamer, et al., 2010), this might indicate a processing shift from negative to positive social cues. Along these lines, one stream of research suggests that oxytocin increases the sensitivity for positively-valenced social stimuli (e.g., Di Simplicio, Massey-Chase, Cowen, & Harmer, 2009; Gamer et. al, 2010; Marsh, et al., 2010). In contrast, recent views on oxytocin emphasize the importance of motivational direction and postulate increases in approach-related social behavior and social engagement, i.e., the social-approach hypothesis (Kemp & Guastella, 2010b; Kemp, et al., 2012). However, until now, oxytocin's modulatory effects on amygdala reactivity remain to be investigated in terms of motivation, i.e., when social cues require motivational actions such as social approach or avoidance. Given that the regulation of social approach by the autonomic nervous system is compromised in many psychiatric disorders (Porges, 2011), it is of particular relevance to advance our knowledge on the neuroendocrine mechanisms and possible interventions supporting social approach. On the assumption that oxytocin enhances the capacity for social approach, oxytocin administration should lead to increased amygdala responses during approach of social safety signals, i.e., happy facial expressions, and to decreased amygdala responses during approach of social threat signals, i.e., angry facial expressions. The current oxytocin administration study is the first to put this hypothesis to test by measuring brain activity during a social approach-avoidance task in healthy individuals.

Whereas earlier oxytocin research focused on the recognition of facial expressions (for a review see Van Ijzendoorn & Bakermans-Kranenburg, 2012), three recent behavioral studies have measured action tendencies elicited by emotional stimuli after oxytocin administration (Radke, Roelofs, & De Bruijn, 2013; Scheele et al., 2012; Theodoridou, Penton-Voak, & Rowe, 2013). Action tendencies, i.e., approach and avoidance movements, can be reliably assessed by reaction times (RT) in joy-stick-paradigms based on the Approach-Avoidance Task (Roelofs, et al., 2010; Rotteveel & Phaf, 2004). In a recent experiment from our group, typical behavior, i.e., approach tendencies for happy faces and avoidance tendencies for angry faces,

was evident under placebo (Radke, et al., 2013). However, oxytocin specifically increased approach towards angry faces with direct, but not averted, gaze in participants with low levels of social anxiety. Using both faces and non-social scenes as stimuli, Theodoridou et al. (2013) observed faster RTs to facial expressions of disgust, but not to other stimuli and irrespective of movement direction, after oxytocin administration. In contrast, in another study that compared single heterosexual men to those in a stable relationship, only monogamous, but not single men having received oxytocin showed slower approach responses and more errors to pictures of attractive women (Scheele, et al., 2012). Taken together, oxytocin affected behavioral reactions to social stimuli that signify a threat to an individual's social position (aggression), health (contamination) or relationship (infidelity). Next to its anxiolytic properties (Heinrichs, et al., 2003; Heinrichs & Domes, 2008), oxytocin might thus possess a protective function. Both animal and human research point to an elevated concern for offspring or other fellow group members that is absent or even reversed (e.g., as in aggression) when interacting with individuals belonging to different groups (Bosch, Meddle, Beiderbeck, Douglas, & Neumann, 2005; De Dreu, et al., 2010; De Dreu, Shalvi, Greer, Van Kleef, & Handgraaf, 2012; Ferris et al., 1992). In other words, oxytocin could facilitate tuning social motivational behavior in accordance with current goals and individual dispositions such as anxiety or relationship status. Consequently, counterintuitive, yet adaptive, responses might manifest in overcoming natural avoidance tendencies (as in Radke, et al., 2013) or in decelerated approach to affiliative temptations (as in Scheele, et al., 2012).

On a neural level, the implementation of counterintuitive responses in the AAT is subserved by the anterior prefrontal cortex (aPFC) (Volman, Roelofs, et al., 2011; Volman, Toni, et al., 2011; Volman, et al., 2013). Specifically, during motivationally incongruent trials, i.e., when approach of angry and avoidance of happy faces is required, this region shows increased activation, while downregulating amygdala responses. This well-established fMRI-adapted task allows not only for separating congruent from incongruent responses, but also for separating the opposing motivational directions of approach and avoidance. As previous neuroimaging studies on emotional processing after oxytocin administration lack this crucial action component, it remains unresolved whether an increased capacity for social approach is supported by the amygdala.

The current study was designed to bridge this gap by investigating the role of oxytocin on differential activation patterns in the amygdala during social motivational behavior. For this purpose, a randomized, placebo-controlled, double-blind between-subjects design was used to build upon earlier findings on oxytocin's modulatory effects on amygdala reactivity and on the involvement of the aPFC during regulation of approach-avoidance tendencies. We expected oxytocin administration to yield increased amygdala responses during approach of happy facial expressions,

along with decreased amygdala responses during approach of angry facial expressions. For avoidance reactions, this pattern could either be similar, indicating valence-specific amygdala responses regardless of action motivation, or, alternatively, be reversed. Particularly a decreased amygdala response during avoidance of happy faces might be suggestive of a complementary effect of oxytocin and its involvement in the inhibition of social withdrawal (Kemp & Guastella, 2010b). Moreover, we predicted increased aPFC activity for trials requiring motivationally incongruent compared to congruent reactions, i.e., a general task-effect (Volman, Toni, et al., 2011; Volman, et al., 2013).

Methods

Participants

Fifty-seven male volunteers were recruited through advertisements placed across the university's campus and gave written informed consent in accordance with the study procedures approved by the Medical Ethics Committee of the Radboud University Nijmegen Medical Center (Commissie Mensengebonden Onderzoek Region Arnhem-Nijmegen). Participants were financially compensated.

All participants were healthy and did neither report current nor a history of neurological or endocrine disease, medication, and drug or alcohol abuse. Exclusion criteria included age of <18 or >35, smoking more than 5 cigarettes per day, participation in another pharmacological study or blood donation within the last two months, and presence of metal objects in the body. Participants were asked to abstain from caffeine, alcohol and nicotine for 24 h as well as from eating and drinking (except water) 2 h prior to substance administration.

Five participants (N = 4 oxytocin, N = 1 placebo) were excluded due to technical problems or poor task compliance, i.e., less than 50% of usable trials for analyses, resulting in 52 participants (M age = 22.4 years, SD = 3) for the final analyses.

Pharmacological procedure

A randomized, placebo-controlled, double-blind between-subjects design was used in this study. Participants self-administered either oxytocin (Syntocinon; Novartis, Basel, Switzerland; N = 24) or a saline solution (i.e., placebo N = 28) via a nasal spray with three puffs per nostril (each with 4 IU, i.e., a dose of 24 IU). Both sprays were manufactured according to the guidelines on Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP). All sessions were scheduled for the afternoon on weekdays. In order to preclude any experimenter's biases due to potential differences between the sprays, she was not present during substance administration. An independent assistant who was blind to the experimental

hypotheses supervised substance administration. Participants were not able to identify the substance they had received (chi-square $\chi^2(2) = 416$, p = .812). After a waiting period of 30 min, participants were positioned in the MR scanner and completed a short training session (5 min) before the experiment began (45 min after substance administration).

AAT

During this fMRI-adapted reaction time task (Roelofs, Minelli, et al., 2009; Volman, Toni, et al., 2011; Volman, et al., 2013) participants had to respond to visually presented emotional facial expressions by pulling a joystick either towards their body (approach movement) or pushing it away from their body (avoidance movement). As stimuli, happy and angry facial expressions (of 18 female and 18 male models) from several databases were used (Ekman & Friesen, 1976; Lundqvist, et al., 1998; Martinez & Benavente, 1998; Matsumoto & Ekman, 1988). Pictures were trimmed to exclude influences from hair and non-facial contours (van Peer, et al., 2007) and matched for brightness and contrast values.

In 16 blocks with 12 trials each, participants had to categorize the affective expression. Written instructions on the stimulus-response mapping were presented at the beginning of each block. The mapping changed after each block, with the order being counterbalanced across participants. Blocks were separated by an interblock-interval of 21-24 s.

Each trial started with a blank screen (300 ms), after which the stimulus was presented in grayscale against a black background (100 ms). Valid responses were defined as joystick displacements of at least 80% along the sagittal plane within 2s after stimulus presentation. Subsequent to their response, participants had to move the joystick back to the starting position (the central area of 20% on the sagittal plane) before the end of the inter-trial interval (blank screen; 2-4s). Written feedback was given only for invalid responses ("you did not move the joystick far enough"; "please return the joystick to the starting position"). Participants completed a training session of 4 blocks (each 8 trials) inside the MR scanner, for which different stimuli were used. Stimuli were projected (visual angle 4° x 6°) at the center of a screen that was viewed via a mirror above participants' head. An MR-compatible joystick (Fiber Optic Joystick, Current Designs; sampling rate 550 Hz) was placed on the abdomen of the participants. Stimulus presentation and response acquisition were run by Presentation software version 16.

Image acquisition

Functional images were acquired on a 1.5 T MRI scanner (Avanto, Siemens Medical Systems, Erlangen, Germany) equipped with a 32-channel head coil using a multi-echo GRAPPA sequence (Poser, Versluis, Hoogduin, & Norris, 2006) (repetition

time [TR]: 2.14 ms, echo times [TEs, 5]: 9.4/21/33/44/56 ms, 34 transversal slices, ascending acquisition, distance factor: 17%, voxel size $3.3 \times 3.3 \times 3.0$ mm, field of view [FoV]: 212 mm, flip angle 90 degrees). Subsequently, a multi-echo resting-state functional MRI scan (TR: 2000 ms, TE: 6.9/16.2/25/35/44 ms, 39 slices, voxel size $3.5 \times 3.5 \times 3.0$ mm, FoV: 224 mm, distance factor 17%, EPI-Factor 64; 9 min, not included in this report) and an anatomical scan (TR: 2730 ms, TE: 2.95 ms, 176 sagittal slices, voxel size $1.0 \times 1.0 \times 1.0$ mm, FoV: 256 mm, flip angle 7 degrees) were performed.

Liebowitz Social Anxiety Scale

The Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987) assesses fear and avoidance in 24 social situations via self-report. After the MR scans, participants rated on a 4-point scale how anxious they would feel during a particular social situation (anxiety) and how often they would avoid this situation (avoidance). The LSAS is a valid and reliable measure of social anxiety (Heimberg et al., 1999).

Salivary hormone measures

Three saliva samples (prior to substance administration, 15 min after substance administration and 100 min after substance administration) were obtained with salicaps (Immuno-Biological Laboratories GmbH, Hamburg, Germany) and stored at -25 °C. Samples were analyzed in duplicate for testosterone and cortisol and the average was used in subsequent analyses. Hormone concentrations were measured using Luminescence Immunoassays (Immuno-Biological Laboratories GmbH, Hamburg, Germany). For the cortisol assay, the intraassay and interassay coefficients were less than 4% and for the testosterone analyses, these were 0-2% and 5-9%, respectively.

Behavioral analyses

The time from stimulus presentation until movement onset reflects the time of movement initiation (MI). The movement time (MT) was defined as the time from movement onset until the target position of the joystick, and the reaction time (RT) was defined as the time from stimulus presentation until attainment of the target position.

Trials with missed, incorrect and extreme responses (MTs <400 ms; MI <100 or >1500 ms and >3 SDs of the subject-specific mean) were excluded. Blocks in which the error rate exceeded chance level were regarded as a misapprehension of the instructions and therefore not used for the analyses (cf. Volman, Roelofs, et al., 2011; Volman, Toni, et al., 2011; Volman, et al., 2013). After log-transformation to correct for a skewed distribution as in previous studies (cf. Volman, Roelofs, et al., 2011; Von Borries, et al., 2012), mean RTs were calculated for each level of the two experimental factors (Emotion, Movement) and subjected to a repeated measures (rm) ANOVA,

with the within-subject factors Emotion (happy, angry) and Movement (approach, avoid) and the between-subject factor Substance (oxytocin, placebo).

For inferences about the motivational direction, AAT effect scores were calculated by subtracting the (log-transformed) individual mean RTs for joystick pulls from the (log-transformed) individual mean RTs for pushes. Negative values indicate a relative avoidance tendency, and positive values a relative approach tendency (Heuer, et al., 2007; Roelofs, et al., 2010). The AAT effect scores were entered into a rm ANOVA (Substance x Emotion).

In addition, the amount of trials showing either no response or a joystick movement in the wrong direction was summed per level of the two experimental factors per participant. These error rates were subjected to a rm ANOVA (Substance x Emotion x Movement).

Independent t–tests were used to compare baseline levels of testosterone and cortisol. The standardized testosterone and cortisol levels from the first saliva measurement were included in the ANOVAs as covariates as previously done (cf. Volman, Toni, et al., 2011; Volman, et al., 2013). Moreover, following earlier research (Radke, et al., 2013), the LSAS total score was included in the ANOVAs as a covariate. The α -level was set at p < .05. For the ANOVAs, within-subject effects with Greenhouse Geisser correction are reported with partial eta squared as an indication of effect size. Statistical testing was performed with the Statistical Package for the Social Sciences (IBM SPSS 19).

Imaging data

Preprocessing and analyses of the imaging data was performed with statistical parametric mapping (SPM8, Wellcome Department of Imaging Neuroscience, London). For each data set, the first four volumes were excluded to allow for magnetic saturation. Head motion parameters were derived from the MR images of the first echo (TE 9.4s; Volman, Toni, et al., 2011) and estimated by using a least-squares approach with 6 rigid body transformation parameters (translations, rotations). They were then applied to all five echo images. Subsequently, the five echo images were combined into single volumes based on an optimized echo weighting method (Poser, et al., 2006). After slice-time correction, the anatomical scan was coregistered with the mean of the functional images, and images were normalized into Montreal Neurological Institute (MNI) space on the basis of a segmentation algorithm (Ashburner & Friston, 2005). Images were resampled to 2 mm³ and smoothed with an 8mm³ full-width-at-half-maximum Gaussian kernel.

The first-level analyses were based on an event-related approach in the general linear model with four task-relevant regressors: approach-happy, avoid-happy, approach-angry, avoid-angry. Furthermore, trials without responses were modeled as misses, and presentation of task instructions were modeled as info, resulting in

two additional regressors not of interest to the experimental question. Regressors were constructed for the times of stimulus onset with RT as duration and convolved with the canonical hemodynamic response function to model brain activity. To minimize residual head movement effects, additional regressors were derived from incorporating the original, squared, cubic, first-order, and second-order derivatives of the movement parameters (Lund, et al., 2005) as well as signal intensities of white matter, cerebrospinal fluid, and the portion of the MR image outside the skull. Lastly, a high pass filter (128s) and an autoregressive AR(1) model were applied to the images to account for serial correlations in the functional series.

On the group level, a random effects multiple regression analysis was performed based on participants' four task-relevant contrast images (approach-happy, avoid-happy, approach-angry, avoid-angry). Standardized endogenous testosterone and cortisol levels (obtained from the first saliva sample) as well as the total score on the LSAS were included as covariates, resulting in another 24 regressors (cf. e.g., Volman, Toni, et al., 2011). In the context of a Substance x Emotion x Movement analysis, we focused on two regions of interest (ROI): the amygdala based on the aal atlas (Tzourio-Mazoyer et al., 2002) using the Wake Forest University (WFU) PickAtlas tool (Maldjian, Laurienti, Kraft, & Burdette, 2003) and the aPFC from Volman et al. (2011; 2011; 2013) with two spheres (8mm radius) centered on 32 54 8 and -30 58 2, respectively.

First, within the amygdala, we tested for the 3-way interactions of Substance x Emotion x Movement. To understand potential interaction effects, parameter estimates were extracted from the activation cluster within the amygdala for further investigation and visualization of effects in SPSS.

Second, to examine task-related involvement of the aPFC irrespective of hormonal modulations as previously reported (Volman, Roelofs, et al., 2011; Volman, Toni, et al., 2011; Volman, et al., 2013), activation during incongruent trials (approachangry, avoid-happy) was compared to that on congruent trials (approach-happy, avoid-angry) across the whole sample. Inferences were made based on small volume family-wise error corrections (FWE: p < .05) (Friston, 1997).

Results

Endogenous hormone levels

Salivary levels did not differ between substance groups for neither testosterone nor cortisol, for baseline testosterone: t(50) = -.10, p = .92, for baseline cortisol: t(50) = .46, p = .65 (see Table 3.1 for all means).

Table 3.1. Endocrine and behavioral characteristics of study participants (Mean [SE]; N = 28 Placebo, N = 24 Oxytocin, otherwise indicated)

	Placebo		Oxytocin	
Testosterone in pg/mL				
T1 (baseline)	79.4 (9.6)		85.2 (7.9)	
T2	84.9 (11.9)		77.0 (9.7)	
T3	95.2 (17.7) [N = 27]		88.8 (13.0) [N = 21]	
Cortisol in nmol/L				
T1 (baseline)	10.4 (1.1)		10.2 (1.8)	
T2	10.7 (1.2)		9.5 (1.3)	
T3	6.5 (0.8) [N = 27]		7.1 (0.7) [N = 23]	
LSAS	26.5 (3.4)		29.9 (3.3)	
RTs on the AAT in ms	Approach	Avoid	Approach	Avoid
Нарру	671 (27)	729 (26)	739 (20)	794 (25)
Angry	703 (25)	711 (29)	764 (21)	785 (22)
Error rates on the AAT in %	Approach	Avoid	Approach	Avoid
Нарру	5.4 (0.9)	6.8 (0.9)	7.6 (1.6)	10.8 (1.6)
Angry	6.5 (0.9)	5.7 (1.4)	9.9 (1.9)	8.4 (2.0)

Note. LSAS = Total score on the Liebowitz Social Anxiety Scale (Liebowitz, 1987), AAT = Approach-Avoidance Task

Behavior

Table 3.1 provides an overview of RTs and error rates for each substance group (see also Figure 3.1). The rm ANOVA on the log-transformed RTs showed significant effects of Movement, F (1, 47) = 48.33, p < .001, η^2 = .51, and Emotion, F (1, 47) = 6.15, p = .017, η^2 = .12. There was also a significant Emotion x Movement interaction, F (1, 47) = 18.44, p < .001, η^2 = .31. Most importantly, there was a main effect of Substance, F (1, 47) = 4.70, p = .035, η^2 = .09. Apart from a trend for a Movement x testosterone interaction, F (1, 47) = 3.88, p = .055, q^2 = .08, no other effects approached significance (all Fs < 2.69, all ps > .11).

The main effect of Movement was due to faster approach movements (M = 719.52 ms, SD = 120.15) than avoidance movements (M = 755.31 ms, SD = 131.39),

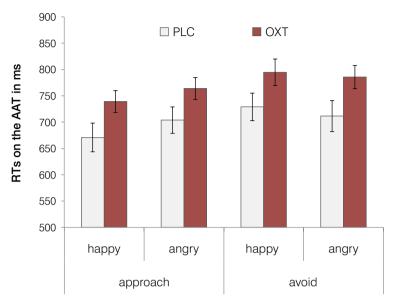


Figure 3.1. Mean RTs on the AAT in ms. Error bars represent standard errors. All RTs differ significantly between placebo (PLC) and oxytocin (OXT).

and the main effect of Emotion was caused by faster reactions to happy faces (M = 733.52 ms, SD = 126.78) than to angry faces (M = 741.31 ms, SD = 124.76).

The Emotion x Movement interaction was qualified by a congruency effect for happy faces, i.e., faster approach than avoidance reactions (F (1, 47) = 62.50, p < .001, η^2 = .57; $M_{approach}$ = 702.46 ms, $SD_{approach}$ = 129.93; M_{avoid} = 759.41 ms, SD_{avoid} = 134.27). For angry faces, there was a trend of faster approach than avoidance reactions (F (1, 47) = 3.0, p = .09, η^2 = .06; $M_{approach}$ = 731.62 ms, $SD_{approach}$ = 122.17; M_{avoid} = 745.84 ms, SD_{avoid} = 139.89). An Emotion x Movement interaction was significant in both groups, indicating the presence of the congruency effect irrespective of Substance.

The main effect of Substance was due to faster reactions after placebo (M = 703.84 ms, SD = 142.85) than after oxytocin administration (M = 770.99 ms, SD = 108.69). Interestingly, this was not specific for any emotion or movement direction, which was further underlined by analyses on the AAT effect scores which did not reveal significant differences between substance conditions (for happy faces: F(1, 47) = .72, p = .402, p = .02, for angry faces: F(1, 47) = 1.03, p = .314, p = .02).

¹ The trend for the Movement x testosterone interaction was due to a larger RT difference between approach and avoidance movements in participants with low testosterone than in those with high baseline testosterone. Additionally, note that Substance-related effects were not specific for one stimulus gender or the other.

The rm ANOVA on the error rates revealed a significant effect of Substance, F(1, 47) = 4.28, p = .044, $\eta^2 = .08$, which was due to higher error rates after oxytocin administration (M = 9.18%, SD = 8.71) than after placebo (M = 6.12%, SD = 5.46). No other effects were significant (all Fs < 2 all ps > .16). Taken together, these results indicate that oxytocin administration entailed longer RTs and more errors, i.e., impaired task performance.

fMRI regional effects

First, within the amygdala ROI, a Substance (oxytocin > placebo) x Emotion (happy > angry) x Movement (approach > avoid) effect was evident in the right amygdala (coordinates of local maxima: 24 -4 -24; z-value = 3.37; p_{FWE} = .037; see also Figure 3.2). There were no significant effects for the reverse contrast (all p_{FWE} s> .108). Extracted parameter estimates for the cluster revealed that the 3-way interaction was qualified by differential patterns in amygdala activity particularly during approach reactions (see also Figure 3.2): Compared to placebo, oxytocin increased amygdala responses when approaching happy faces, F (1, 50) = 9.06, p = .004, q²= .15, and decreased it when approaching angry faces, F (1, 50) = 5.40, p = .024, q²= .10. For avoidance reactions, oxytocin decreased amygdala response for happy faces, F (1, 50) = 5.81, p = .02, q²= .10, but did not significantly alter it for angry faces, F (1, 50) = 2.94, p = .093, q²= .06.

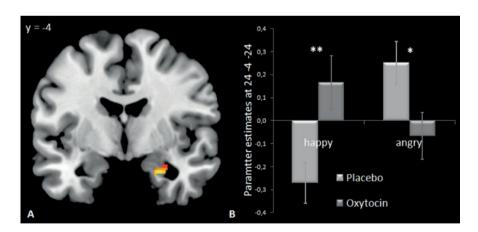


Figure 3.2. A) Amygdala reactivity (local maxima: 24 -4 -24) showing a significant Substance x Emotion x Movement interaction, i.e., enhanced activation for approach of happy versus approach of angry faces (compared to avoidance) after oxytocin administration compared to placebo within the amygdala ROI. The image is thresholded at p < .05 uncorrected for visualization purposes. B) Contrast estimates for the amygdala cluster during social approach. Error bars represent SEM. *p < .05, **p < .01.

Second, when contrasting incongruent and congruent trials, activation of the right aPFC (coordinates of local maxima: 26 58 8; z-value = 3.75; p_{FWE} = .007; see also Figure 3.3) was evident. As in previous studies (Volman, Toni, et al., 2011; Volman, et al., 2013), involvement of the aPFC was stronger when participants approached an angry face or avoided a happy face than during the reverse, more intuitive responses.

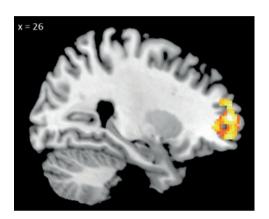


Figure 3.3. Across group aPFC activity (local maxima: 26 58 8) for motivationally incongruent versus congruent trials. The image is thresholded at p < .05 uncorrected, k > 50 for visualization purposes.

Discussion

The present study focused on the modulatory role of oxytocin on amygdala activation during approach and avoidance reactions. The main finding was that oxytocin increased amygdala responses when approaching happy faces and decreased it when approaching angry faces. This converges with previously reported reduced amygdala activity to threat-related faces (Domes, Heinrichs, Glascher, et al., 2007; Gamer, et al., 2010; Kirsch, et al., 2005; Petrovic, et al., 2008) and enhanced amygdala activity to happy facial expressions (Gamer, et al., 2010) after oxytocin administration. Yet, the current activation pattern emerged only during social approach and therefore extends earlier research which employed tasks that did not differentiate between motivational directions, i.e., visual tasks with emotional stimuli (Kirsch, et al., 2005; Petrovic, et al., 2008) or emotion recognition paradigms (Domes, Heinrichs, Glascher, et al., 2007; Gamer, et al., 2010).

Crucially, a conceptualization of oxytocin's psychosocial effects on a motivational continuum rather than based on valence has been proposed (Kemp & Guastella, 2010b; Kemp, et al., 2012). Within this framework, oxytocin facilitates approach-

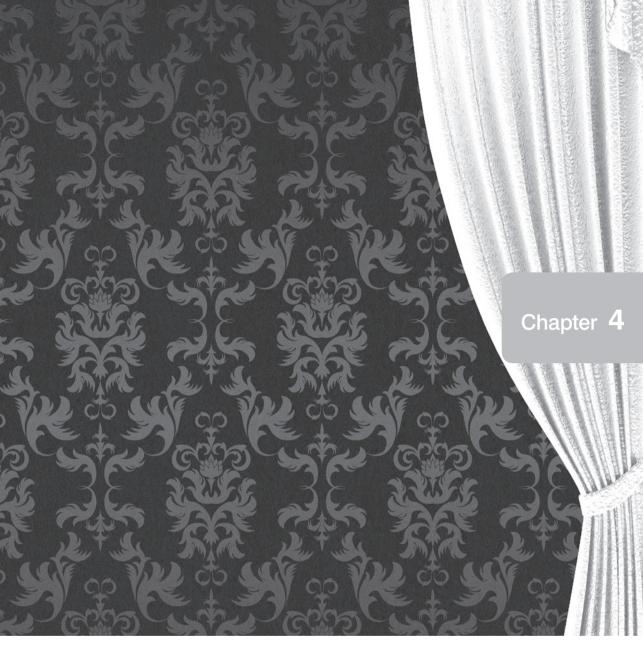
related processing and social engagement in safe environments, as apparent in cardiovascular indicators, e.g., heart rate variability (Gamer & Büchel, 2012; Kemp, et al., 2012; Kubzansky, Mendes, Appleton, Block, & Adler, 2011; Norman, et al., 2011; see also Porges, 2011; Quintana, Kemp, Alvares, & Guastella, 2013). Whereas the approach of happy faces is likely to signify such a safe environment in which an enhanced capacity for social approach could emerge, approach of angry faces is rather associated with threat. The differential modulation of amygdala activity during 'safe' vs. threat approach after oxytocin administration might thus reflect the adaptive regulation of social engagement by neural structures. Reduced amygdala responses during avoidance of happy faces might indicate a complementary mechanism of oxytocin, i.e., the inhibition of withdrawal-related processes (cf. the social-approach/withdrawal hypothesis; Kemp & Guastella, 2010b).

These neural mechanisms, however, did not translate to specific behavior in the current study. In contrast, more general effects of oxytocin were evident, i.e., prolonged reactions and more errors, which might have occluded a statistically significant increase of approach towards angry faces after oxytocin administration (as in Radke, et al., 2013). Given the absence of such an increase, the lack of an association with social anxiety (as in Radke, et al.) is not surprising. Interestingly, descriptive comparisons reveal an approach tendency towards angry faces after oxytocin administration of 21 ms in the current study vs. 8 ms in Radke et al., tentatively suggesting a similar behavioral pattern. In addition, there was, however, not only an overall movement bias towards approach with this joystick, as previously reported (Volman, et al., 2013), but even a trend for a reverse congruency effect for angry faces, i.e., faster approach than avoidance reactions. This renders the interpretation of the behavioral patterns difficult, so that conclusions about the discrepancy with our previous findings (Radke, et al., 2013) should be drawn with caution. Besides, several methodological differences between the two studies might account for the lack of convergence such as the use of a between- instead of a within-subject design and the task adaptations necessary for its application in the MR. Most notably are the shorter stimulus presentation times and the lack of the 'zooming' component in order to prevent visually-induced confounds, but also the elimination of socially less salient stimuli, i.e., faces with averted gaze, might have contributed. Taken together, this might imply that the behavioral task variant is more sensitive for eliciting action tendencies reflecting social approach and avoidance, whereas the fMRI adaptations allow for an assessment of brain activity during motivational actions (see e.g., Volman, Toni, et al., 2011 for differences in hormonal modulations of behavior vs. brain activity). One should also bear in mind the supine body position necessitated by the MR environment, which is likely to oppose approach-related behaviors, e.g., leaning, that occur in upright body positions, thereby counteracting approach-motivational responses, particularly those related to anger (Harmon-Jones & Peterson, 2009).

Moreover, the current results replicate previously reported task-related effects on both a behavioral and a neural level, i.e., congruency effects for happy faces and enhanced activity of the aPFC for motivationally incongruent compared to congruent responses (Volman, Toni, et al., 2011; Volman, et al., 2013). Anterior prefrontal and orbitofrontal cortices subserve cognitive flexibility and the selection of appropriate reactions to social and emotional stimuli (Elliott, Dolan, & Frith, 2000; Koechlin, 2011; Kringelbach & Rolls, 2004).

In conclusion, the present investigation shows that during social approach, oxytocin increased amygdala activation for happy faces and decreased it for angry faces, which may reflect a neural mechanism for regulating social engagement. This fits with the notion that oxytocin facilitates approach-related processing in safe environments. Additionally, the finding that oxytocin increased amygdala activation during approach of happy faces, and decreased it when the same stimuli were avoided, speaks against a purely valence-based distinction of oxytocin's effects on social information processing (e.g., Di Simplicio, et al. 2009; Marsh, et al., 2010). Instead, they give further support to accounts such as the social approach/withdrawal hypothesis (Kemp & Guastella, 2010b) which emphasize the organization of affective processes along motivational dimensions. Finally, the current study provides a first insight into oxytocin's modulation of neural circuits in promoting 'safe' social approach, which is important for future translational applications for individuals suffering from dysregulations of social engagement such as patients with anxiety disorders or depression.





Ready to go!

Abstract

Testosterone increases amygdala responses to threatening social stimuli, suggesting enhancement of approach-related attention. Following from the role of the amygdala in motivational action preparation, this endocrine modulation of amygdala activity likely depends on the motivational context. Therefore, we tested in a randomized, double-blind, between-subjects design whether testosterone increases amygdala responses to angry faces specifically when they need to be approached. Testosterone and placebo were administered to 54 healthy females before measuring brain activity during performance of a social approach-avoidance task. Compared to placebo, testosterone increased amygdala activation during the motivational challenge of approaching social threat, and decreased it during avoidance of the same stimuli. These results present the first neuroendocrine extension of the motivational salience model by demonstrating motivation-specific effects of testosterone on amygdala processing of social threat cues. They also provide important insights in the neuroendocrine regulation of motivational behavior when dealing with social challenges.

Based on:

Radke, S., Volman, I., Mehta, P. H., van Son, V., Toni, I., Sanfey, A. G., de Bruijn, E. R. A., Roelofs, K. (in prep). Ready to go! Testosterone prepares the amygdala for social threat approach.

Introduction

Testosterone acts on the amygdala, a key brain structure in emotion processing and threat detection (for reviews see Davis & Whalen, 2001; Sergerie, et al., 2008). Heightened amygdala responses to threatening social cues after testosterone administration suggest an increased attention to threat (Bos. van Honk, Ramsey, Stein, & Hermans, 2012; Hermans, et al., 2008; van Wingen et al., 2009). However, it has recently been proposed that enhanced amyodala activation is not a function of emotional, but of motivational salience, preparing for adaptive responding to relevant stimuli on the basis of the motivational context (Cunningham, Arbuckle, Jahn, Mowrer, & Abdulialil, 2010: Cunningham, Van Bavel, & Johnsen, 2008). Given the approachfacilitating properties of testosterone during social challenges (Wingfield, et al., 1990), administration of this steroid hormone should increase amygdala activity to motivationally challenging cues, i.e., social threat that has to be approached (see also Enter, Spinhoven, & Roelofs, submitted). Such a motivation-specific effect of testosterone on amygdala function would provide important insights into the neuroendocrinological underpinnings of motivational action preparation and social approach. Therefore, we investigated opposing social motivational reactions to emotional faces by using a social approach-avoidance task during fMRI. Specifically, we tested whether testosterone indeed differentially increases amygdala reactivity to angry faces depending on the motivational action required.

The steroid hormone testosterone modulates the perception of social challenges and facilitates motivational reactions, in particular those related to social approach. i.e., approach to conspecifics in the context of reproduction and aggression (Archer, 2006). Following this premise, administration studies in healthy females have demonstrated that testosterone increases social vigilance, for instance by downregulating trust in high-trusting individuals (Bos, Terburg, et al., 2010) and by maintaining eye contact with faces signaling social threat (Terburg, et al., 2012). On a neural level, testosterone administration enhanced activity in subcortical brain circuits associated with different expressions of motivational behavior, e.g., aggression and reward anticipation, and increased amygdala reactivity to salient social cues, i.e., angry and fearful faces (Bos, van Honk, et al., 2012; Hermans, et al., 2010; Hermans, et al., 2008; van Wingen, Mattern, Verkes, Buitelaar, & Fernandez, 2010; van Wingen et al., 2008). Whereas these studies suggest heightened approach-related attention to signals of social threat after testosterone administration, it should also be noted that the paradigms previously used rely either on passive viewing of faces or require reactions unrelated to the emotional or motivational content of the stimuli.

However, beyond perception, interpersonal cues also function to prime subsequent motivational behavior. For example, signals of social safety, i.e., happy facial expressions, elicit the tendency to approach, whereas signals of social threat, i.e., angry facial expressions, vield avoidance (Roelofs, et al., 2010; Rotteveel & Phaf, 2004). These action tendencies can be reliably assessed by social approach-avoidance tasks in which participants react to facial expressions by pulling a joystick towards (approach) or pushing it away from their body (avoidance) (Roelofs, et al., 2010; Rotteveel & Phaf, 2004). Healthy individuals display faster automatic reactions, i.e., approach movements to happy faces and avoidance movements to angry faces, than when the opposite, motivationally more challenging responses are required ('congruency effect'). During these more challenging (affect-incongruent) trials, the anterior prefrontal cortex (aPFC) is particularly engaged and supports the control of emotional behavior by downregulating amygdala activity (Volman, Roelofs, et al., 2011; Volman, Toni, et al., 2011: Volman, et al., 2013), Correlational analyses have indicated that higher endogenous testosterone levels were associated with reduced aPFC activity and reduced aPFC-amygdala coupling during social motivational behavior (Volman, Toni, et al., 2011). The present study investigated the effects of testosterone on amygdala and prefrontal activity in a randomized, placebo-controlled, double-blind between-subjects design. We predicted that testosterone administration would increase amygdala activity during approach compared to avoidance responses to angry faces. In addition, following Volman et al. (2011; 2011; 2013), we tested for increased aPFC activity during trials requiring motivationally incongruent compared to congruent responses and substance differences within the aPFC.

Methods

Participants

Fifty-four female volunteers (M age 21.6 years, SD = 2.4, range 18-30) were enrolled for participation. Exclusion criteria were history of endocrine, neurological or psychiatric disorder, left hand dominance, uncorrected vision, habitual smoking, use of medication or drugs (except for paracetamol and contraceptives), current parodontitis, pregnancy or breast-feeding, and irregular sleep patterns.

All participants used hormonal contraceptives, i.e., Intra-Uterine Device (N=8), vaginal ring (N=1), Implanon (N=1) or single-phase pill (N=44) in order to control for changes in endocrine levels over the menstrual cycle. Participants were asked to abstain from alcohol and nicotine 24 hours before testing and received a standardized light lunch on the day of testing. Written informed consent was obtained from all participants and the study protocol was approved by the CMO Nijmegen-Arnhem in accordance with the declaration of Helsinki. All participants received financial compensation.

Substance administration and procedure

In a double-blind, randomized, placebo-controlled, between-subjects design participants received either a single dose of 0.5 mg testosterone (N = 26; testosterone was

suspended in 0.5 ml solution with 0.5 mg hydroxypropyl-beta-cyclodextrin, 0.005 ml ethanol 96%, and distilled water) or a matched placebo (N = 28) containing the same ingredients, except for the testosterone. Both liquids were manufactured by the pharmacy of the Leiden University Medical Center (Leiden, the Netherlands) in accordance with Good Manufacturing Practice.

About 30 minutes after arrival in the laboratory between 10:00 am and 12:30 pm, participants self-administered the liquid under the supervision of the experimenter. Specifically, they held the solution under their tongue for 60 seconds before swallowing it. This procedure entails the direct absorption of testosterone into the bloodstream, leading to a sharp increase in plasma testosterone 15 minutes post-administration (van Rooij et al., 2012). Previous research has demonstrated that behavioral and physiological effects are measureable approximately 4 to 6 hours after testosterone intake (Tuiten, et al., 2000), which has been further confirmed in investigations of social-emotional behaviors in young females (e.g., Bos, Hermans, et al., 2010; Bos, Hermans, et al., 2012; Bos, Terburg, et al., 2010; Hermans, et al., 2010; Hermans, Putman, Baas, et al., 2006; Hermans, Putman, & van Honk, 2006).

Subsequent to substance administration and before testosterone effects were expected to emerge, participants filled out several questionnaires and received instructions and training for the experimental tasks. Additionally, they were allowed to do school work or reading in the waiting room for the remaining time, but social interaction was restricted. Four hours later, participants were positioned in the MRI for an anatomical scan (6 min), the AAT (20-25 min) and another experimental task (20 min; reported elsewhere). After the MRI session, participants completed several exit questionnaires and were debriefed. Saliva samples for cortisol and testosterone analyses were obtained at baseline (upon arrival in the lab), 30 minutes post-administration, 3 hours post-administration and 5 hours post-administration. The total duration of the experimental session was 6.5 hours.

Approach-Avoidance Task

In this fMRI-adapted reaction time task (Roelofs, Minelli, et al., 2009; Volman, Toni, et al., 2011), participants had to respond to visually presented emotional facial expressions by pulling a joystick either towards their body (approach movement) or pushing it away from their body (avoidance movement). Stimuli were taken from several databases (Ekman & Friesen, 1976; Lundqvist, et al., 1998; Martinez & Benavente, 1998; Matsumoto & Ekman, 1988) and contained two affective expressions (happy and angry) for each of the 36 models (18 female). The faces were trimmed to exclude influences from hair and non-facial contours (van Peer, et al., 2007) and matched for brightness and contrast values.

The task comprised 16 blocks with 12 trials per block in which participants had to categorize the affective expression. At the start of each block, participants received

written instructions regarding the stimulus-response mapping. The mapping changed after each block and its order was counterbalanced across participants. Blocks were separated by an inter-block-interval of 21-24 s.

Each trial started with a blank screen for 300 ms. Subsequently, the stimulus was presented in grayscale against a black background for 100 ms, followed by the participants' response and a variable inter-trial interval (ITI; blank screen; 2-4s). Valid responses were defined as joystick displacements of at least 80% along the sagittal plane occurring within 2s after stimulus presentation. After their response, participants had to move the joystick back to the starting position (the central area of 20% on the sagittal plane) before the end of the ITI. Participants received feedback in the case of kinematically invalid responses ("you did not move the joystick far enough"; "please return the joystick to the starting position").

Stimuli were projected (visual angle $4^{\circ} \times 6^{\circ}$) at the center of a screen that was viewed via a mirror above participants' head. An MR-compatible joystick (Fiber Optic Joystick, Current Designs; sampling rate 550 Hz) was positioned on the abdomen of the participants. Presentation of stimuli and acquisition of responses were controlled by a PC running Presentation software version 13.

Image acquisition

Images were acquired on a 1.5 T MRI scanner (Avanto, Siemens Medical Systems, Erlangen, Germany) equipped with an 8-channel head coil using a multi-echo GRAPPA sequence (Poser, et al., 2006)(repetition time [TR]: 2.14 ms, echo times [TEs, 5]: 9.4/21/33/44/56 ms, 34 transversal slices, ascending acquisition, distance factor: 17%, effective voxel size 3.3 x 3.3 x 3.5 mm, field of view [FoV]: 212 mm). Anatomical images were acquired using an MP_RAGE sequence (TR: 2250 ms, TE: 2.95 ms, 176 sagittal slices, voxel size 1.0 x 1.0 x 1.0 mm, FoV: 256 mm).

Salivary hormone measures

Saliva was collected in 15 mL Cellstar tubes (Greiner Bio-one, Frickenhausen, Germany) and stored at -25 °C. Samples were analyzed in duplicate for testosterone and cortisol and the average was used in subsequent analyses. Hormone concentrations were measured using Luminescence Immunoassays (Immuno-Biological Laboratories GmbH, Hamburg, Germany). The average intraassay and interassay coefficients were between 4.8% and 7.8% for cortisol and 6.5% and 8.6% for testosterone.

Behavioral analyses

Trials with incorrect or no responses were classified as errors and analyzed separately. The error rate was calculated per level of the two experimental factors per participant. When the error rate in a block was above chance level, the whole block was excluded

as it can be expected that participants misunderstood the instructions for that specific block (following Volman, Roelofs, et al., 2011; Volman, Toni, et al., 2011; Volman, et al., 2013).

The time from stimulus presentation until movement onset corresponds to movement initiation, and the time from movement onset until reaching the target position of the joystick reflects the movement duration. The RT was defined as the time from stimulus presentation until attainment of the target position. Trials with a movement duration shorter than 400 ms and those with a movement initiation outside the 100-1500 ms range or exceeding 3 SDs from the subject-specific mean were excluded. Median RTs were calculated for each level of the two experimental factors (Emotion, Movement) and subjected to a repeated measures (rm) ANOVA, with the within-subject factors Emotion (angry, happy) and Movement (approach, avoid) and the between-subjects factor Substance (testosterone, placebo).

Independent t–tests were used to assess group difference on baseline levels of testosterone and cortisol. The standardized testosterone and cortisol levels from the first saliva measurement were included in the ANOVAs as covariates. For all analyses, the α -level was set at p < .05. For the ANOVAs, within-subject effects with Greenhouse Geisser correction are reported with partial eta squared as an indication of effect size. Statistical testing was performed with the Statistical Package for the Social Sciences (IBM SPSS 19).

Imaging data

Statistical parametric mapping (SPM8, Wellcome Department of Imaging Neuroscience, London) was used for preprocessing and analyzing the imaging data. In order to allow for magnetic saturation, the first four volumes of each data set were discarded. Using a least-squares approach with 6 rigid body transformation parameters (translations, rotations), motion parameters were estimated on the basis of the MR images of the first echo (TE 9.4s; Volman, Toni, et al., 2011). After applying the motion correction parameters to the images from all echoes, single MR volumes were obtained by combining the five echo images based on an optimized echo weighting method (Poser, et al., 2006). Subsequently, images were slice-time corrected and the anatomical scan was coregistered with the mean of the functional images. Normalization into Montreal Neurological Institute (MNI) space was based on a segmentation algorithm (Ashburner & Friston, 2005). Images were resampled at a 2x2x2 mm voxel size and spatially smoothed using an 8 mm full-width-at-half-maximum Gaussian kernel.

The general linear model was applied to the time series of each participant. For this event-related design, trials were averaged separately for each condition, yielding four task-relevant regressors: approach-happy, avoid-happy, approach-angry, avoid-angry. Two additional regressors were derived from modeling missed responses and

periods where instructions were presented. Events were isolated by convolving vectors of stimulus onset times and RT as duration with the canonical hemodynamic response function. Potentially confounding residual head movement effects were modeled with regressors based on the original, squared, cubic, first-order, and second-order derivatives of the movement parameters (Lund, Norgaard, Rostrup, Rowe, & Paulson, 2005) as well as signal intensities of white matter, cerebrospinal fluid, and the portion of the MR image outside the skull. Finally, images were high-pass filtered at 128s, and an autoregressive AR(1) model was used to account for serial correlations in fMRI time series.

Analyses on the group level were performed by subjecting the four task-relevant contrast images per participant (approach-happy, avoid-happy, approach-angry, avoid-angry) to a random effects multiple regression analysis (Substance x Emotion x Movement). Standardized endogenous testosterone and cortisol levels (obtained from the first saliva sample) were included as covariates, resulting in another 16 regressors (as in e.g., Volman, Toni, et al., 2011). The following effects were considered: First, to address our main question of whether testosterone administration modulates amygdala reactivity to angry faces, we performed a region of interest (ROI) analysis on the amygdala based on the anatomical amygdala region according to the Wake Forest University (WFU) PickAtlas tool (Maldjian, et al., 2003). Here, we tested for the 3-way interactions of Substance x Emotion x Movement. To understand potential interaction effects, parameter estimates were extracted from the activation cluster within the amygdala and subjected to statistical analyses in SPSS.

Second, to examine the involvement of the aPFC in motivationally incongruent responses irrespective of hormonal modulations, the congruency effect (Emotion x Movement) was assessed for both groups together and separately with a ROI based on Brodmann area (BA) 10, which has previously been implicated during this task (Volman, Roelofs, et al., 2011; Volman, Toni, et al., 2011; Volman, et al., 2013). In other words, activation during affect-incongruent trials (approach-angry, avoid-happy) was compared to that on affect-congruent trials (approach-happy, avoid-angry). The reported activations from the ROI analyses are corrected for multiple comparisons over the search volume using family-wise error (FWE: p < .05) (Friston, 1997).

Results

Endogenous hormone levels

There were no differences on salivary levels of testosterone and cortisol between substance groups at baseline (before administration), for testosterone: t(52) = .33, p = .74, for cortisol: t(52) = .81, p = .42 (see Table 4.1 for means).

Table 4.1. Endocrine and behavioral characteristics of study participants (Mean [SE]).

	Placebo	Testosterone	
Hormone levels			
Baseline testosterone (pg/mL)	22.2 (2.8)	23.6 (3.0)	
Baseline cortisol (nmol/L)	16.7 (2.4)	14.5 (1.2)	

RTs on the AAT in ms	Approach	Avoid	Approach	Avoid
Нарру	676 (29)	745 (29)	655 (19)	692 (22)
Angry	723 (29)	713 (29)	683 (23)	680 (20)

Note. LSAS = Total score on the Liebowitz Social Anxiety Scale (Liebowitz, 1987), AAT = Approach-Avoidance Task

Behavior

Table 4.1 provides an overview of RTs for each substance group. The rm ANOVA on the RTs showed a significant effect of Movement, F(1, 50) = 29.16, p < .001, $\eta^2 = .37$ and, most importantly, a significant Emotion x Movement interaction, F(1, 50) = 28.91, p < .001, $\eta^2 = .37$. No other effects were significant (all Fs < 2.9, ps > .09). The main effect of Movement was due to faster approach movements (M = 684.08 ms, SD = 130.88) than avoidance movements (M = 707.78 ms, SD = 132.69), as previously reported with this joystick (Volman, et al., 2013).

The Emotion x Movement interaction was qualified by a congruency effect for happy faces, i.e., faster approach than avoidance reactions (F (1, 50) = 52.91, p < .001, q^2 = .51; $M_{approach}$ = 665.58 ms, $SD_{approach}$ = 128.44; M_{avoid} = 719.72 ms, SD_{avoid} = 139.44). However, there was no significant congruency effect for angry faces (F (1, 50) = .82, p = .37, q^2 = .02; $M_{approach}$ = 703.69 ms, $SD_{approach}$ = 138.20; M_{avoid} = 697.42 ms, SD_{avoid} = 133.34). An Emotion x Movement interaction was significant in both groups, indicating the presence of the congruency effect irrespective of Substance.²

fMRI regional effects

For the ROI analyses on the amygdala, there was a significant Substance (testosterone > placebo) x Emotion (angry > happy) x Movement (approach > avoid) effect in the right amygdala (coordinates of local maxima: 32 -2 -16; z-value = 3.63; $p_{FWE} =$.015). Importantly, the extracted parameters revealed that the 3-way interaction was due to differential patterns in amygdala activity for reactions towards angry faces (see also

² Error rates of the whole group showed analogous task effects, i.e., significant effects of Movement and Emotion x Movement, but no Substance-related effects.

Figure 4.1), as evident in a Substance x Movement interaction, F (1, 52) = 8.58, p = .005, η^2 = .14. Compared to placebo, testosterone increased amygdala activity for approach, F (1, 52) = 6.06, p = .017, η^2 = .10, but decreased it for avoidance, F (1, 52) = 8.68, p = .005, η^2 = .14. In addition, after testosterone administration, amygdala activity significantly differed between approach and avoidance, F (1, 25) = 6.33, p = .019, q^2 = .20 (which was not the case after placebo, F (1, 27) = 2.86, p = .10, q^2 = .10). For happy faces, apart from a trend for a Substance x Movement interaction, F (1, 52) = 3.39, p = .071, q^2 = .06, no significant effects were found.

Within the ROI of BA 10, contrasting motivationally incongruent and congruent trials yielded activation of the right aPFC (coordinates of local maxima: 30 62 -4; z-value = 4.30; $p_{\rm FWE}$ = .03; see Figure 4.2). In other words, the aPFC response was stronger when participants approached an angry face or avoided a happy face, compared to the motivationally less demanding reactions of approaching a happy face and avoiding an angry face (as in Volman, Toni, et al., 2011; Volman, et al., 2013). Assessing these effects within the two groups revealed that the aPFC activations were present under both substances (for placebo: coordinates of local maxima: 26 54 18; z-value = 4.36; $p_{\rm FWE}$ = .024; for testosterone: coordinates of local maxima: 30 64 -4; z-value = 4.64; $p_{\rm FWE}$ = .008) and there were no substance differences. No other clusters reached significance for the comparison between incongruent and congruent responses in the whole group (i.e., none reached whole-brain FWE correction).

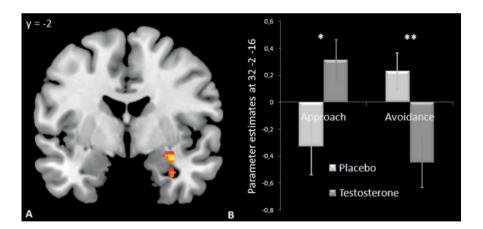


Figure 4.1. A) Amygdala reactivity (local maxima: 32 - 2 - 16) showing a significant Substance x Emotion x Movement interaction, i.e., enhanced activation for approach versus avoidance of angry faces versus happy faces after testosterone administration compared to placebo within the amygdala ROI. The image is thresholded at p < .05 uncorrected for visualization purposes. B) Contrast estimates for this cluster during approach and avoidance of angry faces. Error bars represent SEM. *p < .05, **p < .01.



Figure 4.2. Across group aPFC activity (local maxima: 30 62 -4) for motivationally incompatible versus compatible trials within BA 10. The image is thresholded at $\rho < .05$ uncorrected for visualization purposes.

Discussion

This study investigated the causal role of testosterone in the neural regulation of social motivational behavior. Importantly, it was the first neuroimaging study to differentiate between opposing motivational reactions to signals of social threat, i.e., approach versus avoidance, after testosterone administration. Compared to placebo, testosterone increased amygdala activation during the motivational challenge of approaching angry faces, and decreased it when the same stimuli could be avoided. By investigating the preparation of actions triggered by socioemotional cues, these results extend previous research on heightened approach-related attention to signals of social threat (Bos, van Honk, et al., 2012; Hermans, et al., 2010; Hermans, et al., 2008; Terburg, et al., 2012; van Wingen, et al., 2010; van Wingen, et al., 2008).

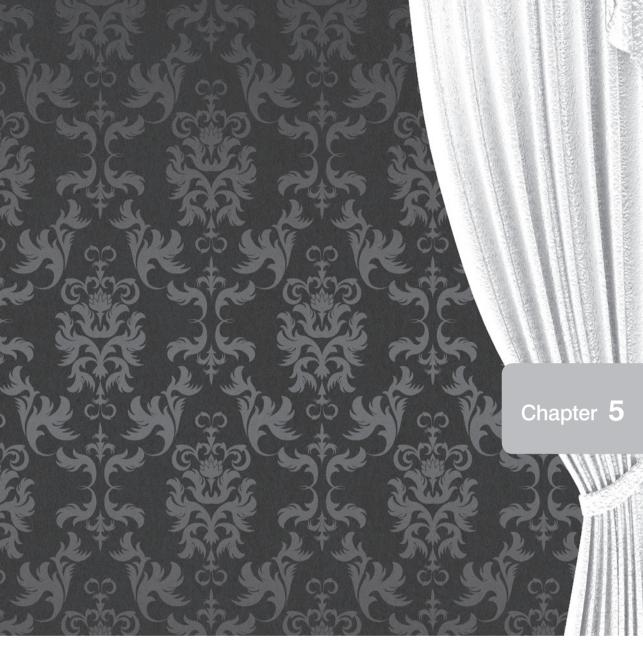
Further, our findings provide the first neuroendocrine extension of the motivational salience model (Cunningham, et al., 2010; Cunningham, et al., 2008) by showing motivation-specific effects of testosterone on amygdala processing of social threat cues. The tuning of amygdala activity to social motivational challenge might be driven by a preferential perception of angry faces under testosterone, in line with its influence on psychophysiological indicators of attention (Terburg, et al., 2012; van Honk, Tuiten, Hermans et al., 1999; van Honk et al., 2000; van Honk, Tuiten, Verbaten et al., 1999). In light of the association of testosterone with social approach and aggression (for reviews see Archer, 2006; Bos, Panksepp, et al., 2012), it is likely that testosterone prepares the individual to deal with social challenges via limbic pathways. Processing advantages for affectively or motivationally salient stimuli precede the actual

encounter with the particular stimulus, whereas behavior clearly occurs subsequent to an encounter (Todd, Cunningham, Anderson, & Thompson, 2012). These distinct timescales might account for the fact that substance differences in brain activity were not mirrored on a behavioral level in the current administration study as well as in the correlational data of Volman, Toni, et al. (2011).

In line with previous findings (Volman, Roelofs, et al., 2011; Volman, Toni, et al., 2011; Volman, et al., 2013), activity of the aPFC was stronger for motivationally incongruent than congruent responses. This replication further underlines the importance of the aPFC and adjacent orbitofrontal regions in the evaluation of socially and emotionally relevant stimuli and the selection of appropriate responses (Elliott, et al., 2000; Kringelbach & Rolls, 2004). Interestingly, we did not observe substance differences in this region, which indicates that the enhanced amygdala activation is not a likely derivative of dissimilar aPFC involvement. Therefore, it appears that the naturally occurring testosterone levels in males (Volman, Toni, et al., 2011) affect motivational actions via different brain circuits than in the current female sample receiving exogenous testosterone. Whereas diurnal and cyclical variations of endogenous testosterone are negligible in the light of the dosage used in administration studies (van Rooii, et al., 2012), gender differences in the endocrine system should be given consideration. In particular, the free fraction of testosterone and sex hormone binding globulin levels might vary, as it remains unresolved whether free testosterone levels or free fraction levels underlie the behavioral effects reported in administration studies (van der Made et al., 2009; van Rooij, et al., 2012). Similarly, we cannot rule out that the hormonal contraceptives used by our participants interact with exogenous testosterone. Gender differences in the effects of testosterone need to be addressed in future administration studies.

In conclusion, we show that testosterone increases amygdala responses during the motivational challenge of approaching social threat. This motivation-specific tuning of the amygdala might go in hand with enhanced attention to social threat cues of high relevance for active goal-attainment. Directing and prioritizing attention to salient social signals prepares an individual to engage in social motivational interactions. Testosterone stimulates this preferential processing, leading to appropriate preparation for facing social challenges.





In action or inaction?

Abstract

In depression, approach deficits often impair everyday social functioning, but empirical findings on performance-based measurements of approach-avoidance behavior remain conflicting. To investigate action tendencies in patients with depression, the current study used an explicit version of the Approach-Avoidance Task. In this task, participants responded to emotional faces by either pulling a iovstick toward (approach) or pushing it away from themselves (avoid). Reaction times to happy and angry expressions with direct and averted gaze were assessed in 30 patients with major depressive disorder and 20 matched healthy controls. In contrast to healthy individuals, depressed patients did not show approach-avoidance tendencies, i.e., there was no dominant behavioral tendency and they reacted to happy and angry expressions likewise. These results indicate that behavioral adjustments to different emotional expressions, gaze directions or motivational demands were lacking in depression. Crucially, this distinguishes depressed patients not only from healthy individuals, but also from other clinical populations that demonstrate aberrant approach-avoidance tendencies, e.g., patients with social anxiety or psychopathy. As responding flexibly to different social signals is integral to social interactions, the absence of any social motivational tendencies seems maladaptive, but may also provide opportunities for modifying action tendencies in a therapeutic context.

Based on:

Radke, S., Güths, F., André, J. A., Müller, B. W., & De Bruijn, E. R. A. (under review). In action or inaction? Social approach-avoidance tendencies in major depression.

Introduction

Individuals with depression often suffer from approach deficits, evident e.g., in anhedonia, reduced energy and social withdrawal. Aberrant approach and avoidance processes may contribute to depression by decreasing reinforcing experiences, along with increasing social isolation (Trew, 2011), thereby likely impeding social functioning. Social adaptive behavior may be guided by facial expressions that communicate emotional and motivational states. Emotional expressions also elicit approach and avoidance tendencies not only in everyday life, but in experimental settings as well.

In the Approach-Avoidance Task (AAT; Roelofs et al., 2010; Rotteveel and Phaf, 2004), for example, participants have to react to facial expressions by pulling a joystick towards (approach) or pushing it away from their body (avoidance). Action tendencies are quantified by means of reaction time (RT) differences between push and pull movements. When explicitly categorizing the emotional expression, healthy individuals typically show an approach tendency in response to positive social cues, i.e., faster pull reactions to happy faces, and an avoidance tendency, i.e., faster pull reactions in response to negatively valenced (angry) faces. In contrast, implicit task variants that require reactions to emotion-irrelevant stimulus properties (color/gender) often do not evoke response tendencies (Derntl et al., 2011; Volman et al., 2011). Instead, behavioral effects strongly depend on additional task features, such as zooming, i.e., stimuli in- and decreasing in size when the joystick is pulled and pushed, respectively (Heuer et al., 2007; Roelofs et al., 2010).

Interestingly, social motivational impairments and clinical symptoms are mirrored in performance on the AAT. Stronger avoidance responses to both happy and angry stimuli were evident in socially anxious individuals (e.g., Heuer et al., 2007; Roelofs et al., 2010, whereas incarcerated psychopathic offenders displayed reduced avoidance of angry faces (Von Borries, et al., 2012). In patients with depression, the processing bias for negative affective information (for reviews see Leppanen, 2006; Stuhrmann et al., 2011) does not directly map onto altered action tendencies, at least when assessed with an implict AAT. Whereas patients showed a pronounced avoidance tendency of angry faces in one study (Seidel et al., 2010), this inclination was absent in the neuroimaging follow-up (Derntl et al., 2011) as well as in both healthy control groups. However, when explicitly asked to rate their approach-avoidance tendencies, depressed patients reported less overall approach. The authors assumed that along with dysfunctional behavioral tendencies, more controlled, explicit processes in interpersonal approach-avoidance behavior are impaired in depression, but given the distinction between explicit and implicit task variants, this hypothesis remains to be investigated.

The current study therefore used an explicit, zooming version of the AAT to investigate approach-avoidance tendencies in depressed patients. In addition, the

direction of eye gaze was manipulated for exploration of potential differential effects and for comparison with populations associated with altered interpersonal behavior (Roelofs et al., 2010; Von Borries et al., 2012). Direct gaze is a strong imperative that initiates an interaction by putting the recipient in the position to react (Adams and Kleck, 2005), whereas averted gaze does not incorporate motivational affordances. Along these lines, we expected more pronounced action tendencies for emotional faces with direct gaze. Depressed patients are likely to show a decreased approach tendency for happy faces, in line with their approach deficits. For angry faces, based on Seidel et al. (2010), increased avoidance might be expected. Yet, disturbances of explicit interpersonal approach-avoidance behavior could also lead to reduced adaptation to different social demands, i.e., a lack of differentiation between emotional expressions. This would be evident in the absence of approach-avoidance biases in patients with depression.

Methods

Participants

Thirty patients of the LVR Clinic, Essen, Germany were matched with 20 healthy volunteers on age and educational level (see Table 5.1 for group characteristics). The study was approved by the local ethics committee of the University Duisburg-Essen, registered in the German Clincal Trials Register (DRKS0003563) and in accordance with the Declaration of Helsinki. All participants received written information about the experiment and gave written informed consent.

Groups were derived based on the German version of the Structured Clinical Interview (Wittchen et al., 1997). All patients were diagnosed with a major depressive disorder without psychotic symptoms during past or current episodes (MDD, recurrent episode; 296.1(0-3), 296.3(0-3)) in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000) and had been taking the same prescribed medication (if any) for the past two weeks. Exclusion criteria were an IQ below 70, neurological disorders, substance dependence, and social anxiety disorder. Severity of affective symptoms was assessed with the Beck Depression Inventory (BDI; Hautzinger et al., 2006).

Materials and data preparation

In the AAT, facial expressions (happy, angry, neutral) with direct or averted gaze were presented in black and white (Figure 5.1 includes stimulus examples; for additional information see e.g., Roelofs et al., 2010). Participants categorized the emotional expression by pulling a joystick (Logitech Attack 3) toward or pushing it away from themselves, which caused the pictures to shrink or grow before disappearing when the minimum, respectively maximum size was reached.

Table 5.1. Sociodemographic and clinical characteristics of study participants (presented as N or Mean [SD], otherwise indicated).

	HC (N = 20)	MDD (N = 30)	p-value
	110 (14 – 20)	WIDD (14 = 30)	p-value
Profile			
Age in years	44.5 (12.5)	46.6 (11.3)	.54
Sex (M/F)	11/9	12/18	.30
Education	16.5 (4.3)	14.8 (2.9)	.12
BDI	4.4 (4.1)	27.0 (11.5)	<.001
Comorbidities			
Specific phobia (writing; heights)		2	
Agoraphobia		1	
Posttraumatic stress disorder		1	
Medication			
Exclusively antidepressants		22	
Antidepressants and antipsychotics		2	
Exclusively antipsychotics		3	
No medication	20	3	

Note: HC = healthy controls, MDD = depressed patients, M = male, F = female, BDI = Beck Depression Inventory

In six blocks (3 emotions x 2 responses), 384 experimental trials were randomly presented, i.e., within each block, pictures of two emotional expressions were depicted (half of which with direct gaze). Block order and response direction were counterbalanced (e.g., approach happy faces-avoid angry faces, approach happy faces-avoid neutral faces, approach angry faces-avoid happy faces, approach neutral faces-avoid happy faces, approach neutral faces-avoid angry faces). The time between stimulus onset and the maximum joystick displacement (30°) was used for all analyses.

After excluding erroneous responses (3%) and RTs <150 ms, median RTs were calculated for each level of the three experimental factors (Emotion, Gaze, Movement). Subtracting individual median RTs for pull movements from individual median RTs for push movements provided effect-scores, i.e., individual dominant behavioral tendencies. Negative effect-scores reflect a stronger avoidance tendency, while positive effect-scores denote a stronger approach tendency (Heuer et al., 2007; Roelofs et al., 2010).

Subsequent to the AAT, participants rated each picture as 'angry' and 'happy' on a 10-point Likert scale. Averages were calculated for all analyses.

Results

AAT: RTs

Following previous AAT analyses focusing on emotional expressions (Radke et al., 2013; Volman et al., 2011), RTs were subjected to a mixed model ANOVA with Emotion (happy, angry), Movement (approach, avoid) and Gaze (direct, averted) as within-subject factors and Group (depressed, healthy) as a between-subject factor. There were significant main effects of Emotion, F (1, 48) = 31.74, p < .001, q²= .40, and Group, F (1, 48) = 9.91, p = .003, q²= .10. Moreover, there was a significant Emotion x Movement interaction, F (1, 48) = 8.13, p = .006, q²= .15, a significant Emotion x Movement x Gaze interaction, F (1, 48) = 4.23, p = .045, q²= .08, and, most importantly, a significant Emotion x Movement x Group interaction, F (1, 48) = 5.14, p = .028, q²= .17. Other effects were not significant (all Fs < 1.67, all ps> .20).

The main effects of Emotion and Group were due to faster reactions to happy (M = 831.79 ms) than to angry faces (M = 876.53 ms) and faster reactions in healthy individuals (M = 788.85 ms) than in depressed patients (M = 919.47 ms), respectively. Interaction effects are best interpreted in the context of AAT effect-scores (see following section and Figure 5.1; Radke et al., 2013) that correct for the observed RT differences between levels of Emotion and Group.

AAT: Behavioral tendencies

The significant interactions in the RT analyses between Emotion x Movement and Emotion x Movement x Gaze were evident in i) the expected pattern of approach of happy (M=24.82) and avoidance of angry faces (M=-24.79) and ii) more pronounced approach-avoidance tendencies for direct gaze stimuli, F (1, 48) = 11.08, p=.002, $q^2=.19$ ($M_{happy}=34.0$, $M_{angry}=-28.9$), than for averted gaze stimuli, F (1, 48) = 3.97, P = .052, P = .08. (P = .054, P = .056).

To further investigate the Emotion x Movement x Group interaction, separate analyses on AAT effect-scores for the two groups were conducted. A significant effect of Emotion was evident in healthy controls, F (1, 19) = 14.04, p = .001, η^2 = 0.43, but not in depressed patients, F (1, 29) = .19, p = .67, η^2 < 0.01. No other effects were significant (all Fs < 2.49, all ps> .14). In healthy controls, the main effect of Emotion was due to higher effect-scores, i.e., approach, towards happy faces (M = 48.2) than towards angry faces (M = -40.84). For depressed patients, the reactions to happy (M = 1.43) and angry faces (M = -8.74) neither differed from each other nor from zero (all ps> 0.38), reflecting a lack of dominant action tendencies.

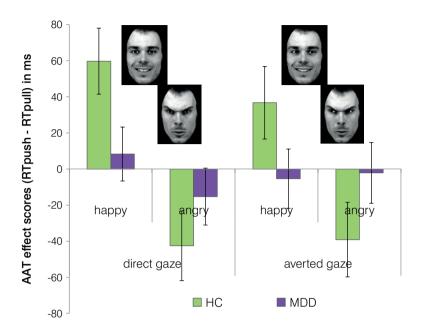


Figure 5.1. Mean effect scores (RTpush-RTpull in ms) and standard errors for direct (left) and averted (right) gaze stimuli for each emotion. Negative effect scores indicate avoidance, while positive effect scores indicate approach tendencies. HC = healthy controls, MDD = depressed patients. Sample stimuli were obtained from KDEF (identity AM29) with permission from the copyright holders.

These group differences are not due to differences in response latency. Specifically, when deriving groups from a median split of average RTs in the entire sample and subjecting AAT effect-scores to an ANOVA, the effects of Emotion and Emotion x Gaze remain significant, but slow and fast responders do not differ in approach-avoidance tendencies.

Correlations

There was a significant negative correlation between symptom severity (BDI) and AAT effect-scores for happy faces with direct gaze, r = .30, p = .038, and a marginally significant correlation between BDI and happy faces with averted gaze, r = .27, p = .057, indicating less approach towards happy faces for participants with a higher BDI. For angry faces, there was no such effect (all p > .13).

Rating

The ANOVA with Emotion (happy, angry) and Gaze (direct, averted) as within-subject factors and Group (depressed, healthy) as a between-subject factor showed the expected significant main effect of Emotion, F (1,48) = 1990.83, p < .001, η^2 = .98, indicating higher happiness ratings for happy faces than for angry faces and vice versa. Other effects were not significant (all Fs < 2.96, all ps> .09), suggesting no group differences in the explicit rating of pictures.

Discussion

The aim of the current study was to investigate explicit approach avoidance-tendencies in depressed individuals. As expected, our data replicate previous findings in healthy individuals, i.e., approach of happy and avoidance of angry faces in the AAT (e.g., Volman et al., 2011; Radke et al. 2013) and underline the stronger motivational affordances of direct gaze, evident in more pronounced approach-avoidance tendencies (Adams and Kleck, 2005). In contrast, depressed patients did not exhibit any dominant action tendencies. More specifically, they did neither show 1) differential behavior based on the emotional content, i.e., they reacted likewise to happy and angry expressions, nor 2) general approach or avoidance tendency distinct from zero, which would imply a bias for one motivational direction or the other.

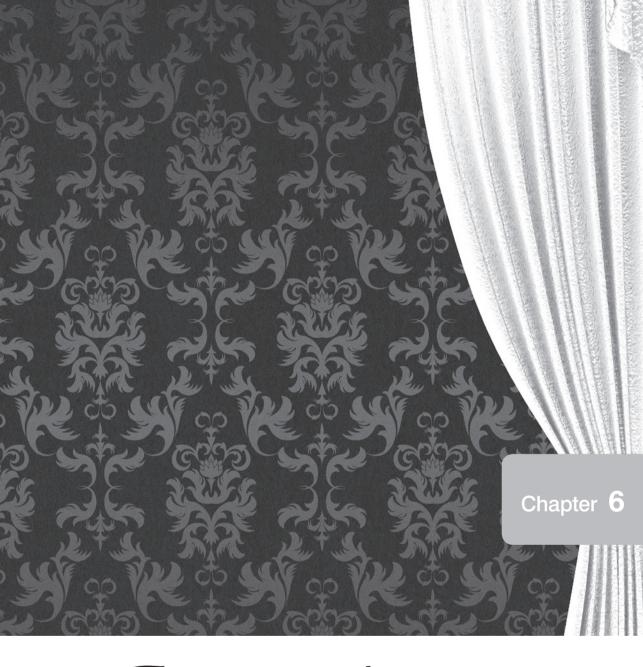
Interestingly, the lack of approach-avoidance tendencies in depressed patients could neither be attributed to increased response latencies nor to potentially altered ratings of the emotional expressions. However, symptom severity was negatively related to approach towards happy faces, which usually signals an invitation to socially interact. As depressed patients seem to perceive happy faces as less engaging (Derntl et al., 2011; Stuhrmann et al., 2011) and are less responsive to reward (Henriques and Davidson, 2000), a decreased sensitivity to positive or reinforcing interpersonal experiences might underlie their approach deficits. Even more, our data indicate that the more depressed the patients subjectively feel, the less they approach and engage in positive social encounters. Therefore, approach deficits might be crucial to the maintenance of depression by reducing the frequency and rewarding experience of positive contacts (Trew, 2011).

Our behavioral findings pose a valuable extension to previous, yet mixed findings obtained from a similar, but implicit joystick task, in which depressed patients exhibited increased avoidance of angry faces (Seidel et al., 2010). However, similar to discrepancies between subjective ratings and behavior, implicit and explicit variants of the AAT assess different processes. In particular, the categorization of the emotion depicted directs attention to the emotional content. The absence of behavioral biases even in such an explicit setting indicates the impairment of controlled. explicit

processes in interpersonal approach-avoidance behavior in depression (Seidel et al., 2010). Crucially, when the experimental context required actions and not judgments, depressed patients did not adapt their behavior to different emotional expressions, gaze directions nor motivational demands. Importantly, these are all integral parts of social communication and interaction and enable humans to act flexibly in different situations. By exhibiting no preferential responses in any respect, depressed patients deviate not only from healthy individuals, but also from populations displaying altered approach-avoidance tendencies both on a clinical and empirical level (Heuer et al., 2007; Roelofs et al., 2010; Von Borries et al., 2012).

To assess a complete picture, future studies should employ both implicit and explicit versions of the AAT for within-subject comparisons. Moreover, overcoming current limitations would be valuable, e.g., using withdrawal-related stimuli (sadness or disgust) to distinguish between valence and motivational direction. Finally, investigating approach-avoidance behavior in everyday life remains important since aberrant motivational tendencies are likely to sustain depression. Although both perceptual and motivational biases may contribute to impairments in social interactions, the actual resulting behavior determines psychosocial functioning and well-being. Here, patients may encounter problems, e.g., social isolation, but there is also room for acquiring new behavioral skills during therapy. In particular, the AAT has been used successfully as an intervention tool for modifying response biases towards salient stimuli such as alcohol (Wiers et al., 2011; Wiers et al., 2010) or spiders (Klein et al., 2011). In individuals with social anxiety, these training effects even extended to social approach behavior when interacting with a putative partner (Taylor and Amir, 2012). Changing behavior on such an automatic level could usefully complement the cognitive, more controlled strategies employed in therapy. Linking approach-avoidance tendencies to actual behavior might provide opportunities to incorporate enjoyable activities back into patients' lives and increase their social satisfaction.





There's something about a fair split

Abstract

Fairness considerations are a strong motivational force in social decision-making. Here, we investigated the role of intentionality in response to unfair offers in the Ultimatum Game by manipulating both proposers' degree of control over the selection of offers and the context pertaining to the outcomes of offers proposers can choose from. As a result, the design enabled us to disentangle intention- and context-based decision-making processes. Rejection rates were higher when an unfair offer was intentionally chosen over a fair alternative than when it was chosen by the computer, outside proposers' control. This finding provides direct evidence for intention-based decision-making. Also, rejection rates in general were sensitive to the context in which an offer was made, indicating the involvement of both intention- and context-based processes in social decision-making. Importantly, however, the current study highlights the role of intention-based fairness considerations in basic decision-making situations where outcomes are explicitly stated and thus easy to compare. Based on these results, we propose that fairness can be judged on different, but additive levels of (social-) cognitive processing that might have different developmental trajectories.

Based on:

Radke, S., Güroğlu, B., & De Bruijn, E.R.A. (2012). There's Something about a Fair Split: Intentionality Moderates Context-Based Fairness Considerations in Social Decision-Making. *PLoS ONE*, *7*(2), e31491.

Introduction

Fairness considerations, i.e., comparisons of self-interest and other-interest, are a strong motivational force in social decision-making. Individuals tend to regard outcomes that sustain normative expectations about fairness as most valuable (Loewenstein, Bazerman, & Thompson, 1989). Fairness norms prevail even in economic situations involving anonymous parties (Kahneman, Knetsch, & Thaler, 1986) and often imply a preference for an equal distribution of resources, i.e., inequity aversion (Fehr & Schmidt, 1999; Nelson, 2001). This process of social comparison is also assumed to be crucial for feelings of injustice, jealousy or envy (Festinger, 1954; Suls & Wheeler, 2000). As many of our decisions are made within social settings, fairness intention models suggest that the intention of the interaction partner is crucial in fairness considerations (Falk, Fehr, & Fischbacher, 2008). Individuals show, for example, a greater desire to sanction intended unfair offers compared to unintended unfair offers in an economic game (DeQuervain et al., 2004).

Perspective-taking is essential for evaluating others' intentions. Falk et al. (2003) developed a modified version of the Ultimatum Game (UG; Güth, et al., 1982) to examine the role of intentionality in fairness considerations. In this version, the first player (proposer) chooses from a fixed set of two distributions of the stake (here 10 coins), which allows for manipulating the reference point of an offer. An unfair offer of 8 coins for the proposer and 2 coins for the responder (8:2) is paired with four different alternatives: a fair- (5:5), a hyperfair- (2:8), a hyperunfair- (10:0), and no-alternative (8:2). Pairing an unfair offer (8:2) with a fair alternative (5:5) can be seen as an explicit version of the classic UG in which decision-making is usually driven by comparing an offer to a potential equal split, although this fairness norm remains implicit in the design. Previous studies using the modified UG paradigm have revealed that responders' behavior is sensitive to the alternative options. Rejection rates are highest when there is a fair-alternative, but lowest when paired with a hyperunfair- or no-alternative (Falk, et al., 2003; Güroğlu, et al., 2009; Sutter, 2007). This suggests that fairness is not only evaluated based on the actual distribution, but also with regard to the alternatives to a given offer (Brandts & Sola, 2001; Nelson, 2002; Sandbu, 2007). The authors (Falk, et al., 2003; Güroğlu, et al., 2009; Sutter, 2007). attributed higher rejection rates of unfair offers in the fair-alternative condition than in the no-alternative condition to intentionality considerations and perspective-taking and termed this 'context effect' (Güroğlu, et al., 2009; Güroğlu, van den Bos, Rombouts, & Crone, 2010). Therefore, throughout this paper the term 'context' will refer to the manipulation of alternative offers, i.e., the unselected alternatives to an unfair offer. Further, it was assumed that the no-alternative condition implies that proposers make an unintended unfair offer because the two identical distributions do not permit a real choice so that neither 'good' nor 'bad' intentions could be inferred.

Alternatively, however, the difference in rejection rates across conditions (i.e., context effect) can be ascribed to comparing outcomes for the self in the proposed offer and the alternative distribution. In other words, the rejection decision may be based on the comparison of the possible gain for oneself (i.e., 2 coins in the 8:2-distribution) and the alternative, but by now unattainable gain, e.g., 5 coins in the fair-alternative condition. Therefore, distributional concerns may lie at the heart of the context effect, which would be a more parsimonious explanation for the rejection pattern previously reported. Varying the reference point of an offer, i.e., the unchosen alternative, and thereby eliciting changes in responder behavior, does not necessarily have to involve perspective-taking or intentionality considerations, but has often been taken as an indication of these higher-order social processes (Falk, et al., 2003; Güroğlu, et al., 2009; Nelson, 2002; Ohmura & Yamaqishi, 2005; Sutter, 2007). Brandts & Sola (2001) highlight that attributing intentions essentially requires non-outcome information, i.e., information that surpass a simple comparison of outcomes, and Sandbu (2007) even claims that the context effect as such "reveals nothing about intentions." Put differently, rejecting an unfair offer because it was of less value than the alternative (i.e., "I can get 2 coins now, but I could have gotten 5 coins") can be anchored in relatively straightforward outcome comparisons without considering other players' perspective and their intentions.

In fact, a crucial factor in attributing intentions is proposers' degree of control in making a choice (Falk, et al., 2008). Previous studies (Blount, 1995; Rilling, et al., 2004; Sanfey, et al., 2003; van't Wout, et al., 2006) have usually tried to capture this aspect by employing computer conditions in which participants play economic games against a computer. However, these studies tend to overlook an important aspect: When playing the UG against a computer - an inanimate proposer neither emotionally nor monetarily (as in Rilling, et al., 2004; Sanfey, et al., 2003; van't Wout, et al., 2006) affected by participants' decisions - considering any potential other-interest becomes pointless. Effectively, instead of depriving human proposers of their control over making an offer, proposers are replaced by computers that neither possess any sensitivity for fairness norms nor any authentic interest for the outcome of the game. The social quality of the interaction missing, it is not surprising that lower rejection rates of unfair offers from computers than from human proposers are reported. Remarkably, the study by Blount (1995) is the only one in an UG setting in which participants' decisions actually had consequences for proposers' payoff, irrespective of who was in control of making an offer (a random device, a neutral third party or the other players themselves). When participants had to indicate the lowest amount that they would accept, a lower benchmark was set for offers generated by a random device than for offers determined by the other players themselves, which resembles the results from studies using computer conditions (Rilling, et al., 2004; Sanfey, et al., 2003; van't Wout, et al., 2006).

Unfortunately, the classic UG used in these experiments (Blount, 1995; Rilling, et al., 2004; Sanfey, et al., 2003; van't Wout, et al., 2006) is - due to its lack of an explicit reference point - not a suitable design to capture the sensitivity to contextual fairness. Conversely, the modified version of the UG (Falk, et al., 2003; Güroğlu, et al., 2009; Sutter, 2007) allows for varying the context of an offer. The no-alternative condition even implies that proposers have no actual choice in making an offer as the two options are equally unfair. Yet, the two factors of control and context comparisons of possible gains are confounded in this condition as an unfair offer involves both no-control over the offer and identical outcomes in the actual and alternative offer. In none of the existing designs (Falk, et al., 2003; Güroğlu, et al., 2009; Nelson, 2002; Ohmura & Yamaqishi, 2005: Sutter, 2007) intentionality is treated as a separate factor that provides information going beyond available and alternative payoffs. Although some authors have proposed the development of models that incorporate both intention- and outcome-based fairness considerations (Bolton & Ockenfels, 2005; Nelson, 2002), the majority of experiments in both psychology and economics has focused on manipulating either intentionality or the context in which an offer occurs, i.e., the reference point. Put differently, replacing human proposers with a computer in order to capture intentionality neglects the influence of social comparisons (Rilling, et al., 2004; Sanfey, et al., 2003; van't Wout, et al., 2006). On the other hand, varying the alternatives to an offer is often assumed to imply intentionality (Falk, et al., 2003; Güroğlu, et al., 2009; Nelson, 2002; Ohmura & Yamaqishi, 2005; Sutter, 2007). Yet, the latter design does not experimentally disentangle intentionality from the context effects, i.e., information about potential outcomes. Notably, no single study exists which adequately, i.e., explicitly, manipulates both contextual fairness and intentionality in an UG setting. Using a closely related game, the Dictator Game, in which the responder remains passive without a choice to accept or reject (Forsythe, Horowitz, Savin, & Sefton, 1994). Houser & Xiao (2010), for instance, manipulate intentionality as well as context to investigate punishment behavior. Their results show that punishment is motivated by both inequality of the allocation and intentionality of the dictator, but with increased punishment when dictators themselves, instead of a computer, split the stake. However, context is created in a rather dimensional approach as dictators are presented with five different alternatives, ranging from none to the dictator's total endowment, so that there is always a better or worse alternative. As this scope is likely to trigger different perceptions of relative (un-)fairness than the binary choice set of the modified UG, we remain cautious to directly compare these two different designs.

The current study therefore aimed to investigate the relative roles of intentionand context-based fairness considerations. To accomplish this, we manipulated both the degree of control, i.e., intentionality, and context, i.e., the alternative offer, using a modified UG. Along with the context manipulations discussed above, we also included no-control conditions in which the computer takes over from the other player and randomly selects one of the two options. Consequently, conditions were established where the absolute payoff of a particular offer is the same, but it is either selected by the human player (control condition) or by the computer (no-control condition). For the control condition, we expected to replicate the previously reported relation between rejection rates and context as determined by the alternatives. For offers outside of proposers' control, we formulated two possible hypotheses: If intentionality is the central determinant of responders' decisions, rejection rates for all no-control conditions should be similar, irrespective of context. Moreover, these rejection rates should not differ from the no-alternative control condition because the same basic tendency for inequity aversion is expected in all conditions where proposers have no real choice, i.e., both in the no-alternative control and in all no-control conditions. Alternatively, however, if fairness considerations based on the comparison of gains in the actual and alternative offer are a central determinant of responders' decisions, the pattern of rejection rates should be similar for control and no-control conditions.

Methods

Participants

Fifty subjects (25 male, 25 female) participated in the experiment (M age = 22.52 years, SD = 5.43). All participants gave written informed consent and the procedure was approved by the local ethics committee (Ethische Commissie Gedragswetenschappelijk Onderzoek of the Faculty of Social Sciences at the Radboud University Nijmegen, The Netherlands).

Design

Participants played the role of the responder in a computerized version of the modified UG. There were two within-subject factors: Control and Context. Control had two levels based on *who* selects the offer for the proposer: the human player him/herself (control) or the computer (no-control). The factor of control captures thus whether an offer was intended or not. Context had four levels based on alternatives to an unfair distribution (8:2): a fair-alternative (5:5 vs. 8:2), a hyperfair-alternative (2:8 vs. 8:2), a hyperunfair-alternative (10:0 vs. 8:2), and no-alternative (8:2 vs. 8:2). Hence, the factor context pertains to the alternative outcome that had not been chosen. The resulting 8 conditions were presented 16 times each (counterbalanced for proposers' gender and position of the unfair offer). As the no-alternative condition entails an 8:2 offer for either alternative, an unfair offer (8:2) was presented in 5 of the 8 conditions, equivalent to 80 trials. The three genuine alternative offers (i.e., 5:5, 2:8 or 10:0) were selected on

48 trials, yielding 128 trials in total. Contrary to subjects' belief, all choices were computer-generated.

Material

Figure 6.1 depicts the timeline of a trial in both fair-alternative conditions. Each round started with a fixation cross (1000 ms), followed by the presentation of the two available options (1000 ms). Next, the selected offer was surrounded by a red square (1000 ms). Subsequently, "Yes" and "No" buttons were presented while the selection remained visible. As the task was self-paced, participants had unlimited amount of time to respond via pressing one of two buttons using the keyboard. Participants' response remained on the screen for 2000 ms before the next round started.

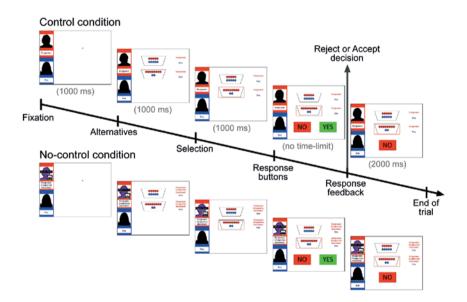


Figure 6.1. Display of a trial in the fair-alternative condition (top: control, bottom: no-control condition). The left part of the screen shows the name of the proposer at the top (here "Proposer") and the name of the participant underneath (here "You"). In the no-control condition, the otherwise black silhouette of the proposer was purple with a banner displaying "Computer chooses". The same banner was also displayed instead of the proposer's name. The two potential distributions are specified by red and blue coins (red for proposer, blue for responder). The offer selected by the proposer was encircled in red. The participant has to decide whether to accept ("Yes") or reject ("No") the offer via button press.

Procedure

Participants were led to believe that they were coupled with data from subjects who had previously participated as proposers and that they would play every round with a new partner. They were told that on some trials the other players would make an offer themselves and on other trials the computer would randomly select one of the two options. Participants' task was to decide whether to accept or reject an offer. If accepted, the coins were distributed as proposed; if rejected, neither player received anything. Participants were informed that at the end of the experiment, a random number of rounds would be selected to determine their payoff. This was done to assure participants' motivation and to strengthen the concept of a one-shot game as every round could influence their financial outcome. Moreover, it was emphasized that participants' decisions also affected the other players' outcome because their payoff would be determined by participants' response, irrespective of who made the proposal in a particular round (i.e., themselves vs. computer). Proposers would be paid after all data from responders had been collected. The payoff was set around 2.50 Euro to manage an equal payment for all participants, resulting in 10 Euro compensation.

Results

A repeated measures ANOVA was conducted for the rejection rate of unfair offers with control (two levels: human vs. computer) and context (four levels: fair vs. hyperfair vs. hyperunfair vs. no alternative) as within-subject factors. There was a main effect of control, F(1, 49) = 4.60, P < .05, partial P = .09, indicating that rejection rates were highest when proposers' decisions were under their full control (33.2%) compared to when the computer took over and selected the offer (30.5%). Moreover, there was a main effect of context, P = .05, P = .001, partial P = .05 (see Figure 6.2).

Post-hoc pairwise comparisons (using Bonferroni correction) revealed that rejection rates were highest for the fair-alternative condition (47.3%) compared to the other alternatives (hyperfair: 39.3%, p < .05; hyperunfair: 18.6%, p < .001; no-alternative: 22.3%, p < .001). Rejection rates for the hyperfair alternative condition were higher than for the hyperunfair and no-alternative condition (both p < .001). The latter two did not differ significantly (p = 1).

Importantly, the interaction between context and control was significant, F (3, 147) = 5.80, p < .01, q ²= .11. Further analyses demonstrated that this was due to the fair-alternative condition. Rejection rates were significantly higher in this condition when the proposal was made under proposers' full control (52.0%) than when the computer selected the offer (42.5%; t(49) = 3.10, p < .01).

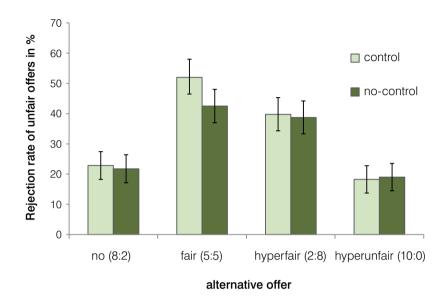


Figure 6.2. Rejection rates of unfair offers with regard to alternative offers and control of the choice. Mean percentage and standard errors of rejection of 8:2-offers are displayed.

For the alternative offers, i.e., for trials on which not the 8:2, but the alternative distribution was chosen, hyperunfair offers were nearly always rejected (87.1%), whereas fair (5.1%) as well as hyperfair offers (2.5%) were nearly always accepted. This shows that the presence of basic fairness evaluations among participants can be assumed. There were no sex differences (all ps > .48).

Discussion

The aim of the current study was to investigate the relative roles of intention- and context-based fairness considerations that drive social decision-making. Based on influential factors identified in earlier research (Falk, et al., 2008), we manipulated (1) control, i.e., intentionality, as assessed by whether proposers themselves or the computer selected the offer, and (2) context, i.e., the outcome of the alternative in the modified UG.

An effect of control was evident when an unfair treatment was made explicit, namely when an unfair offer was paired with a fair alternative. Faced with a fair alternative, participants rejected unfair offers more often when the offer was selected by proposers themselves than when selected by the computer. In this specific

situation, proposers' intentional deviation from the social norm of fairness was most salient. This finding thus provides direct evidence for intention-based decision-making processes in fairness considerations. When presuming that the situation in the classic UG most resembles the fair-alternative condition in the current design, our findings are technically in line with previous studies (Blount, 1995; Rilling, et al., 2004; Sanfey, et al., 2003; van't Wout, et al., 2006) reporting lower rejection rates of unfair offers from computers than from human proposers. However, one should bear in mind that the classic UG lacks an explicit reference point and is therefore not able to capture context effects and their potential interplay with other factors. Conversely, when playing the UG against a computer, responders' decisions usually do not have consequences for another player (as in Rilling, et al., 2004; Sanfey, et al., 2003; van't Wout, et al., 2006).

Responder behavior in conditions where proposers have full control over choosing an offer are in line with earlier studies investigating context effects (Falk, et al., 2003; Güroğlu, et al., 2009; Sutter, 2007). Unfair offers were more often rejected when the alternative was fair compared to a hyperfair-, hyperunfair- or no-alternative. Moreover, the no-control conditions depicted a similar pattern of results as the control conditions, indicating that unfair offers were more often rejected when paired with a better (i.e., fair- or hyperfair-) alternative, even when the decision was not under proposers' control and clearly made unintentionally.

Taken together, the current results show that fairness considerations are sensitive to both intentionality and context. Comparing outcomes of the actual and the alternative offer remains an integral part of fairness evaluations even when the offers are beyond proposers' control. Importantly, however, intentionality becomes crucial when the unfair treatment is obvious: When proposers clearly choose not to offer an equal split by favoring an unfair distribution, the intentional social norm violation is instantly and unambiguously recognizable. Participants' increased tendency to reject these unfair offers can be regarded as a form of altruistic punishment - punishing proposers for the norm violation at a cost to themselves (Fehr & Fischbacher, 2003). Previous studies have shown that altruistic punishment occurs frequently even in one-shot encounters, hence in absence of direct reciprocity or reputation formation (Fehr & Gächter, 2002). It may be triggered by negative emotions like anger (Pillutla & Murnighan, 1996; van't Wout, et al., 2006) and is often used in order to reduce inequality (Dawes, Fowler, Johnson, McElreath, & Smirnov, 2007; Falk & Fischbacher, 2006). The current study shows that when confronted with two alternatives where one is strictly fair and the other undoubtedly unfair, the desire for compliance with fairness norms is most evident as participants were least willing to accept an intentional unfair offer. These results corroborate a study by Nelissen et al. (2009) in which responders had an outside option that yielded a larger personal payoff when rejecting than when accepting an equal split. The majority of responders decided on behalf of an equal split, thus missing an additional monetary benefit. The preference for fairness norms overrules the motive of maximizing personal payoff, verifying that fairness is a normal good (Nelson, 2001). Despite a greater punishment tendency in response to intentional unfairness, altruistic punishment also occurs when the source of inequality is random, i.e., unintentional (DeQuervain, et al., 2004; Houser & Xiao, 2010), supporting the importance of egalitarian motives (Dawes, et al., 2007).

Although the strict and mutually exclusive differentiation between intention-based and outcome-based fairness seems to prevail in the literature (Falk, et al., 2008; Falk & Fischbacher, 2006; Fehr & Camerer, 2007; Fehr & Fischbacher, 2004; Nelissen, et al., 2009), some authors have already expressed the need for models that include both intention- and outcome-based fairness considerations (Bolton & Ockenfels, 2005; Nelson, 2002). Since our data suggest a broader perspective on fairness dimensions, we would like to propose a new framework that integrates key factors identified previously (Falk, et al., 2008) as well as (social-)cognitive demands that accompany each level of fairness considerations.

In this new framework, outcome-based fairness considerations comprise the first and basic level of social decision-making. It is anchored in social comparison processes, that is, a comparison of outcomes of the self and the other. On this level, the concept of fairness primarily refers to an equal split, which is a very salient signal. A preference for an equal split - also referred to as inequity aversion - is already observable in young children (Blake & McAuliffe, 2011; Takagishi, et al., 2010) and non-human species like capuchins, chimpanzees and domesticated dogs (Brosnan, et al., 2010). Experimental paradigms investigating this level usually involve the division of resources, as in the UG. Note that the context effects observed here and previously (Brandts & Sola, 2001; Falk, et al., 2003; Güroğlu, et al., 2009; Ohmura & Yamagishi, 2005; Sandbu, 2007; Sutter, 2007) exceed pure inequity aversion. As the magnitude of an offer, i.e., its absolute payoff for the self and the other, remains identical across contexts and degrees of control, objective fairness is violated in all unfair offers

Taking into account the context in which an offer occurs characterizes the next level of fairness considerations. Here, additional information about the unchosen alternative has to be processed and integrated. This requires counterfactual thinking, i.e., mental representations of alternatives to past events (Roese, 1997) that, in this case, involve both the self and the other. Thinking about hypothetical events has been linked to executive functioning, especially working memory and inhibitory control (Drayton, Turley-Ames, & Guajardo, 2011). Apart from engaging additional cognitive competencies, this level is likely to also pose more demands on mentalizing skills as chimpanzees and children do not show context effects in a modified UG (Güroğlu, et al., 2009; Jensen, Call, & Tomasello, 2007; Sutter, 2007). The sensitivity to contextual fairness seems to go in hand with maturation in adolescence and

seems to play an increasingly significant role in the decision-making process. Yet, the phenomenon of inequity aversion does not utterly disappear as rejection rates in the no-alternative conditions do not drop to zero, but remain substantial (Falk, et al., 2003; Güroğlu, et al., 2009; Sutter, 2007). Hence, the rejection rate in the no-alternative conditions might reflect a basic tendency for inequity aversion (Falk, et al., 2003; Ohmura & Yamaqishi, 2005) that continues to exert influence on decision-making.

Intentionality can be viewed as the next level in fairness considerations. Judging whether observed behavior was intentional is crucial in social interactions as it may lead to different perceptions of responsibility and morality (Cushman, 2008; L. Young & Saxe, 2011). In criminal law, for instance, intentionality comprises, apart from the voluntary element, also a cognitive facet, namely whether someone was aware of the probable consequences of an action. It is therefore often linked with outcome information and not regarded in isolation, as fairness intention models seem to suggest (Falk, et al., 2008). Our results support the notion that intentionality does not completely override the conclusions derived from previous levels as both the preference for equitable outcomes, i.e., a basic tendency for inequity aversion, as well as the sensitivity to contextual fairness remain. When an unfair treatment is explicit and salient, intentionality moderates context-based preferences. For future studies, it would be interesting to assess developmental changes that might complement the shift towards this level of decision-making.

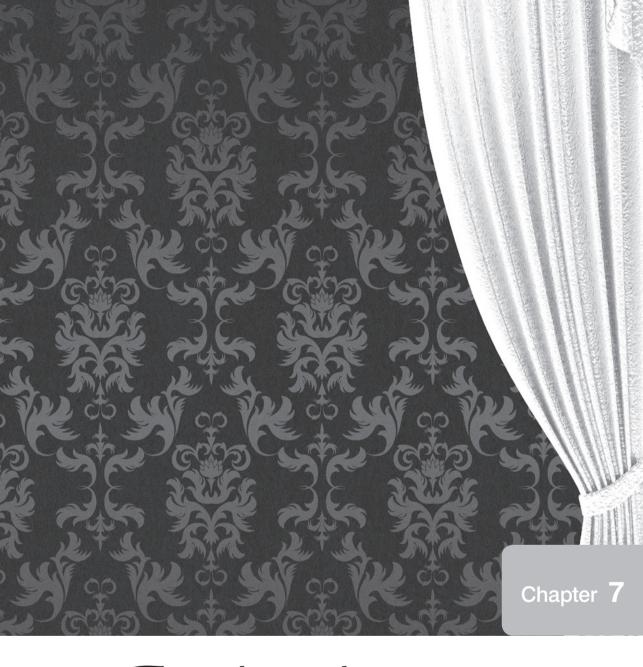
These additive levels correspond to an increasing amount of information that is considered and integrated before a decision is made. Note that - unlike more complex everyday life situations - in the current task, all potential consequences are explicitly stated and can easily be compared using the same 'currency' (i.e., coins). In contrast, decoding and understanding intentions in real-life interactions is usually more complex and requires additional abilities, such as perspective-taking or mentalizing processes (Frith & Frith, 2001; Van Overwalle, 2009) known to continue developing in humans until late adolescence (Güroğlu, et al., 2009). The development of these different factors throughout adolescence is intriguing and should be explored in more detail.

Further research should be devoted to altered social decision-making that is frequently observed in clinical populations. Impairments in social decision-making have been associated with ventromedial prefrontal cortex (vmPFC) malfunction in e.g., lesion patients and patients with psychopathy or depression (Koenigs & Grafman, 2009; Koenigs, Kruepke, & Newman, 2010; Koenigs & Tranel, 2007) and might be linked with specific processing deficits at one of these levels of fairness considerations. The use of sensitive methods such as eye-tracking could provide insight in the fixation patterns of both patient and healthy populations, e.g., the amount of time spent looking at the actual vs. the alternative offer and how this might be modulated by proposers' intention or other salient features.

6

To conclude, the current study was the first to show that intentionality moderates context-based preferences when an unfair treatment is explicit and salient. However, outcome comparisons of the options that had initially been available shape fairness considerations even when unfairness was unintentional. Based on these results, we propose that fairness can be judged on different levels, which might have separate developmental trajectories. Whereas focusing on salient outcomes might be a useful initial rule of thumb, incorporating context-related information as well as correctly attributing intentionality is necessary for the complex social decision-making humans encounter in everyday life. In such real-life situations, information about all possible outcomes is not only sparse, but also highly complex and uncertain, yielding elevated fairness considerations to be efficiently driven by intention-based decision-making.





The other side of the coin

Abstract

Oxytocin has been implicated in prosocial behaviors such as trust and generosity. Yet, these effects appear to strongly depend on characteristics of the situation and the people with whom we interact or make decisions. Norms and rules can facilitate and guide our actions, with fairness being a particularly salient and fundamental norm. The current study investigated the effects of intranasal oxytocin administration on fairness considerations in social decision-making in a double-blind, placebocontrolled within-subject design. After having received 24 IU of oxytocin or placebo, participants completed a one-shot Dictator Game and played the role of the responder in a modified version of the Ultimatum Game, in which an unfair offer of 8 coins for the proposer and 2 coins for the responder is paired with either a fair- (5:5) or no-alternative (8:2). Rejection rates were higher when a fair alternative had been available than when there was no alternative to an unfair offer. Importantly, oxytocin did not de- or increase rejection rates overall, but reduced the sensitivity to contextual fairness, i.e., the context of alternatives in which an offer was made. As dictators, participants allocated less coins to the recipient when given oxytocin than when given placebo, indicating a decline in generosity. These results suggest that oxytocin decreases the adherence to fairness norms in social settings where others are likely to be perceived as not belonging to one's ingroup. While our findings do not support the prosocial conception of oxytocin, they corroborate recent ideas that the effects of oxytocin are more nuanced than assumed in the past.

Based on:

Radke, S. & De Bruijn, E.R.A. (2012). The other side of the coin: Oxytocin decreases the adherence to fairness norms. *Frontiers in Human Neuroscience*. 6. 193.

Introduction

The neuropeptide oxytocin (OXT) has received much attention for its role in social cognition and prosocial behavior (K. Macdonald & Macdonald, 2010; Meyer-Lindenberg, 2008). Previous studies have revealed that OXT strengthens cooperation by stimulating trust (Baumgartner, et al., 2008; Delgado, 2008; Kosfeld, et al., 2005; Mikolajczak, Gross, et al., 2010; Mikolajczak, Pinon, et al., 2010), generosity (Zak, et al., 2007), and social perception (Gamer, et al., 2010; Guastella, Mitchell, & Dadds, 2008; Guastella, Mitchell, & Mathews, 2008; Keri & Benedek, 2009), suggesting a strong association between OXT and empathy (Barraza & Zak, 2009; Zak, et al., 2007).

However, recent evidence specifies that these effects are more nuanced than once assumed and often moderated by situational or personal characteristics (Bartz, et al., 2011). Some findings even point to rather 'antisocial' effects of OXT (Bartz, et al., 2011), such as increased envy and Schadenfreude (Shamay-Tsoory, et al., 2009) as well as ingroup-favoritism and aggression towards outgroup members (De Dreu, et al., 2010; De Dreu, et al., 2011a). Similarly, OXT diminishes cooperation when social information about the interaction partner is lacking (Declerck, Boone, & Kiyonari, 2010) and loses its trust-enhancing effect when interaction partners are perceived as unreliable (Mikolajczak, Gross, et al., 2010).

Since the central decisions in our life occur during interactions with others, commonly shared beliefs, i.e., social norms, provide a useful framework for our decisions and deeds. Fairness is a very elementary and salient norm, for which a preference is already observable in young children (Blake & McAuliffe, 2011; Takagishi, et al., 2010). These social preferences are frequently investigated with one-shot games, among others, the Ultimatum Game (UG; Güth, et al., 1982) and the Dictator Game (DG; Fehr, 2008; Fehr & Camerer, 2007; Forsythe, et al., 1994). Both games involve monetary allocations between two players, with the first player offering a division. In the UG, the second player can decide whether to accept or reject this proposal. If accepted, the stake is split as proposed. If the offer is rejected, neither player receives anything. In the DG, on the contrary, the decision in unilateral on behalf of the allocator and the second player must accept any offer, thus remaining utterly powerless. In both games, empirical data differs from a 'rational' approach of maximizing one's payoff (Güth, et al., 1982).

The study by Zak et al. (2007) is, up to now, the only one to investigate the influence of OXT on the behavior in the UG and the DG. Here, participants were asked to indicate the value they would choose if they were assigned to be proposers (offer), responders (minimum acceptable offer or, in other words, rejection threshold) and dictators (endowment/giving), respectively. OXT enlarged the (positive) difference between proposers' offers and their rejection threshold in the UG, while leaving

rejection thresholds and DG giving unchanged. The authors conclude that OXT increases generosity, based on the definition that generosity means giving away more than the recipient needs or expects. In fact, in this study, proposers were not informed about the actual expectations (or needs) of the second player, but made hypothetical 'what-if'-decisions before being assigned to a role. Zak et al. (2007) propose that this procedure, in combination with OXT, stimulates perspective-taking and empathy in the UG, and in turn motivates to reduce the negative emotional reaction of the other player. They do not, however, provide an explanation why this only holds in the role of proposers and not responders. A true concern for others' welfare should also be evident in altered rejection thresholds and DG allocations. An OXT-induced 'generosity' that is only evident when the second player has the power of rejecting one's offer, which would leave oneself empty-handed, does not seem very generous after all, but might reflect strategic considerations (see also De Dreu, 2012). In line with the conclusions of Zak et al. (2007), no OXT effects on the decision to donate have been found (Barraza, McCullough, Ahmadi, & Zak, 2011). A different study by the same authors, however, reported increased generosity in unilateral monetary allocations in relation to OXT levels in blood (Barraza & Zak, 2009). With respect to the relation between genetic variations in the OXT receptor and monetary transfers, results are similarly divergent (Apicella et al., 2011; Israel et al., 2009). Fehr (2008) and Conlisk (2011) even reason that OXT does not boost generosity or prosociality, which is also supported by the absence of OXT effects on the back-transfer of trustees in a trust game (Kosfeld, et al., 2005). Likewise, the initial transfer of investors did not differ between OXT and placebo (PLC) (Baumgartner, et al., 2008) or when trustees were depicted as unreliable (Mikolajczak, Gross, et al., 2010). All in all, the experimental findings are mixed and it remains thus unresolved whether OXT actually motivates prosociality by stimulating perspective-taking.

A modified version of the UG developed by Falk et al. (2003) allows for a more thorough examination of perspective-taking particularly from the side of responders. Here, the proposer chooses from a fixed set of two distributions of the stake. An unfair offer of 8 coins for the proposer and 2 coins for the responder is paired with different alternatives, most critically either a fair- (5:5) or no-alternative (8:2). Previous studies using the modified UG paradigm have repeatedly demonstrated that rejection rates are higher when there was a fair-alternative than when there was no-alternative to an unfair offer (Falk, et al., 2003; Güroğlu, et al., 2009; Radke, Güroğlu, & De Bruijn, 2012; Sutter, 2007). Although identical in terms of absolute payoff, the unfair offers differ with respect to signaling fairness depending on the available alternative. Importantly, pairing an unfair offer (8:2) with a fair alternative (5:5) signifies an explicit violation of fairness norms because the proposer clearly preferred *not* to offer an equal split, but favored an unfair division (Radke, et al., 2012). Incorporating proposers' perspective and judging this behavior as unkind and unfair underlies the increased

tendency to reject. In contrast, when no alternative was available, rejection is solely based on disliking the unfair outcome as such, i.e., inequity aversion (Falk et al., 2003). Developmental studies support the notion that the sensitivity to this manipulation of 'context', i.e., the alternative offer (as in Güroğlu, et al., 2009; Radke, et al., 2012), reflects perspective-taking (Güroğlu, et al., 2009; Sutter, 2007).

We used the modified version of the UG to contrast behavior in response to unfair offers when no alternative was available to unfair offers which were deliberately chosen over a fair alternative, i.e., an equal split. Here, the no-alternative condition captures the tendency to dislike and reject unequal outcomes, i.e., inequity aversion, which is a basic social preference (Radke, et al., 2012). In accordance with previous findings (Falk, et al., 2003; Güroğlu, et al., 2009; Radke, et al., 2012; Sutter, 2007), we expected responders' rejection rates to remain substantial, but lower than in the fair-alternative condition. The difference in rejection rates between these two conditions assesses how sensitive responders are to the alternative, but unselected, offer that had initially been available to proposers. In other words, the sensitivity to the context in which an unfair offer occurred goes beyond pure inequity aversion by stirring social expectations about fairness. Importantly, examining responder behavior in an UG setting allows for distinguishing social norm concerns from other motivational dynamics that accompany proposals, e.g., the strategic rationale of offering fair splits to minimize rejection and thereby maximize self-gain. The current study is the first to assess the role of OXT on actual responder behavior in the UG, i.e., reactions to others' proposals. If OXT promotes prosociality and perspective-taking in general, then a larger sensitivity to context should emerge. In a similar vein, unilateral 'prosocial' allocations should be higher after OXT administration. The DG has been highlighted as a measure of unconditional prosociality and altruism (Camerer & Thaler, 1995; Conlisk, 2011). On the other hand, however, newer research suggests (De Dreu, 2012) that OXT motivates only parochial cooperation. When others are unknown or unfamiliar, OXT can effectively reduce cooperative conduct (Declerck, et al., 2010). Since no personal inferences about the other players could be drawn in the current setting, they are likely to be perceived as not belonging to the same group, i.e., ingroup, as oneself. Moreover, the UG involves a limited stake, i.e., coins, with the payoffs for the two players being inversely related. Particularly when competing for the same resources, potential prosocial tendencies or privileges might not extend to principally unknown interaction partners. Consequently, we expected participants to adhere less to social norms of reciprocity and fairness when distributing money with an anonymous other. Still, as the results from previous studies are mixed, the character of the current experiment remains rather explorative.

Methods

Participants

Twenty-four male volunteers (M age = 21.46 years, SD = 1.93) participated in this study. All of them were students and recruited through advertisements placed across campus.

All participants were healthy and did neither report current nor a history of neurological or endocrine disease, medication, and drug or alcohol abuse. Exclusion criteria included age of <18 or >30, smoking more than 5 cigarettes per day, participation in another pharmacological study or blood donation within the last two months, and suffering from fever, common cold or allergic rhinitis ("hay fever") on the day of testing. Participants were asked to abstain from caffeine, alcohol and nicotine for 24 h as well as from eating and drinking (except water) 2 h prior to substance administration.

All participants gave written informed consent to the procedures which were in accordance with the Declaration of Helsinki and had previously been approved by the Medical Ethics Committee of the Radboud University Nijmegen Medical Center (Commissie Mensengebonden Onderzoek Region Arnhem-Nijmegen). Participants were paid for participation.

Pharmacological procedure

A randomized, placebo-controlled, double-blind within-subjects design was used in this study. Participants received OXT (Syntocinon: Novartis) or a saline solution via a nasal spray during two sessions separated by 14 days. All sessions were scheduled for weekdays, started at 10 a.m. and involved two participants, who did not know each other before, being tested simultaneously. In order to avoid any bias due to potential differences in scent between the OXT and the saline spray, the experimenter was not present during substance administration. An independent assistant who was blind to the experimental hypotheses supervised the procedure and left immediately after substance administration. Participants self-administered the nasal spray with three puffs per nostril (each with 4 IU OXT, i.e., a total dose of 24 IU). To control for belief effects, participants as well as the experimenter had to indicate at the end of each session which substance they think was administered. In addition, mood questionnaires were completed throughout the sessions to assess nonspecific effects of OXT. Several tasks were carried out after a waiting period of approximately 40 min, a time window derived from earlier OXT and related peptide nasal spray studies (Born, et al., 2002; Domes, Heinrichs, Michel, et al., 2007; Gamer & Büchel, 2012; Kosfeld, et al., 2005), with subjects starting the UG and DG approximately 75 min after substance administration. Participants were not allowed to talk to each other during the UG and DG.

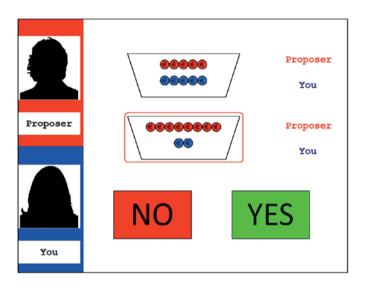


Figure 7.1. Display of the decision phase in the fair-alternative condition of the modified UG. The left panel shows the name and silhouette of the proposer at the top (here "Proposer") and the name of the participant underneath (here "You"). The two potential distributions are specified by red and blue coins (here 8:2 vs. 5:5). The selected offer is encircled in red. The participant has to decide whether to accept ("Yes") or reject ("No") the offer.

Modified Ultimatum Game: Procedure

Participants played the role of the responder in a computerized version of the modified UG. Each trial started with a fixation cross (1000 ms), followed by the presentation of the two available options (1000 ms). Next, the selected offer was encircled in red (1000 ms). Subsequently, "Yes" and "No" icons were presented while the alternatives remained visible (as depicted in Figure 7.1). The task being self-paced, participants had unlimited amount of time to press one of two buttons on the keyboard to indicate their decision. Participants' response remained on the screen for 2000 ms before the next round started.

Participants were led to believe that they were coupled with data from subjects who had previously participated as proposers. They were told that they would play every round with a new partner who would make an offer by selecting one of the two options and their task was to decide whether to accept or reject that particular offer. If accepted, the coins were distributed as proposed; if rejected, neither player received anything. Participants were notified that at the end of the experiment, a random number of rounds would be selected to determine their payoff and that proposers would be paid in the same manner after all data from responders had

been collected. It was pointed out that participants' decisions affected both their own and the other players' financial outcome. It was ensured that participants' earnings varied between the two experimental sessions and between participants sitting in the same room. None of the participants indicated doubt about the cover story or about the bonus not being linked to their actual choices.

Modified Ultimatum Game: Design & Analyses

In order to contrast behavior in response to unfair offers (8:2) when no alternative (8:2) vs. 8:2) was available to unfair offers which were deliberately chosen over a fair alternative (5:5 vs. 8:2), i.e., an equal split, a repeated measures ANOVA was conducted for the rejection rate of unfair offers with substance (two levels: OXT vs. PLC) and context (two levels: fair vs. no alternative) as within-subject factors. Hence, the factor context pertains to the alternative outcome that had not been selected. The fair-alternative condition can be seen as an explicit version of the classic UG where any offer is usually compared to a potential equal split. Pairing an unfair offer with a fair alternative consistently leads to highest rejection rates (Falk, et al., 2003; Güroğlu, et al., 2009; Radke, et al., 2012; Sutter, 2007). In contrast, the rejection rate in the no-alternative condition is likely to reflect the basic tendency for inequity aversion (Falk, et al., 2003; Ohmura & Yamagishi, 2005). Although the two identical distributions do not permit a real choice for proposers, responders' rejection rates remain substantial (Falk, et al., 2003; Güroğlu, et al., 2009; Radke, et al., 2012; Sutter, 2007). Importantly, the difference in rejection rates between the no-alternative and the fair-alternative condition can be regarded as a measure of the sensitivity to contextual fairness.

Two additional distributions were used as to induce variance in the set of offers and to avoid suspicion from participants being faced with only 8:2 and 5:5 splits on all trials. For this purpose, we included hyperfair (2:8 vs. 8:2) and hyperunfair (10:0 vs. 8:2) conditions in the game. However, for the hyperfair condition, it is still unresolved what motivates the decision to accept or reject (Güroğlu, et al., 2009; Sutter, 2007). Importantly, with regard to fairness norms, both offers are equally unfair, one being advantageous to the proposer and the other being advantageous to the responder. As it is not obvious which choice is favorable according to social norms and expectations, interpreting this condition remains particularly challenging. With regard to the hyperunfair condition, results based on similar paradigms are mixed. Whereas Falk et al. (2003), Güroğlu et al. (2009) and Radke et al. (2012) do not find significant differences between the hyperunfair and no-alternative condition, the experiment of Sutter (2007) reveals higher rejection rates in the no-alternative (8:2) than in the hyperunfair-alternative condition (10:0) for university students. These inconsistent findings warrant caution when interpreting the results from the hyperunfair-alternative condition and have entailed its exclusion from the design and analyses previously (Güroğlu, et

al., 2010). ³ For these reasons, we restricted the analyses to the two levels of context that permit a solid, unambiguous investigation of the role of OXT in fairness considerations.

Each combination of selected and unselected offers was presented 16 times (counterbalanced for proposers' gender and position of the unfair offer). As the no-alternative condition leads to an 8:2 offer for either alternative, an unfair offer (8:2) was presented in 5 of the 8 conditions, equivalent to 80 trials. The three genuine alternative offers (i.e., 5:5, 2:8 or 10:0) were selected on 48 trials, yielding 128 trials in total. Contrary to subjects' belief, all choices were computer-generated.

Dictator Game

After completion of the modified UG, participants played a single-trial DG with an anonymous other who was represented by a gender-ambiguous silhouette and name. Ten red coins were presented similar to the display in the modified UG. Participants had an unlimited amount of time to choose how many coins they wanted to give to the other player who, as it was emphasized, could not influence the outcome, but would be paid contingent upon their decision. Responses were made by pressing the corresponding number on the keyboard.

Results

Modified Ultimatum Game

The ANOVA revealed a main effect of context, F (1, 23) = 15.80, p < .01, partial q^2 = .41, indicating that rejection rates were higher in the fair-alternative condition (M = 54.95%) than in the no-alternative condition (M = 22.4%). Moreover, there was an interaction between substance and context, F (1, 23) = 4.44, p < .05, partial q^2 = .16. Further analyses demonstrated that the difference in rejection rates between the fair-alternative condition and the no-alternative condition was smaller after OXT administration (M = 27.08) than after PLC (M = 38.02). The effect of substance was not significant, F (1, 23) = .02, p = .88, partial q^2 < .01. Rejection rates are depicted in Figure 7.2.

Dictator Game

The number of coins allocated to the recipient was smaller when participants had received OXT (M = 1.63, SD = 2.3; Median = 0) than when they had received PLC (M = 2.71, SD = 2.44; Median = 2), Z = -2.06, p = .04 (two-tailed Wilcoxon Test). Figure 7.3 depicts the histogram of allocations. In the PLC condition, the distribution is bimodal, with seven participants giving zero coins (29.2%) and six giving five coins,

³ Note that there was another condition in which proposers were deprived of their control over an offer, which, however, extends the focus of the current paper and will be reported elsewhere.

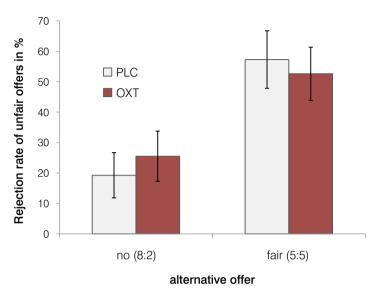


Figure 7.2. Rejection rates of unfair offers with regard to the alternative offers and the substance received (PLC = placebo; OXT = oxytocin). Overall mean percentage and standard errors of rejection of 8:2-offers are displayed.

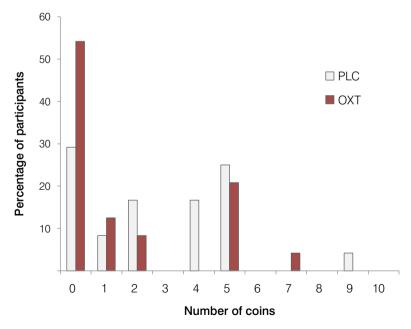


Figure 7.3. Distribution of Dictator allocations after placebo (PLC) vs. oxytocin (OXT) administration.

i.e., half of the stake (25%). After OXT administration, the distribution of endowments is unimodal, peaking at zero (N = 13; 54.2%) and five participants splitting equally (20.8%).

Effects of order or participants' belief of substance administration

Adding the order of substance administration or subjects' belief about the substance administered as between-subject factors to the ANOVAs did not yield any significant effects or interactions (all ps>.28). Neither participants nor the experimenter were able to detect the correct order of substance administration above chance level (participants: M = 47.83%; t(22) = -.204, p = .84; experimenter: M = 33.13%; t(23) = -1.696, p = .10).

Discussion

This study aimed to explore the role of OXT in fairness considerations that imply social norms. It was the first experimental approach of administering OXT intranasally in order to assess actual responder *behavior* in an UG setting. The modified version of the UG allowed for investigating perspective-taking from the side of responders as this role is related less to strategic, but more to fairness considerations. Additionally, for a direct comparison with the only previous pharmacological study using the UG/DG (Zak, et al., 2007), the DG was included to capture unconditional generosity.

Rejection rates in the modified UG were higher when a fair alternative had been available than when there was no alternative to an unfair offer – an effect that has been frequently shown (Falk, et al., 2003; Güroğlu, et al., 2009; Radke, et al., 2012; Sutter, 2007). Importantly, OXT did not generally de- or increase rejection rates, but reduced the sensitivity to contextual fairness. Whereas a typical, bimodal distribution of allocations was observed in the PLC condition of the DG, OXT skewed this pattern in the direction of enlarging one's own gain. Taken together, OXT appears to decrease the amount to which one acts according to social rules and norms. In the DG, it decreases unconditional generosity, and in the UG, the alternative, unselected offer is taken less into account. Notably, participants were less responsive to cues that stimulate perspective-taking by means of inferring proposers' motives for selecting an unfair offer (Güroğlu, et al., 2010).

These results are clearly at odds with the notion of OXT inducing generally prosocial tendencies (K. Macdonald & Macdonald, 2010; Meyer-Lindenberg, 2008; Zak, et al., 2007). Instead, they fit with recent evidence suggesting rather 'antisocial' effects of OXT (Bartz, et al., 2011), ranging from negative interpersonal feelings, such as increased envy and Schadenfreude (Shamay-Tsoory, et al., 2009) to intergroup behavior, e.g., ingroup-favoritism (De Dreu, et al., 2010; De Dreu, et al., 2011a).

Importantly, in the absence of social information about the interaction partner, OXT decreases cooperation (Declerck, et al., 2010). Along these lines, De Dreu (De Dreu, 2012; De Dreu, Greer, Van Kleef, Shalvi, & Handgraaf, 2011b) argues that OXT-induced 'goodwill' is not general, but in fact parochial, and does not extend to members that are perceived to be unreliable (Mikolajczak, Gross, et al., 2010) or do not belong to one's ingroup. This limited benevolence is likely to sustain intra-group reciprocity and fits with findings from animal literature (e.g., Campbell, 2008).

Social norms are not merely shared by others, but, importantly, also sustained by others' endorsement and therefore serve the cohesion of social groups. Violating social expectations often leads to disapproval by others and, depending on the nature of the particular norm, feelings of anxiety, quilt or embarrassment on the side of the violator (Elster, 1989). Importantly, these negative emotions can also arise when anticipating to violate social norms (Elster, 1989). Enhanced amygdala activation has been associated with own intentional norm violations (Berthoz, Grèzes, Armony, Passingham, & Dolane, 2006) as well as with judging actions as reflecting deceptive intentions (Grèzes, Frith, & Passingham, 2004). Even in anonymous settings, individuals avoid circumstances that enable them to deceive others to their own financial advantage (Shalvi, Handgraaf, & De Dreu, 2011). Rooted in the desire not to behave in an immoral and socially inconsiderate manner, people are inclined to satisfy others' expectations and to avoid social interactions that involve conflicting interests or a temptation to exploit (Dana, Cain, & Dawes, 2006; Shalvi, et al., 2011). Given that OXT attenuates responses to stress, threat and anxiety, particularly in social situations (Bartz, et al., 2011; Ditzen, et al., 2009; Heinrichs & Domes, 2008; Heinrichs, et al., 2006; Norman, et al., 2010), OXT is likely to diminish the concern about other people's disapproval. In patients with social anxiety disorder, OXT reduced exaggerated negative mental self representations (Guastella, et al., 2009). Therefore, acting against the rules of social conduct could be viewed as less threatening and more permissive, resulting in being a more feasible behavioral option.

Apart from its anxiolytic effects, OXT is involved in facilitating social categorization (De Dreu, 2012). Although we did not intend to manipulate group membership, the setting of our experiment may have contributed to such a classification. The other players with whom participants interacted via the computer were represented by black silhouettes and names consisting of their first name and the first letter of their last name. Moreover, every UG round was played with a new partner, preventing participants from familiarizing with them and developing reciprocal patterns. In contrast, a fellow participant of the same gender was present in the same room and busy with the same task. This might have induced a distinction between the fellow participants being similar to oneself and belonging to the same group, whereas the other players changed frequently and did not share these 'established' commonality

of the ingroup. OXT might have fostered the perception of this contrast, which is in line with previous evidence on unkind behavior towards non-ingroup members (De Dreu, 2012). Bearing in mind that the gender-ambiguous silhouette and name used in the DG does not allow for deducing any identity - not even for a fundamental inference based on gender - it appears that 'antisocial' effects of OXT are inversely related to the information available about the other player (see also (Declerck, et al., 2010). However, these speculations need to be directly tested in future studies since our design did not manipulate intergroup dynamics on purpose. In addition, it should be investigated in how far OXT might alter the perception of and reaction to ambiguous social cues.

Note that our study differs from the one of Zak et al. (2007) in two central methodological aspects: First, participants of Zak et al. made choices in rather hypothetical situations, i.e., as if they were proposers, responders, and dictators, preceding the assignment of definite roles. In contrast, in the current study, participants (as responders) always reacted to offers from proposers, which puts more emphasis on actual decision behavior. Closely related is the lack of an explicit reference point in the classic UG (as used by Zak et al.) so that the fairness norm of a potential equal split remains implicit (Radke, et al., 2012). By pairing an unfair offer with a fair alternative (as in the current design), an explicit violation of fairness norms can be signified and context effects can be captured. Second, Zak et al. (2007) administered 40 IU in a between-subject manner, whereas the current study made use of a dose of 24 IU and a within-subjects design. Although 24 IU has emerged as the conventional dosage for OXT research, the effects of dose, e.g., whether they are linear or follow a different functional mapping, should be thoroughly investigated in clinical trials. In the absence of such trials, the exact pharmacokinetics of OXT remain unknown. Importantly, however, the current study is based on data suggesting a time window of up to 100-120 minutes in CSF after intranasal neuropeptide administration (Born, et al., 2002) and OXT effects for at least 90 minutes (e.g., Domes & Heinrichs, 2009; Gamer & Büchel, 2012; Gamer, et al., 2010). Recently, results were reported for tasks starting 75-85 minutes after OXT administration, with the entire experimental session lasting from 45 until 120 minutes post-administration (Ellenbogen, et al., 2012).

As the DG was always administered after the UG, we cannot entirely rule out possible carry-over effects from the previous interactions in which participants faced many unfair offers. Yet, it seems unlikely that the task order is responsible for the current results as the effect was restricted to the OXT session and not present when participants received PLC. Besides, we found no effects of session order or mood that might explain our results in terms of unspecific substance effects.

In conclusion, our results indicate that OXT reduces the sensitivity to fairness considerations based on perspective-taking (UG) and generosity (DG). The current findings add to a growing body of literature on differential effects of OXT that essentially depend on situational or personal characteristics (Bartz, et al., 2011) as well as the nature of social cues (De Dreu, 2012; Declerck, et al., 2010). Tuning one's behavior according to the attributes of one's interaction partner is highly adaptive and restricting prosocial behavior to one's ingroup is likely to strengthen group cohesion and fitness. A facilitated social categorization, e.g., based on group membership, can be useful under conditions of uncertainty as it reduces the threat of non-reciprocation. Along these lines, the currently demonstrated decreased adherence to social norms is usually only advantageous in the short run and towards non-ingroup members. Therefore, replications and extensions to long-lasting social relationships are necessary to investigate the mechanisms behind OXT-induced alterations of social behavior and their modulation by situational and interpersonal factors. After all, it might be beneficial that OXT does not motivate prosocial tendencies towards anyone.





Unfair offers, unfair offenders?

Chapter 8

Abstract

Offenders with psychopathy have often committed crimes violating social norms, which may suggest a biased moral reasoning in psychopathy. Yet, as findings on utilitarian decisions remain conflicting, the current study investigated different aspects of fairness considerations in offenders with psychopathy, offenders without psychopathy and healthy individuals (N = 18/14/18, respectively). Unfair offers in a modified Ultimatum Game were paired with different unselected alternatives, thereby establishing the context of a proposal, and made under opposing intentionality constraints (intentional vs. unintentional). As in previous studies, unfair offers were most often rejected when the alternative was fair and when the offer was made intentionally. Importantly, however, offenders with psychopathy demonstrated a similar rejection pattern to that of healthy individuals, i.e., taking the unselected alternative into account. In contrast, delinquents without psychopathy did not adjust their decision behavior to the alternatives to an offer, suggesting stronger impairments in social decision-making. Crucially, the mechanisms and processes underlying rejection decisions might differ, particularly with regard to cognitive versus emotional competencies. While preserved cognitive perspective-taking could drive seemingly intact decision patterns in psychopathy, emotional empathy is likely to be compromised.

Based on:

Radke, S., Brazil, I.A., Scheper, I., Bulten, B.H. & De Bruijn, E.R.A. (2013). Unfair offers, unfair offenders? Fairness considerations in incarcerated individuals with and without psychopathy. *Frontiers in Human Neuroscience*, *7*, 406.

8

Introduction

Social deficits are evident in various psychiatric disorders with their expression ranging from withdrawal in e.g., social phobia to antisocial behavior and even social predation as observed in psychopathy. Offenders with psychopathy often show a history of serious violent crimes committed against another person (i.e., murder, rape) and increased recidivism of criminal behavior (D'Silva, Duggan, & McCarthy, 2004) that exceeds the relapse rate of offenders without psychopathy by a factor of up to four (Harris, Rice, & Cormier, 1991; Hemphill, Hare, & Wong, 1998).

The initial concept of psychopaths as 'moral imbeciles' (Maudsley, 1895) attributed their deviations to a decreased ability for moral reasoning. Indeed, core traits of psychopathy such as manipulative behavior, callousness, and lack of quilt/ remorse have been associated with overlooking moral principles for non-moral incentives such as money as well as a negative appreciation of the moral values of fairness and harm prevention (Glenn, Iver, Graham, Koleva, & Haidt, 2009). In order to target the cognitive component of morality, hypothetical moral dilemmas that assess decisive judgments, e.g., how "appropriate" an action in the given situation is or whether one would execute that action, are frequently used (Greene, Sommerville, Nystrom, Darley, & Cohen, 2001). Although offenders with psychopathy tend to maximize overall benefit in these scenarios, i.e., demonstrate utilitarian choice patterns (Koenigs, Baskin-Sommers, Zeier, & Newman, 2011), there is no consistent evidence that individuals with psychopathy differ from healthy groups in explicit moral iudaments (Aharoni, Sinnott-Armstrona, & Kiehl, 2012; R. J. Blair, Jones, Clark, & Smith, 1995; Cima, Tonnaer, & Hauser, 2010). Findings on differences in moral reasoning between incarcerated populations with and without psychopathy are similarly inconsistent (Cima, et al., 2010; Koenigs, et al., 2011) and a recent meta-analysis reported a negative relation between moral development and recidivism for offenders in general, irrespective of psychopathic traits (Van Vugt et al., 2011). It therefore remains important to compare individuals with psychopathy not only to a healthy, but also to another forensic reference group which has also been convicted for serious offenses that essentially violate social and moral norms.

In contrast to hypothetical scenarios, an association between psychopathic traits and an increased focus on self-interest has been derived from social decision-making paradigms (Koenigs, et al., 2010; Mokros et al., 2008; Osumi & Ohira, 2010; Rilling et al., 2007). Economic games, such as the Ultimatum Game (UG; Güth, et al., 1982), are frequently used to capture strategies in interpersonal settings that involve weighting self-interest and other-interest. Here, the first player proposes a split of a resource, which can be either accepted or rejected by the second player (responder). Acceptance implements the proposal, but rejection leaves both players with nothing. Instead of 'rationally' maximizing their payoff by accepting anything, responders

frequently reject unfair offers, which has been attributed to fairness considerations (Güth, et al., 1982).

In individuals with psychopathic traits, the observed disregard for fairness norms (Aharoni, Antonenko, & Kiehl, 2011; Glenn, et al., 2009) is mirrored in altered responder behavior in the UG, although the findings remain conflicting. On the one hand, students scoring high on psychopathic traits displayed lower rejection rates of unfair offers, interpreted as favoring self-interest (Osumi & Ohira, 2010). On the other hand, incarcerated patients with psychopathy showed the opposite pattern: individuals with primary psychopathy, i.e., psychopathy with low trait anxiety, rejected more unfair offers relative to individuals with secondary psychopathy or without psychopathy, which the authors relate to deficits in regulating anger and frustration (Koenigs, et al., 2010). A recently published study found similar rejection behavior in participants with high and low psychopathic tendencies and suggests different underlying decision mechanisms, i.e., rejection as a reaction to frustration in individuals scoring high on psychopathic traits (Vieira et al., 2013).

As the classic UG assesses outcome-based fairness considerations, i.e., a comparison of outcomes of the self and the other (Radke, et al., 2012), without an explicit normative reference point, it remains unresolved which factors underlie the deviations in social decision-making. Along these lines, previous results on psychopathy and UG decisions (Koenigs, et al., 2010; Osumi & Ohira, 2010) can only be interpreted on the basis of outcome-driven judgments, but not in terms of social dynamics. In contrast, information derived from context and perceived intentionality guide not only social interactions in our daily lives, but also influence UG decisions (Blount, 1995; Falk, et al., 2003, , 2008; Güroğlu, et al., 2009; Radke, et al., 2012).

Interestingly, a recent finding revealed that offenders with psychopathy rate accidents as more morally permissible than delinquents without psychopathy (L. Young, Koenigs, Kruepke, & Newman, 2012). This inclination suggests that they might weight the intention behind an action greater than its (harmful) outcome, stemming from the deficit of generating an emotional response to the victim's suffering (L. Young, et al., 2012). It remains open, however, in how far this partiality in moral judgments might also apply to imbalanced decision-making. Of note, in laboratory settings, moral judgments are made from a detached perspective as the situation to be judged remains hypothetical, even when probed by a "would you do... in order to...?" question. Therefore, both the implementation of one's choice and the absence vs. presence of self-interest are important methodological distinctions between the use of hypothetical scenarios and socioeconomic games. Whereas the former usually depict vignettes or actions that do not affect oneself, economic games traditionally involve real, to-be-paid-out stakes and thus outcomes relevant to oneself and one's interaction partner.

Using a modified UG enables us to investigate how social decisions involving fairness considerations are resolved. In this version, information is provided about an unselected alternative, thereby establishing the 'context' in which an offer is selected, and about the intentionality of an offer. From a fixed set of two allocations of 10 coins, either the first player (proposer) himself or the computer randomly chooses one. The fixed set allows to manipulate the reference point ('context') of the proposal (Falk, et al., 2003; Güroğlu, et al., 2009; Radke, et al., 2012), whereas the agency of the proposer constitutes the manipulation of intentionality, i.e., whether the offer was selected by proposers themselves vs. by the computer (Radke, et al., 2012). This setup allows to investigate perspective-taking from the side of responders. Here, of particular interest are unfair proposals (8 coins for the proposer and 2 coins for the responder) that are contrasted against either fair, hyperfair or hyperunfair alternatives, or no alternative at all. Previous findings show that unfair offers are more often rejected when the alternative was fair compared to all other three alternatives (Falk, et al., 2003; Güroğlu, et al., 2009; Radke, et al., 2012), which has also been associated with developmental advances in cognitive perspective-taking abilities (Güroğlu, et al., 2009). In adults, a similar rejection pattern was evident for intentional and unintentional decisions (Radke, et al., 2012). However, intentionality played a crucial role in the decision process when an unfair treatment was made explicit and salient, i.e., when paired with a fair alternative: These unfair offers were more often rejected when the offer was selected by proposers themselves than when selected by the computer, underlining the importance of punishing intentional social norm violations (Radke, et al., 2012).

The current study is the first to investigate social decision-making based on different aspects of fairness considerations and their (social-) cognitive demands (Radke, et al., 2012) in a forensic sample. The behavior of offenders with psychopathy was compared to a group of offenders without psychopathy and a group of healthy controls. For healthy individuals, we expected to replicate previous findings on the effects of context (referring to the manipulation of alternative offers as in (Güroğlu, et al., 2009; Radke, et al., 2012) and intentionality (Radke, et al., 2012). As these features of social decision-making have not been assessed in our populations of interest until now, it is difficult to predict the rejection patterns in the offender groups.

Based on studies pointing to a relative integrity of cognitive functioning in psychopathy as opposed to non-psychopathy (Brazil et al., 2012; Gao & Raine, 2009; Morgan & Lilienfeld, 2000), one might expect the group with psychopathy to take the context or the intentionality of an offer into account. On the contrary, offenders without psychopathy might show a more impulsive behavioral pattern, not differentiating on the basis of additional information. In sum, we aimed to investigate to what extent the alterations in moral judgments in psychopathy and non-psychopathy translate to decisions with not only moral, but also utilitarian outcomes.

Methods

Participants

The offender groups were recruited from the patient population of the Pompestichting Forensic Psychiatric Institute in Nijmegen, The Netherlands⁴. The study was approved by the local medical ethics committee and in accordance with the Declaration of Helsinki. All participants received written information about the experiment and gave written informed consent.

All participants were male. The group with psychopathy consisted of 18 offenders, the forensic group without psychopathy consisted of 14 offenders and the control group comprised 18 healthy volunteers without criminal records or a history of psychiatric disorders who were recruited through advertisements and matched with the delinquents on age and intelligence (see Table 8.1 for characteristics of the study population). The Psychopathy Checklist-Revised (PCL-R; Hare, 2003) was used to assess psychopathy. The PCL-R is an instrument that allows the assessment of psychopathy through a semi structured interview and information on criminal history (Hare, 2003), and is regarded as the golden standard for the assessment of clinical psychopathy. The instrument consists of 20 items capturing behavioral correlates of core aspects of psychopathy, which are coded as either not present (0), moderately present (1), or certainly present (2). Certified psychologists administered the PCL-R after placement in the Dutch forensic mental health system and for the present study the PCL-R scores were retrieved from offenders' files. As common in European countries, participants with a score of 26 or more were included in the group with psychopathy and participants with a score below 26 were assigned to the non-psychopathy group (Hildebrand, De Ruiter, & Nijman, 2004). As healthy controls did not have criminal records, is was not possible to obtain reliable PCL-R scores in this group. Exclusion criteria were assessed with the Dutch version of Mini International Neuropsychiatric Interview Plus 5.0.0. (Van Vliet, Leroy, & Van Megen, 2000) and Structured Clinical Interview for DSM-IV Axis II Personality Disorders (Weertman, Arntz, & Kerkhofs, 2000) and included all major Axis I and Axis II disorders (except antisocial personality disorder in the offender groups) or any CNS injuries (Brazil et al., 2009; Brazil et al., 2011; Brazil, et al., 2012). Additional information was retrieved from each offender's clinical files. An estimation of intelligence level was made for all participants by using the Dutch version of the Adult Reading Test (NLV; Schmand, Bakker, Saan, & Louman, 1991). All assessments were carried out by trained psychologists.

⁴ The Pompestichting is a "TBS-clinic" located in Nijmegen. TBS is a disposal to be treated, on behalf of the state, for people who committed serious criminal offences in connection with having a mental disorder. TBS is not a punishment, but an entrustment act for mentally disordered offenders (diminished responsibility). These court orders are an alternative to either long term imprisonment or confinement in psychiatric hospital, with the goal to strike a balance between security, treatment and protection.

Table 8.1. Sociodemographic and clinical characteristics of study participants (Mean [SD]).

	PP (N = 18)	nonPP (N = 14)	HC (N = 18)	p-value
Age in years	42.5 (6.7)	39.7 (7.7)	37.4 (8.8)	.15
PCL-R	31.0 (3.6)	15.8 (5.1)	n/a	.00*

Note. PP = offenders with psychopathy, nonPP = offenders without psychopathy HC = healthy controls. * = significant difference between PP and nonPP

Design

Participants were responders in a computerized version of the modified UG with two within-subject factors: Intentionality and Context. Intentionality had two levels based on who selects the offer: the human player (i.e., the proposer) him/herself (intentional) or the computer (unintentional). Intentionality was thus manipulated in a binary fashion. Context had four levels based on alternatives to an unfair distribution (8:2): a fair-alternative (5:5 vs. 8:2), a hyperfair-alternative (2:8 vs. 8:2), a hyperunfair-alternative (10:0 vs. 8:2), and no-alternative (8:2 vs. 8:2). Hence, the factor Context pertains to the alternative outcome that had not been chosen. Pitting an unfair offer (8:2) against a fair alternative (5:5) can be seen as an explicit version of the classic UG in which decision-making is generally based on comparing any offer to a potential equal split. The resulting 8 conditions were presented 16 times each (counterbalanced for proposers' gender and position of the unfair offer). As the no-alternative condition entails an 8:2 offer for either alternative, an unfair offer (8:2) was presented in 5 of the 8 conditions, equivalent to 80 trials. The three genuine alternative offers (i.e., 5:5, 2:8 or 10:0) were selected on 48 trials, yielding 128 trials in total. Contrary to subjects' belief, all choices were computer-generated.

Material

Figure 8.1 depicts the timeline of a trial in the intentional fair-alternative condition. Each round started with a fixation cross (1000 ms), followed by the presentation of the two available options (1000 ms). Next, the selected offer was surrounded by a red square (1000 ms). Subsequently, "Yes" and "No" buttons were presented while the selection remained visible. As the task was self-paced, participants had unlimited amount of time to respond via pressing one of two buttons using the keyboard. Participants' response remained on the screen for 2000 ms before the next round started.

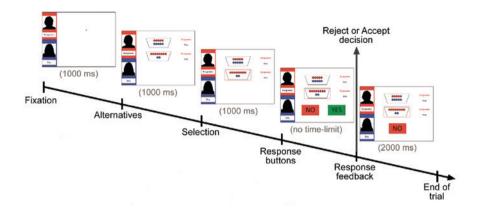


Figure 8.1. Display of a trial in the intentional fair-alternative condition. The name of the proposer is shown at the top (here "Proposer") and the name of the participant is shown underneath (here "You"). The two potential distributions are specified by red and blue coins (red for proposer, blue for responder), with the offer selected by the proposer encircled in red. Participants have to indicate via button press whether to accept ("Yes") or reject ("No") the offer. Note that for unintentional offers (not shown here), the otherwise black silhouette of the proposer was purple with a banner displaying "Computer chooses", which was also depicted instead of the proposer's name.

Procedure

Participants were led to believe that they were coupled with data from others who had previously participated as proposers and that they would play every trial with a new partner (Güroğlu, et al., 2009; Radke, et al., 2012). They were told that on some trials the other players would make an offer themselves and on other trials the computer would take over and randomly select one of the two options. Participants' task was to decide whether to accept or reject an offer. If accepted, the coins were distributed as proposed; if rejected, neither player received anything. Participants were informed that at the end of the experiment, a random number of rounds would be selected to determine their payoff. This was done to assure participants' motivation and to strengthen the concept of a one-shot game as every round could influence their financial outcome. Moreover, it was emphasized that participants' decisions also affected the other players' outcome because their payoff would be determined by participants' response, irrespective of who made the proposal in a particular round (i.e., themselves vs. computer). Proposers would be paid after all data from responders had been collected. The payoff was set around 5 Euro (-/+ 5 cent) to manage an equal payment for all participants, but simultaneously minimize suspicion.

Statistical analyses

Rejection rates of unfair offers were entered into a repeated measures ANOVA with Intentionality (two levels: intentional vs. unintentional) and Context (four levels: fair vs. hyperfair vs. hyperfair vs. hyperunfair vs. no alternative) as within-subject factors and Group (three levels: offenders with psychopathy, offenders without psychopathy, healthy controls) as a between-subject factor. In case of interactions involving the factor Group, separate ANOVAs for the three different groups are conducted with the above mentioned within-subject factors.

In order to test for replicating the results of Radke et al. (2012), i.e., higher rejection rates for unfair offers paired with a fair alternative when the offer was selected by proposers themselves than when selected by the computer, the effect of intentionality will be tested in the fair-alternative context on the whole group level by means of a repeated measures ANOVA with Intentionality (two levels: intentional vs. unintentional) as a within-subject factor.

Results

There were significant main effects of Context, F (3, 141) = 16.49, p < .001, partial η^2 = .26, and Intentionality, F (1, 47) = 4.95, p = .03, partial η^2 = .10. Moreover, the interaction between Context and Group was significant, F (6, 141) = 3.58, p = .01, partial η^2 = .13. None of the interactions involving the within-subject factor Intentionality (Intentionality x Context, Intentionality x Group, Intentionality x Context x Group) was significant (all ps > .27) nor was the main effect of Group (p = .98).

Pairwise comparisons revealed that rejection rates were highest for the fairalternative condition (63.3%) compared to the more disadvantageous alternatives (no-alternative: 41.8%, p=.001; hyperunfair: 39.1%, p<.001). Rejection rates for the hyperfair alternative condition (53.8%) were higher than for the hyperunfair and no-alternative condition (both ps=.001). The latter two conditions did not differ significantly (p=1). With respect to the main effect of intentionality, rejection rates were higher when the offer was selected intentionally (52.2%) than when selected unintentionally/by the computer (49.2%).

To investigate the Context x Group interaction, separate analyses for the three different groups were conducted (see Figure 8.2 and 8.3). There was a significant effect of Context in healthy controls, F (3, 51) = 14.03, p < .001, partial η^2 = .45, as well as in the forensic sample with psychopathy, F (3, 51) = 3.96, p = .039, partial η^2 = .19, but not in offenders without psychopathy, F (3, 39) = 1.63, p = .27, partial η^2 = .10. For the healthy controls, the same pattern as on the whole-group level was evident: Rejection rates were highest for the fair-alternative condition (72.2%) compared to the more disadvantageous alternatives (no-alternative: 36.7%, p < .001;

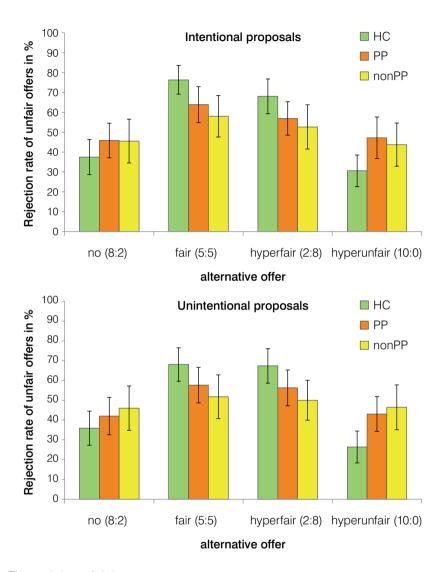


Figure 8.2. and **8.3.** Rejection rates of intentional (Figure 8.2; above) and unintentional (Figure 8.3; below) unfair offers with regard to alternative offers and group. Mean percentage and standard errors of rejection of 8:2-offers are displayed. PP = offenders with psychopathy, nonPP = offenders without psychopathy, HC = healthy controls.

hyperunfair: 28.5%, p=.001). Rejection rates for the hyperfair alternative condition (67.7%) were higher than for the hyperunfair and no-alternative condition (both ps<.002), with the latter two not differing significantly (p=.15). Reactions to the fair and

hyperfair alternative conditions did not differ (p=.48). For the forensic sample with psychopathy, rejection rates were highest for the fair-alternative condition (60.7%) compared to the more disadvantageous alternatives (no-alternative: 45.1%, p=.03; hyperunfair: 43.9%, p=.02). The remaining pairwise comparisons did not yield significant differences (p>.08)

In order to directly test for replication of Radke et al. (2012), analysis of the fair alternative condition indicated higher rejection rates for intentional (66.8%) vs. unintentional/computer offers (59.8%), F (1, 47) = 6.78, p = .01, partial η^2 = .13. In contrast, the effect of Intentionality did not reach significance for the other three contexts (all Fs < .69, all ps > .41; see also Figure 8.4).

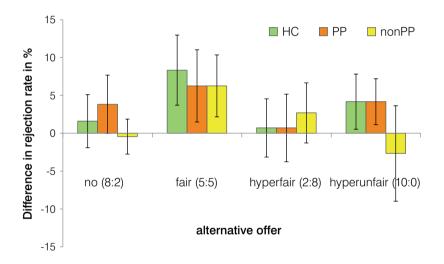


Figure 8.4. Difference between intentional and unintentional unfair offers with regard to alternative offers and group. Mean percentage and standard errors of rejection of 8:2-offers are displayed. PP = offenders with psychopathy, nonPP = offenders without psychopathy, HC = healthy controls.

Discussion

In the current study, social decision-making based on different aspects of fairness considerations was investigated in a forensic sample and a matched healthy control group. In particular, we sought to explore in how far altered moral judgments in psychopathy apply to decisions when not only moral values, but also self-relevant outcomes are at stake.

In addition to replicating previous findings on context and intentionality (Falk, et al., 2003; Güroğlu, et al., 2009; Radke, et al., 2012), group differences in context sensitivity were evident. Essentially, offenders with psychopathy displayed a similar pattern of rejection behavior to that of healthy individuals, i.e., an effect of context. In contrast, the decisions in delinquents without psychopathy were not influenced by the alternative offer to an unfair proposal.

Recently, there has been some disagreement on which processes in fairness considerations are targeted by the context manipulation, i.e., higher-order social functions like perspective-taking (Falk, et al., 2003; Güroğlu, et al., 2009) or straightforward outcome comparisons (Brandts & Sola, 2001; Sandbu, 2007). This discussion (see also Radke et al., 2012) is crucial with regard to drawing inferences about possible impaired and preserved (social-) cognitive abilities in psychiatric/forensic populations. Although both processes rely on counterfactual thinking, i.e., representations of alternatives to past events (Roese, 1997), the representation of another, social agent is not necessary for comparing the outcomes for the self resulting from the chosen and the unchosen alternative. Such a quantitative evaluation can be achieved – quite parsimoniously – without taking the perspective of another person. Our design resolves this disagreement by making the social dimension explicit, i.e., contrasting intentional and unintentional offers. The processes of outcome comparisons and intentionality considerations can thereby easily be disentangled. Importantly, the current data replicates previous findings on their relative contribution to social decision-making (Radke, et al., 2012), which provides a solid basis for the investigation of intergroup variations.

As delinquents without psychopathy did not adjust their behavior to the context or intentionality of an offer, their decisions might be dominated by rather basic motives not directly targeted by these manipulations. Given that their overall mean rejection rate did not differ from the other groups either, the offenders without psychopathy seem to be guided by the magnitude of the proposal's intrinsic distribution (what the proposer gets vs. what the responder gets) with a dislike of unequal outcomes, i.e., inequity aversion. Fairness is determined by payoffs available in the here and now, which may reflect the preference for immediate options, hinting at a hyperactivity of the impulsive system (Buckholtz et al., 2010; Dean et al., 2013).

Offenders with psychopathy, on the other hand, behaved similarly to healthy volunteers. The lack of differences in overall rejection rates compared to both healthy and incarcerated individuals is in line with the behavioral results of Vieira et al. (2013), but at odds with other earlier, yet inconsistent, findings on altered responder behavior in the UG reporting higher (Koenigs, et al., 2010), and lower rejection rates (Osumi & Ohira, 2010), respectively. These studies, however, also diverge in sample characteristics, with the group being either very small (N = 6 for high anxious psychopaths, Koenigs, et al., 2010) or consisting of students (Osumi & Ohira, 2010) or a community

sample (Vieira, et al., 2013), warranting caution for generalization to a large forensic population. The main focus of the current study, however, lay not on rejection rates as such, but on its modulation by context and intentionality.

Most interestingly therefore, in the current sample, individuals with psychopathy showed an analogous sensitivity to the alternatives to a given outcome, which converges with findings on intact moral judgments (Aharoni, et al., 2012; R. J. Blair, et al., 1995; Cima, et al., 2010), Theory of Mind (R. J. Blair et al., 1996; Richell et al., 2003) and other aspects of cognitive functioning (K. S. Blair et al., 2006; Brazil, et al., 2012). Despite the behavioral similarity with healthy controls, in psychopathy the underlying mechanisms might differ and reflect a distinct motivation. For instance, in healthy individuals with psychopathic traits, rejection of unfair offers was associated with increased activation in the anterior cingulate cortex and ventromedial prefrontal cortex (Vieira, et al., 2013). The recruitment of these clusters might indicate impairments in automatic emotion regulation, leading to anger-motivated instead of fairness-motivated rejection (Vieira, et al., 2013).

Conversely, we observed behavioral differences in the context-dependency of rejection decisions between offenders with psychopathy compared to offenders without psychopathy. This differentiation between subgroups of violent offenders might be attributable to the cognitive nature of the task, i.e., its assessment of cognitive perspective-taking (Güroğlu, et al., 2009). Previous research suggests relatively intact cognitive functioning in psychopathy, but shortages in non-psychopathy (Brazil, et al., 2012; Gao & Raine, 2009; Morgan & Lilienfeld, 2000). Moreover, in contrast to emotional aspects of empathy, making inferences about others' mental states, i.e., mentalizing or cognitive inferences, does not seem to be compromised in clinical psychopathy (R. J. Blair, et al., 1996; Cima, et al., 2010; Shamay-Tsoory, Harari, Aharon-Peretz, & Levkovitz, 2010).

Along these lines, other (than financial) self-serving motivations supported by mentalizing might underlie the different decision patterns between offenders with psychopathy and those without. While both groups show an increased risk for frustration (R. J. Blair, 2010), individuals with psychopathy might be more successful in cognitively regulating impulsive tendencies and possibly even use a 'fair' disguise instrumentally in order to obtain unobtrusive advantages, e.g., the appreciation of the experimenter. One might also speculate in how far the initial emotional responses to unfairness differ between the forensic groups. Both might react equally fervently to potentially frustrating unfair offers, but base their decisions on other features, leading to the distinct behavioral patterns. Future studies assessing physiological indicators of emotional reactivity, such as skin conductance, would be useful to explore in how far initial, affective reactions might be restrained by cognitive mechanisms of control or impression management. More tailored paradigms could also identify effects of impulsivity or serial decisions.

With regard to the relative weighting of the intention behind an action and its outcome in offenders with psychopathy (L. Young, et al., 2012), the current data does not allow for drawing firm conclusions on the influence of intentionality for the subgroup of offenders with psychopathy. Its effects manifested only on the whole-group level, which precludes further investigation for the groups separately. Likewise, in contrast to the study by Young et al. (L. Young, et al., 2012) who used hypothetical scenarios in which negative outcomes meant harm or death of another person, even the worst consequences in the current design were, naturally due to the implementation of choices, much less severe. Besides, they did not imply positive punishment, i.e., harm, but negative punishment, i.e., the withholding of coins in the case of an rejection decision and thereby forgoing potential gain. Despite the methodological strength of executing the choices in an interactive setting, this approach is less likely to trigger empathetic reactions, also since in UG settings, the most pronounced emotions arise in responders facing unfairness (Pillutla & Murnighan, 1996; Xiao & Houser, 2005).

In sum, our findings indicate discrepancies between the two offender samples: On the one hand, offenders without psychopathy seem to neglect aspects of fairness considerations that go beyond the comparisons based on payoffs, whereas, on the other hand, the decisions of offenders with psychopathy did not differ from those of healthy individuals. Distinct processes in cognition and affect might underlie these behavioral similarities. Importantly, central features of psychopathy, i.e., manipulating or deceiving others, require certain knowledge about social rules as well as cognitively taking the perspective of others, so that offenders with psychopathy might succeed in an environment where all possible outcome variants, intentions, self- and other-interests are explicitly stated. In contrast, real-life interactions with others are not only more complex and subtle, but also require emotional skills, such as generating empathic responses, regulating one's emotions and adequately reacting to others' feelings, that are likely to be impaired in psychopathy, as evident in their antisocial lifestyles and violent crimes.





Facing unfairness

Abstract

Although 'irrational' decision-making has been linked to depression, the contribution of biases in information processing to these findings remains unknown. To investigate the impact of cognitive biases and aberrant processing of facial emotions on social decision-making, we manipulated both context-related and emotion-related information in a modified Ultimatum Game. Unfair offers were (1) paired with different unselected alternatives, establishing the context in which an offer was made, and (2) accompanied by emotional facial expressions of proposers. Responder behavior was assessed in patients with major depressive disorder and healthy controls. In both groups alike, rejection rates were highest following unambiguous signals of unfairness, i.e., an angry proposer face or when an unfair distribution had deliberately been chosen over an equal split. However, depressed patients showed overall higher rejection rates than healthy volunteers, without exhibiting differential processing biases. This suggests that depressed patients were, as healthy individuals, basing their decisions on informative, salient features and differentiating between (i) fair and unfair offers, (ii) alternatives to unfair offers and (iii) proposers' facial emotions. Although more fundamental processes, e.g., reduced reward sensitivity, might underlie increased rejection in depression, the current study provides insight into mechanisms that shape fairness considerations in both depressed and healthy individuals

Based on:

Radke, S., Schäfer, I.C., Müller, B.W. & De Bruijn, E.R.A. (2013). Do different fairness contexts and facial emotions motivate 'irrational' social decision-making in major depression? An exploratory patient study. *Psychiatry Research*, *210*, 438-443.

Introduction

'Irrational' decision-making is often associated with affective disorders, such as depression (Cella, et al., 2010; Murphy et al., 2001; Rubinsztein, Michael, Underwood, Tempest, & Sahakian, 2006). While these impairments are usually defined as accomplishing suboptimal outcomes in terms of monetary payoff, the processes that underlie these findings, however, remain largely unknown. Explanatory accounts emphasize cognitive biases (e.g., Beck, 2008) as well as altered emotion-processing (for a review see Leppanen, 2006). Depressed individuals are inclined to interpret ambiguous information negatively (Mogg, Bradbury, & Bradley, 2006) and to focus more on negative attributes (Gotlib, et al., 2004; Leppanen, 2006). This strong dominance of negative affect at a very basic and automatic level of information processing is also reflected in clinical symptoms like excessive rumination and might lead to disturbances in social interactions and communication (Suslow et al., 2010).

The contribution of 'rational' vs. 'affective' components in social decision-making has been studied with the use of the ultimatum game (UG; Güth, et al., 1982). In the UG, one player proposes how a sum of money is divided, the other player (responder) either accepts or rejects the offer. While accepting the offer implements the split, rejecting the offer leaves both players with nothing. Despite the anonymous, one-shot nature of the interaction, unfair offers are frequently rejected (Güth, et al., 1982). Therefore, responders' behavior is not entirely shaped by the desire to maximize one's payoff ('rational'), but also by fairness considerations and emotional responses ('affective'). Particularly alterations in affect that are associated with depressive disorders have recently received more attention in the UG literature, for instance by investigating the effect of mood inductions on rejection behavior. In healthy volunteers, higher rejection rates of unfair offers were observed after induction of sad mood (Harlé, Chang, van 't Wout, & Sanfey, 2012; Harlé & Sanfey, 2007) and withdrawal-based emotions (Harlé & Sanfey, 2010). In addition to a negative, often sad mood, a common symptom of depression is withdrawal, evident in anhedonia and reduced energy (American Psychiatric Association, 2000). Another aspect related to depressive disorders is disturbed serotonin functioning. Being a precursor of serotonin, depleting tryptophan leads to a temporarily decrease of central serotonin levels, which resulted in higher rejection rates in response to unfair offers in healthy volunteers (Crockett, Clark, Tabibnia, Lieberman, & Robbins, 2008).

In contrast, no difference in responder behavior was found between patients with severe depression and healthy controls (Destoop, Schrijvers, De Grave, Sabbe, & De Bruijn, 2012). However, these results were obtained with a repetitive version of the UG, i.e., participants interacted with the same partner on subsequent trials. This is likely to induce a motivation distinct from a one-shot setting, e.g., rejecting less in order to avoid rejection after switching roles with their partner (Destoop, et al., 2012).

Besides, for students scoring high on depression, lower rejection rates of unfair offers have been reported (Harlé, Allen, & Sanfey, 2010). This pattern has also been observed in patients with schizophrenia (Csukly, Polgar, Tombor, Rethelyi, & Keri, 2010), which was initially presumed to reflect more 'rational' decision-making behavior. Yet, patients with schizophrenia actually depicted an inconsistent decision pattern. Similarly, depressed individuals reported more negative emotional reactions towards unfairness (Harlé, et al., 2010) and presumably aimed to avoid rejection (Destoop, et al., 2012). These discrepancies might hint at a less well-balanced underlying decision-making process in depressed and schizophrenic individuals than in healthy populations even at this basic level. Until now, it remains open in how far these impairments might translate to more complex social decision-making that involves numerous facets of the setting as well as one's interaction partner, which potentially need to be weighed against each other.

To investigate how depressed patients resolve social decisions involving fairness considerations, we used a modified UG in which information about an unselected alternative is available. In this version, the first player (proposer) chooses from a fixed set of two distributions of the stake (here 10 coins), thereby establishing the 'context' of an offer. An unfair offer of 8 coins for the proposer and 2 coins for the responder (8:2) is paired with three different alternatives: a fair- (5:5), a hyperfair- (2:8), and no-alternative (8:2).

Another crucial element that drives fairness considerations is intentionality, which can be signaled by emotional expressions. For instance, social decision-making studies show that a smiling, happy face induces cooperation (Krumhuber et al., 2007; Scharlemann, Eckel, Kacelnik, & Wilson, 2001), whereas an angry competitor may stimulate retaliation (Van Kleef, De Dreu, Manstead, & Mark, 2010). Similarly, proposers' psychological characteristics, i.e., being depicted as generous or selfish, (Marchetti, Castelli, Harle, & Sanfey, 2011) as well as their facial expressions (Schreiner, Alexopoulos, Pfabigan, & Sailer, 2010) alter responder behavior in the UG. In particular, offers from angry proposers are more often rejected than offers from happy ones (Schreiner, et al., 2010).

The aim of the current study was to explore how the decision-making impairments observed in depressed patients relate to specific elements of fairness considerations. Based on a recently proposed framework (Radke, et al., 2012), we sought to disentangle the different processes involved: The first one relies on comparisons of outcomes and is defined by the fairness of the proposed offer, e.g., fair or unfair. On the next level, features pertaining to the context in which an offer occurs are taken into account, i.e., the unselected alternative that had been available. In addition, cues about intentionality, i.e., proposers' facial expressions, are integrated into the decision-making process. Note that the main focus of the current design lay on the two latter aspects of fairness considerations, which are captured by the two

within-subject manipulations of context and emotion. Indeed, we expected both patients and healthy controls to be able to make basic, first-level fairness judgments and to reject more unfair offers than fair offers. For this purpose, the reactions to the offers that differ in their absolute payoff, but are constantly paired with (unselected) unfair offers, i.e., unfair offers with no-alternative (8:2), fair offers (5:5) and hyperfair offers (2:8), were analyzed as a manipulation check (as in Sutter et al., 2007, Güroğlu et al., 2009; Radke et al., 2012).

For reactions to unfair offers, based on previous findings we expected to find main effects of context (referring to alternative offers as in Sutter et al., 2007, Güroğlu et al., 2009; Radke et al., 2012) and emotion in healthy controls. Signals with the highest informative value about unfairness should increase rejection. Specifically, we hypothesized that the fair-alternative condition and angry faces of proposers (Schreiner, et al., 2010), respectively, would entail the highest rejection rates, without further being influenced by other factors. However, we presumed modulating effects of context and emotion to be present in the other conditions, i.e., in response to sad, happy and neutral faces, and in the hyperfair- and no-alternative conditions.

Biases in the processing of facial emotions have frequently been reported in depression, e.g., the tendency to interpret ambiguous stimuli as mood-congruent, i.e., sad (Bourke, Douglas, & Porter, 2010; Suslow, et al., 2010). Depressed patients are assumed to exhibit an increased sensitivity to particularly sad and neutral facial expressions, leading to heightened rejection. In line with the results of Harlé et al. (2010) and Crockett et al. (2008), we therefore expected depressed patients to reject more unfair offers than healthy controls. Given the absence of any previous studies on context effects in fairness considerations in depressed patients (or generally psychiatric populations) and the complexity of our design, we refrained from formulating specific hypotheses about modulatory influences of the context of an unfair offer on group differences in rejection rates.

Methods

Participants

The depressed group comprised 15 inpatients of the LVR Clinic, Essen, Germany (M age = 38.5 years, SD = 9.7; 9 females) and the control group consisted of 15 healthy volunteers (M age = 38.3 years, SD = 14.7; 6 females) who were recruited through advertisements and matched with the patients on age (see Table 9.1 for group characteristics). The study was approved by the local ethics committee of the University Duisburg-Essen and in accordance with the Declaration of Helsinki. All participants received written information about the experiment and gave written informed consent. Groups were derived based on the German version of the Structured Clinical Interview

(SCID; Wittchen, et al., 1997). All patients were diagnosed with a major depressive disorder (MDD, recurrent episode; 296.1(0-3), 296.3(0-3) in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000) and had been taking the same prescribed medication for the past two weeks (12 receiving antidepressants, 2 receiving anticonvulsants, i.e., benzodiazepines, 1 receiving an atypical antipsychotic). None of them experienced psychotic symptoms during the current or previous episodes. Four patients had anxious comorbidities and three patients also had psychoactive substance related disorders. Exclusion criteria were an IQ below 70, neurological disorders, alcohol dependence and, for controls, MDD. Severity of affective symptoms was assessed with the German version of the Beck Depression Inventory (BDI; Hautzinger, et al., 2006).

Table 9.1. Sociodemographic and clinical characteristics of study participants (Mean [SD], otherwise indicated).

	DP (N = 15)	HC (N = 15)	p-value
Age in years	38.5 (9.7)	38.3 (14.7)	.82
Sex (M/F)	6/9	9/6	.28
BDI	32.0 (8.8)	3.3 (2.6)	.000
Comorbid anxiety disorder	N = 4		
Comorbid psychoactive substance related disorders	N = 3		

Note: DP = depressed patients, HC = healthy controls, M = male, F = female, BDI = Beck Depression Inventory

Material & Procedure

Participants played the role of the responder in a computerized version of the modified UG (see Figure 9.1). They were led to believe that they were coupled with data from subjects who had previously participated as proposers and that they would play every round with a new partner who would be depicted on the photo. On each trial, a picture of a different proposer was shown in the upper left part of the screen. Contrary to participants' belief, these pictures depicting proposers were derived from databases (Ebner, Riediger, & Lindenberger, 2010; Langner et al., 2010; Lundqvist, et al., 1998).

Participants' task was to decide whether to accept or reject an offer. If accepted, the coins were distributed as proposed; if rejected, neither player received anything. Participants were informed that at the end of the experiment, a random number of

Figure 9.1. Display of the decision phase in the fair-alternative condition with a neutral proposer. On the left, name and picture (here neutral expression) of the proposer (here "Proposer") and the name of the participant (here "You") are shown. Red and blue coins specify the two potential distributions. The selected offer is encircled in red. The participant has to decide whether to accept ("Yes") or reject ("No") the offer.

rounds would be selected to determine their payoff. This was done to assure participants' motivation and to strengthen the concept of a one-shot game as every round could influence their financial outcome. Moreover, it was emphasized that participants' decisions also affected the other players' outcome because their payoff would be determined by participants' response. Proposers would be paid after all data from responders had been collected. The payoff was set around 2.50 Euro to manage an equal payment for all participants.

Each round started with a fixation cross (1000 ms), followed by the presentation of the two available options (1000 ms). Next, the selected offer was surrounded by a red square (1000 ms). Subsequently, "Yes" and "No" buttons were presented while the selection remained visible (as depicted in Figure 9.1). As the task was self-paced, participants had unlimited amount of time to respond via pressing one of two buttons using the keyboard. Participants' response remained on the screen for 2000 ms before the next round started. Proposers' gender and the position of the unfair offer were counterbalanced. Contrary to subjects' belief, all choices were computergenerated.

Design & Analyses

The 128 trials presented in total were split based on the selected offer: On 96 trials, the unfair offer (8:2) was selected (8 trials per context, thus on 24 trials per emotion), and on 32 trials, alternative offers were selected (4 trials per fairness level, thus on 8 trials per emotion).

For the analyses of basic rejection behavior based on inherent fairness reactions to the alternative offers were examined. Note that the alternative offers differed in absolute payoff, but were all presented in the same context of an (unselected) unfair offer. Specifically, rejection rates to unfair offers with no-alternative (8:2), fair offers (5:5) and hyperfair offers (2:8) were subjected to a repeated measures ANOVA with fairness (three levels: fair, hyperfair, unfair with no alternative) and emotion (four levels: angry, sad, happy, neutral) as within-subject factors and group (two levels: patients with depression, healthy controls) as a between-subject factor.

Subsequently, reactions to unfair offers (with the same absolute payoff of 8:2) were analyzed. Importantly, these offers differ in their relative/contextual fairness due to manipulation of the within-subject factors context and emotion. The factor emotion had four levels pertaining to the emotional expression of proposers' face: angry, sad, happy, or neutral. The factor context had three levels based on alternatives to the selected unfair distribution (8:2): a fair-alternative (5:5 vs. 8:2), a hyperfair-alternative (2:8 vs. 8:2), and no-alternative (8:2 vs. 8:2). Hence, the factor context pertains to the alternative outcome that had not been chosen. The rejection rate of unfair offers were subjected to a repeated measures ANOVA with context (three levels: fair, hyperfair, no alternative) and emotion (four levels: angry, sad, happy, neutral) as within-subject factors and group (two levels: patients with depression, healthy controls) as a between-subject factor.

To investigate interactions involving the within-subject factors, separate repeated measures ANOVAs were conducted for each of the three different contexts and the four different facial emotions (see Supplementary Results). All within-subject effects are reported with Greenhouse-Geisser correction.

Results

Rejection behavior

The ANOVA revealed a significant main effect of fairness, F (1, 28) = 11.98, p < .001, partial η^2 = .30, and a main effect of group, F (1, 28) = 7.35, p = .01, partial η^2 = .21. Furthermore, there were trends for an effect of emotion, F (3, 84) = 2.60, p = .08, partial η^2 = .09, and for an interaction between fairness and emotion, F (6, 186) = 2.20, p = .07, partial η^2 = .07. The interactions involving the between-subject factor group were not significant (emotion x group: F (3, 84) = .293, p = .75, partial η^2 = .01;

fairness x group: F (2, 56) = .932, p = .384, partial η^2 = .03; emotion x fairness x group: F (6, 168) = .255, p = .923, partial η^2 < .01).

The main effect of fairness (see Figure 9.2) was driven by higher rejection rates for unfair offers with no alternative (M=47.8%) than for fair offers (M=15.6%; p<.001). Hyperfair offers (M=32.9%) were also more often rejected than fair offers (p=.002). The presence of basic fairness judgments can therefore be assumed. The significant group difference was the result of depressed patients rejecting more offers than healthy controls (M=44.1% vs. M=20.1%).

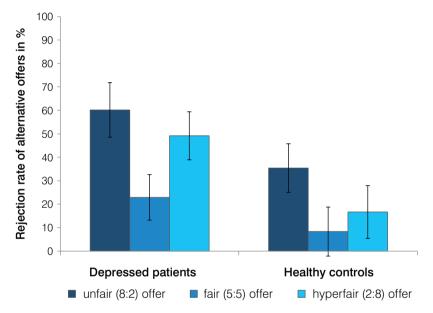


Figure 9.2. Rejection rates of alternative offers with regard to the fairness of the offer (collapsed over emotions). Overall mean percentage and standard errors are displayed.

Reactions to unfairness

Figures 9.3 and 9.4 depict the rejection rates for unfair offers for the two groups. The ANOVA showed significant main effects of context, F (2, 56) = 6.67, p = .005, partial η^2 = .19, and emotion, F (3, 84) = 3.67, p = .03, partial η^2 = .12. The interaction between context and emotion was also significant, F (6, 168) = 3.40, p = .01, partial η^2 = .11 (see Figure 9.2). Furthermore, there was a significant difference between the two groups, F (1, 28) = 4.43, p = .045, partial η^2 = .14, with depressed patients (70.4%) rejecting more unfair offers than healthy controls (48.5%). The interactions involving the between-subject factor group were not significant (emotion x group: F (3, 84) = .279, p = .782, partial η^2 = .01; context x group: F (2, 56) = .119, p = .284, partial η^2 < .01; emotion x context x group: F (6, 168) = .056, p = .996, partial η^2 < .01).

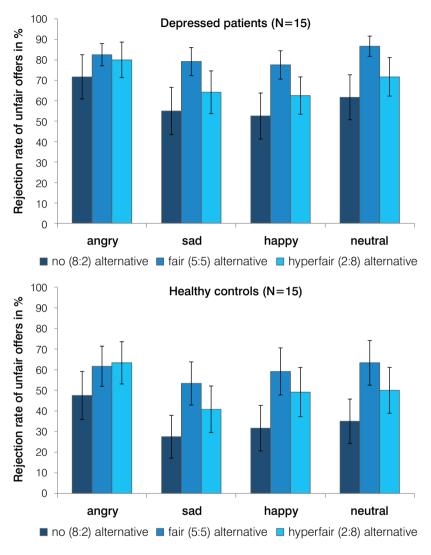


Figure 9.3. **and 9.4**. Rejection rates of unfair offers with regard to the facial emotion of the proposer and alternative offers. Overall mean percentage and standard errors of rejection of 8:2-offers are displayed for patients with depression (Figure 9.3; above) and healthy individuals (Figure 9.4; below).

Follow-up analyses of the main effects revealed that rejection rates were highest in the fair-alternative condition (70.4%), which were significantly higher than in the no alternative condition (47.8%, p=.006). Rejection rates for the hyperfair alternative condition (60.2%) were also higher than when there was no alternative, (p=.03). For

the factor emotion, rejection rates were highest when proposers' facial expression was angry (67.8%) compared to when it was sad (53.3%, p=.01) or happy (55.4%, p=.005).⁵

Discussion

The aim of the current study was to investigate how decision-making impairments observed in depression relate to specific elements of fairness considerations. In order to achieve this and to disentangle the different processes involved, we manipulated (1) context, that is, the outcome of the unselected alternative in the modified UG and (2) emotion, that is, the facial expression of proposers.

Our results are in line with previously reported context effects in healthy individuals (Falk, et al., 2003; Güroğlu, et al., 2009; Radke, et al., 2012; Sutter, 2007). Unfair offers were more often rejected when the alternative was fair compared to a hyperfair- or no-alternative. Moreover, proposers' facial emotions affected decision behavior: Unfair offers were more often rejected in response to angry faces than sad or happy faces, which is consistent with earlier findings (Schreiner, et al., 2010). Both an angry face and an intentionally unfair offer are very strong informative signals, which was also supported by the disappearance of the robust context effect for angry faces and the absence of emotion effects in the fair-alternative condition, respectively. Importantly, both signals also have a vital social implication: Intentionally making an unfair offer when a fair alternative had been available is a salient, unambiguous indication of a social norm violation and leads to high rejection rates (Radke & De Bruijn, 2012; Radke, et al., 2012). Similarly, an angry face implies potential threat and aggression (Lang, Bradley, & Cuthbert, 1997) and can thereby easily damage or even completely destroy cooperation. The fact that both the fair-alternative condition and the angry-face condition provoke almost equally high rejection rates suggests that both groups are sensitive to these salient signs of unfairness. Indeed, relying one's decisions on the most salient and valuable information can be adaptive in rapidly changing social environments, e.g., for detecting potential conflict, treason or even threat, which all demand immediate action. In addition, deliberately being treated unfair as well as being confronted with an angry interaction partner may evoke reciprocal emotions, which can in turn influence decision behavior (Pillutla & Murnighan, 1996; van't Wout, et al., 2006).

On none of these measures, patients with and without comorbidities differed from each other (all ps > .26). When excluding the patients receiving benzodiazepines (leaving N = 13 for the patient group), the main effect of group in the UG becomes marginally significant (p = .053), but all other effects remain significant. Importantly, these two patients did not differ significantly from the other 13 patients on any variable (most critical p-value for an emotion x medication interaction in the ANOVA on basic rejection behavior: p = .105).

Overall, depressed patients rejected more unfair offers than healthy controls, which supports the findings of Harlé et al. (2007; 2010; 2012) and Crockett et al. (2008) in healthy volunteers after mood induction and acute tryptophan depletion respectively, but is at odds with the results of Harlé et al. (2010) that point to lower rejection rates in depressed than control students. Although the majority of the 'depressed' individuals in Harlé et al. (2010) met the DSM-IV criteria for MDD, the sample was derived from a student population (as in Crockett et al., 2008; Harlé et al., 2007; 2010; 2012) and classified based on BDI scores, which tend to be lower than those obtained from the patients of the current study ($M_{RDI} = 27.8$ and $M_{RDI} = 32.0$, respectively). In terms of its characteristics, our sample is most comparable to that of Destoop et al. (2012; $M_{\rm RDI}=$ 32.3; all patients diagnosed with a MDD according to DSM-IV by SCID). However, in a repetitive UG, as used there, rejecting fewer unfair offers might serve the purpose of reducing rejection on the subsequent trial when one's own offer is to be evaluated by the same partner. Since the motivation to avoid rejection seemed to underlie altered proposer behavior in depressed patients (Destoop, et al., 2012), this tendency might also have concealed differences in responder behavior between patients and controls, rendering it difficult to directly compare the findings of Destoop et al. and the current ones.

Interestingly, depressed patients did not only reject more unfair offers across contexts, but also more fair and hyperfair offers compared to healthy individuals, i.e., offers that were advantageous to the unfair alternative they were constantly paired with. Originally meant as a manipulation check for basic fairness evaluations, this finding is particularly noteworthy because it suggests that impairments in decision-making in depression are not specific for negative experiences, as when being faced with an unfair offer. They even extend to situations which, as such, present a beneficial prospect for the individual, hinting at a persistent decision pattern. Although this appears 'irrational' at first sight, reactions to hyperfair offers might reflect depressive realism, i.e., the absence of positive, self-serving biases (Alloy & Abramson, 1979). Here, both distributions are equally unfair, one being advantageous to the proposer and the other being advantageous to the responder. Whereas healthy individuals favor advantageous over disadvantageous inequity, as evident in low rejection rates when 8 coins are offered, depressed patients show no preference as they reject around 50% of the offers that are advantageous to them.

Moreover, there were no differences between depressed and healthy individuals in relation to the manipulations of context and emotion for both unfair and alternative offers. In other words, the increased rejection rates observed in depressed patients were neither further modulated by the alternative outcome nor by proposers' facial emotion, but rather reflect a general tendency of rejecting unfair offers more often than healthy controls. One might argue that depressed patients are more inclined to rumination, i.e., dwelling on negative past events, which were in this study represented

by the alternative offer ("what I could have gotten"). This focus could thereby have attenuated potential cognitive impairments and have counteracted possible group differences in context sensitivity.

Despite the commonly supposed increased sensitivity of depressed patients for sad and neutral cues (Bourke, et al., 2010; Suslow, et al., 2010), the current study does not provide evidence for these biases to specifically shape decision-making in response to associated stimuli. Altered face processing in depression has typically been reported by means of emotion detection or recognition tasks (Bourke, et al., 2010; Stuhrmann, et al., 2011), which are dissimilar to the use of faces for conveying intentionality in a socially interactive paradigm. It remains important, however, to assess not only attentional processes, but also actual behavior as this is the functional level on which patients usually encounter problems in their daily lives, e.g., social isolation. Along these lines, various diagnostic criteria for and clinical symptoms of depression involve behavior, e.g., anhedonia, withdrawal, changes in appetitive behavior and psychophysiological activity. Both attentional biases and aberrant motivational behavior are likely to sustain depression by decreasing positive and reinforcing experiences, while increasing the probability of negative encounters (Trew, 2011).

A limitation of the current study is that the faces used were not balanced in terms of valence; the only positive emotion (happy) was outnumbered by two clearly negative ones (angry, sad) and a neutral expression that might also be perceived as negative by patients. More sensitive measures, such as eye-tracking, could shed more light on the mechanisms underlying the (lack of) group differences and provide insight in the fixation patterns of both depressed and healthy individuals, e.g., the amount of time spent looking at the actual vs. the alternative offer and how this might be modulated by proposers' facial emotion. In addition, given the rather small group size (but comparable to the 15 depressed individuals tested by Harlé et al., 2010), our results are tentative with replication pending in larger samples.

In conclusion, the current study revealed that decision behavior in both depressed and healthy individuals profoundly relies on salient features. Strong, unambiguous signals of unfairness elicited highest rejection rates in both groups alike. Although our data indicate that depressed patients were capable of differentiating between fair and unfair offers, between alternatives to unfair offers and between facial emotions of proposers, they overall rejected more offers. This supports the notion that the impairments in decision-making are not specific for fairness considerations based on context or signaled intentions, which go in hand with increased (social-)cognitive demands. Rather, they seem to be driven by more fundamental biases, e.g., reduced reward sensitivity (Eshel & Roiser, 2011; Henriques & Davidson, 2000). Whereas the present study provides a first insight into the underlying processes of social decisions involving fairness considerations, future research should be devoted to systematic

investigations of additional, e.g., motivational, mechanisms that give rise to 'irrational' decision-making behavior in depression. Notably, these impairments do not only lead to less profit in terms of money, but may also result in inadequate, less well-balanced decisions and severe problems in social interactions.

The significant interaction between context and emotion was further investigated by separate ANOVAs for the different levels of context and emotion. Please note that, due to non-significance of the interactions involving group in the overall ANOVA, the post-hoc analyses will not cover group differences for specific levels of context or emotion.

Detailed analyses for context of unfair offers

Supplementary Results

The separate ANOVAs for the three different contexts revealed no emotion effect in the fair-alternative condition, F (3, 87) = 1.36, p = .27, partial η^2 = .05. However, significant main effects of emotion were evident in both the no-alternative, F (3, 87) = 4.56, p = .01, partial η^2 = .14, and the hyperfair-alternative condition, F (3, 87) = 4.56, p = .09, partial η^2 = .14. As in the overall analyses, unfair offers paired with angry faces were generally rejected most often.

Specifically, in the no-alternative condition, rejection rates in response to angry faces (M=59.6%) were significantly elevated compared to all three other emotions (sad: M=41.3%, happy: M=42.1%, neutral: M=48.3%; all ps<.033). In the hyperfair-alternative condition, the effect of emotion was driven by angry faces (M=71.7%) differing significantly from sad (M=52.5%, p=.008) and happy faces (M=55.8%, p=.002).

Detailed analyses for emotion

Next, the separate ANOVAs for the four different emotions showed no context effect for proposers' angry faces, F (2, 58) = 2.42, p = .12, partial n^2 = .08. However, significant main effects of context were evident for sad, F (2, 58) = 7.87, p = .002, partial n^2 = .21, happy, F (2, 58) = 7.9, p = .002, partial n^2 = .21, and neutral, F (2, 58) = 7.19, p = .002, partial n^2 = .20, facial expressions. The context effect on these three emotions showed a similar pattern as in the overall analyses, i.e., rejection rates being highest in the fair-alternative condition.

More precisely, when being presented with sad proposers' faces, rejection rates in the fair-alternative condition (M=66.3%) were significantly higher than in both the no-alternative (M=41.3%, p=.002) and hyperfair-alternative conditions (M=52.5%, p=.02). In response to happy faces, rejection rates in all three contexts differed significantly from each other (fair alternative: M=68.3%, no alternative: M=42.1, hyperfair alternative: M=55.8; all ps<.038). Likewise, for neutral facial expressions, rejection rates in all three contexts differed significantly from each other (fair alternative: M=75.0%, no alternative: M=48.3%, hyperfair alternative: M=60.8%; all ps<.048).





Summary and Discussion

The aim of this thesis was to advance our knowledge on social approach (**chapter 2-5**) and social decision-making (**chapter 6-9**) by examining the contribution of social and individual factors in both healthy and patient populations. In addition, administration studies experimentally investigated the influence of the hormones oxytocin and testosterone on behavior and brain activity in healthy volunteers.

The first empirical chapter, **chapter 2**, was based on the role of oxytocin in anxiety reduction in animals, testing whether oxytocin facilitates social approach behavior in humans. Approach behavior was assessed with the Approach-Avoidance Task (AAT), which elicited the typical actions to emotional stimuli under placebo: Approach tendencies for happy versus avoidance tendencies for angry faces. However, oxytocin specifically increased approach towards angry faces with direct, but not averted gaze in participants with low levels of social anxiety. These results have three important implications: First, they verify the anxiolytic properties of oxytocin for motivational actions in a human sample. Second, they underline the importance of individual dispositions and potential differences in the sensitivity to hormone administration in the field of social endocrinology. Finally, they provide further insight into discrimination based on the social and motivational salience of stimuli as effects were only observed for the most motivationally relevant cues, i.e., angry faces with direct gaze.

Based on these results and in order to investigate the neural mechanisms through which oxytocin might promote social approach, the study conducted in **chapter 3** focused on amygdala reactivity during performance of an adapted version of the task in the MR scanner. The main finding was that during social approach, oxytocin yielded increased amygdala responses to signals of social safety and decreased amygdala responses to signals of social threat. This pattern might reflect the adaptive regulation of social approach via the amygdala, but notably did not translate into specific behavioral changes. This discrepancy in behavioral effects between **chapter 2** and **3** might be partially due to methodological differences in study and task design such as the supine body position and the abandonment of the 'zooming' component (for a more thorough discussion see page 143). Still, the results suggest that oxytocin enhances the capacity for social approach in safe environments and consolidate a discrimination between socioemotional stimuli based on motivation rather than pure valence.

Rather an opposite expression of social approach, perceptions of and reactions to social threat have been linked to the hormone testosterone. In particular, its approach- and aggression-facilitating properties during social challenges and heightened amygdala responses to threatening cues after testosterone administration point to an enhanced approach-related attention to social threat. The administration study reported in **chapter 4** addressed the question of motivation-specific effects of testosterone on amygdala function using the fMRI-adapted social approach-avoidance task. Compared to placebo, testosterone increased amygdala activation during the

motivational challenge of approaching social threat, and decreased it during avoidance of the same stimuli. This differential modulation of amygdala activity after testosterone administration provides a neuroendocrine extension of the motivational salience model when dealing with social challenges.

In the last chapter on social approach, **chapter 5**, patients diagnosed with major depression were compared to a healthy control group in their approach-avoidance behavior on the AAT. In contrast to healthy individuals, the patients did not display approach-avoidance tendencies, i.e., they showed neither a dominant behavioral tendency nor distinct reaction patterns to faces with different affective valences or motivational affordances. The absence of any adjustments to the context of social stimuli suggests impairments of adaptive motivational behavior in depression.

As to social decision-making, **chapter 6** examined the role of intentionality under different division contexts in a modified Ultimatum Game. By manipulating proposers' control over an offer as well as the outcomes that they could choose from, this study demonstrated that intentionality increased rejection of unfair offers when a fair alternative could have been selected. During fairness evaluations, a fair split is a very salient signal that might be used as a rule of thumb. In general, rejection behavior was sensitive to the alternative outcomes to an unfair offer. The results illustrate that fairness decisions can be based on different attributes such as outcome comparisons and intentionality.

Chapter 7 presented an experiment in which the influence on oxytocin on fairness decisions was investigated by administering this hormone in a within-subject design. Compared to placebo, oxytocin decreased the sensitivity to contextual fairness in the modified Ultimatum Game, and decreased generosity in the Dictator Game. These results indicate a reduced adherence to fairness norms in settings where others are likely to be perceived as not belonging to one's ingroup and thereby point to the boundaries of oxytocin's prosocial effects.

In **chapter 8**, populations of violent offenders with and without psychopathy were compared to healthy controls in their rejection behavior in the modified Ultimatum Game. Individuals with psychopathy demonstrated a similar decision-making pattern as healthy controls by taking the unselected alternative to a proposal into account. In contrast, no adjustment to the context of an offer was evident in the incarcerated sample without psychopathy. Taken together, social decision-making in offenders with psychopathy seemed thus less impaired than in offenders without psychopathy, and even relatively intact when compared to healthy individuals. Since distinct mechanisms are likely to underlie these behavioral findings, it is crucial to distinguish between cognitive versus emotional processing and perspective-taking.

Along these lines, **chapter 9** investigated the role of facial emotions in combination with different fairness contexts. Responder behavior in the modified Ultimatum Game was assessed in patients diagnosed with major depression and in

healthy controls. Both groups based their decisions on informative, salient features and differentiated between (i) fair and unfair offers, (ii) alternatives to unfair offers and (iii) proposers' facial emotions. Although specific processing biases were not observed, depressed patients overall rejected more offers, which might be driven by more fundamental processes. These findings add to our knowledge on factors that contribute to fairness considerations in both typical and altered social decision-making.

In sum, for social approach, the experiments in this thesis showed that the hormones oxytocin and testosterone influence approach behavior and its neural regulation. The differential tuning of the amygdala based on the motivational context highlights the importance of considering not only affective, but also motivational values of social stimuli. Moreover, social approach behavior was modulated by both subclinical characteristics, i.e., social anxiety, and the clinical state of depression, where some symptoms of patients' everyday impairments, e.g., approach deficits, were found to be mirrored on an experimental level.

In the domain of social decision-making, the studies presented in this thesis established different social and situational constraints that shape fairness considerations. Subsequently, decreases in the influence of these factors were found after oxytocin administration as well as in offenders without psychopathy. In contrast, the patient populations with psychopathy and depression, respectively, did show similar patterns of social decision-making as healthy individuals. Tentatively, this might suggest relative intact decision-making, but other underlying biases and disturbances are likely to contribute to patients' maladaptive social interactions.

Psychobiological perspectives on 'social' hormones

Both oxytocin and testosterone have been termed "social hormones" with rather antagonistic effects on social behavior (for reviews see Bos, Panksepp, et al., 2012; Eisenegger, Haushofer, & Fehr, 2011; Meyer-Lindenberg, 2008). Yet, an increasing number of findings are at odds with the conceptualization of oxytocin as a prosocial versus testosterone as an antisocial hormone, particularly with regard to social approach and social decision-making. After oxytocin administration, the strong concern for fellow group members was absent or even reversed, as in non-cooperation and aggression, when interacting with individuals that are perceived not to belong to one's ingroup (De Dreu, 2012; De Dreu, et al., 2010; De Dreu, et al., 2011a; De Dreu, et al., 2012; Declerck, et al., 2010). In contrast, testosterone promoted generosity and cooperation (Eisenegger, et al., 2009; van Honk, Montoya, et al., 2011) and reduced self-serving lying (Wibral, et al., 2012). Taken together, a growing number of findings challenges simplified views on hormonal effects on social behavior

This context-dependency of endocrine modulations of social behavior might be rooted in a prerequisite to social behavior – social discrimination, i.e., recognizing others, their emotions and intentions. Indeed, many pioneering administration studies have investigated emotion detection or passive viewing of emotional stimuli during fMRI (e.g., Domes, Heinrichs, Glascher, et al., 2007; Hermans, et al., 2008; Kirsch, et al., 2005; van Wingen, et al., 2009). Whereas oxytocin attenuated amygdala responses, particularly to negatively valenced stimuli (Domes, Heinrichs, Glascher, et al., 2007; Kirsch, et al., 2005), testosterone enhanced amygdala reactivity to angry faces (Hermans, et al., 2008; van Wingen, et al., 2009). Yet, beyond perception, emotions also possess a crucial motivational function, namely preparing for action. The tuning of social behavior to the characteristics of the individual with whom one is (not yet) interacting is highly adaptive and ensures flexibility. A facilitated perception of others' emotions or group membership (as **chapter 7** suggests) after oxytocin administration, i.e., enhanced social discrimination, could thus indirectly regulate the diverse manifestations of social behaviors.

As an example, social approach involves a wide range of behavioral expressions with various functions that differ depending on the environment and the interaction partner. Affiliation and aggression form the two extremes of the umbrella-term 'social approach', and adjustments to the social context are necessary to balance behavior in safe versus threatening settings. In parental or mating/relationship contexts, social approach usually signifies positive engagement and nurturing, i.e., affiliation and intimacy. At the other end, however, approach can be evoked by threatening stimuli, be experienced as a negative state and be conveyed as aggression (Harmon-Jones. Harmon-Jones, & Price, 2013). Classifying behavioral displays based on their evolutionary motivation might help to understand the contribution of hormones in regulating intimacy and aggression (van Anders, Goldey, & Kuo, 2011). Whereas both oxytocin and testosterone promote sexual, reproduction-oriented intimacy, oxytocin, but not testosterone, is positively related to nurturing intimacy and social bonding (Gettler, McDade, Feranil, & Kuzawa, 2011; Ross & Young, 2009; K. A. Young, Gobrogge, Liu, & Wang, 2011). Similarly, when dividing aggression into offensive versus defensive/protective aggression, it becomes apparent that both oxytocin and testosterone foster protective aggression, e.g., defending offspring against intruders (Campbell, 2008; O'Connor, Gilmour, Van Der Kraak, & Cooke, 2011). However, only testosterone, not oxytocin, is also associated with unprovoked violence and aggression that involves obtaining resources (Dabbs Jr, et al., 1988; Kalin, 1999). Considering the social context of both extremes of social approach and to distinguish between safety-based versus threat-based approach, i.e., affiliation versus aggression, allows to integrate oxytocin's prosocial and antisocial effects into a 'tend-and-defend' pattern (Bakermans-Kranenburg & van Ijzendoorn, 2013; De Dreu, et al., 2010).

Within this framework, the increase in approach behavior toward threatening social cues after oxytocin administration (chapter 2) seems to convey rather an aggressive than an affiliative reaction. For those with low levels of social anxiety, oxytocin might have facilitated prepotent tendencies to the confrontation with social threat, rendering signals of social safety less motivationally salient in this task context. As to the lack of convergence in hormonal effects on action tendencies during fMRI (chapter 3 and 4) with earlier behavioral studies (chapter 2 and Enter, et al., submitted), it should be noted that performance on the behavioral and the fMRI-adapted task version has never directly been compared within the same sample. The contribution of these changes, i.e., stimulus presentation being shorter and lacking the 'zoom', remains thus speculative. Yet, the adaptations necessitated by the MR environment ought to be taken into account. In particular, a supine body position can hamper specific approach-motivational behaviors that are more likely to occur when leaning forward than when reclining backward (Harmon-Jones & Peterson, 2009; Price & Harmon-Jones, 2010). The relative immobility enforced by the confined scanner space and the instruction to minimize all but task-related movements might have limited endocrine effects to the neural, i.e., processing, level.

For these reasons, it remains important to not only investigate behavioral expressions, but also neural substrates to gain more insight into the underlying mechanisms of social adaptations in normal and altered states. Support for this notion is provided by the pharmacological fMRI studies of this thesis (**chapter 3** and **4**) where differential modulations of amygdala activity were evident both after oxytocin and after testosterone administration, yet without analogous specific behavioral effects. In the light of previously reported endocrine modulations on early attention (Guastella, Mitchell, & Dadds, 2008; Terburg, et al., 2012), this divergence might also indicate an adaptive regulation of social approach via limbic pathways that is tuned to the motivational context of socioemotional cues. These processing advantages precede stimulus encounters, whereas behavioral effects are likely to operate and emerge at a later point of the interaction (Todd, et al., 2012).

Moreover, the AAT involves a component of cognitive control, i.e., executing motivationally congruent and incongruent actions, which reliably engages the aPFC in both previous (Volman, Roelofs, et al., 2011; Volman, Toni, et al., 2011; Volman, et al., 2013) and current samples (**chapter 3** and **4**). The aPFC is an ontogenetically as well as phylogenetically late development as it continues to mature throughout adolescence and lacks a functional analog in monkeys (Koechlin, 2011; Tsujimoto, Genovesio, & Wise, 2011). Whereas the neocortex contributes greatly to higher cognitive and executive functions, subcortical regions continue to regulate various human behaviors – often in conjunction with the endocrine system. In fact, many oxytocin and testosterone administration studies show endocrine effects predominantly in subcortical structures such as the amygdala (Bos, Panksepp, et al.,

2012). Being highly conserved hormones with precursors in all vertebrates (Goodson, 2013; Guerriero, 2009), it might not be surprising that neither oxytocin nor testosterone influenced aPFC activity in **chapter 3** and **4**. Exogenous hormones seem to modulate rather evolutionary 'older' structures involved in affective and social processing, i.e., the amygdala (Adolphs, 2010; Davis & Whalen, 2001), than 'newer' structures linked to higher human cognition. Interestingly, the amygdala activations in **chapter 3** and **4** were both located on the right side, underlining the role of the right hemisphere in social and emotional behavior (Andari, Schneider, Mottolese, Vindras, & Sirigu, 2012).

Overall, the context-dependency and divergence of endocrine effects raise the question on the underlying mechanisms. As to oxytocin, several propositions haven been put forward, i.e., an increase in prosocial concerns (Zak, 2008), in the salience of social information (Averbeck, 2010; Shamay-Tsoory, et al., 2009), in approach-related behaviors (Kemp & Guastella, 2010a; 2010b), and a decrease in anxiety (Heinrichs, et al., 2003; Heinrichs & Domes, 2008). The preferred explanation often follows from the choice for the experimental paradigm and the comparison of interest, e.g., contrasting social and non-social stimuli, stimuli of varying affective value or intensity or differential coping with stressful experiences.

Still, the discussed mechanisms might not be mutually exclusive and some of them probably operate in parallel (Churchland & Winkielman, 2012; Groppe et al., 2013; Kemp, et al., 2012). For example, reduced anxiety could go in hand with an increase in social approach behaviors that may happen to be prosocial. Indeed, both affiliative approach, as in e.g., sexual intimacy, and protective aggression might benefit from anxiety reduction. Experiments testing several of these hypotheses against each other unfortunately remain scarce (see also Kemp & Guastella, 2010b). Drawing firm conclusions becomes even more complicated in connection with potential peripheral residua of hormone administration. With regard to the well-cited study by Born et al. (2002), which is viewed as evidence of successfully delivering peptides into the brain, it has often been overlooked that the administration of vasopressin led to heightened concentrations not only in cerebrospinal fluid, but also in blood. In addition, hormones clearly exert broad, non-social effects that are beyond the scope of this thesis. Oxytocin and other peptides influence viscerosensation, thermoregulation, immune and other functions (Goodson, 2013), and steroids such as testosterone are known for their role in the growth of muscle and bone mass (Sinha-Hikim, Taylor, Gonzalez-Cadavid, Zheng, & Bhasin, 2004). These peripheral effects of hormones likely have a different timescale than centrally-mediated effects and might contribute to changes in behavior by acting on more general motivational factors (see Churchland & Winkielman, 2012). Interestingly, increases in cardiovascular responses after oxytocin administration have been reported, e.g., increases in vagal rebound during recovery from a stressful episode (Kubzansky, et al., 2011), in heart

rate to emotional expressions (Gamer & Büchel, 2012) and in heart rate variability during rest (Kemp, et al., 2012) and valence ratings (Norman, et al., 2011), which altogether might signify an enhanced motivation or capacity for social approach (see also Kemp & Guastella, 2010b). Regarding testosterone administration, effects might depend on the rate of metabolization into estradiol which then targets estrogen receptors (Cornil, et al., 2006). To differentiate between effects resulting from testosterone binding to androgen receptors and those caused by estradiol, the use of dihydrotestosterone, which cannot be converted to estradiol, might be advantageous, but its feasibility in research settings is yet to be established (Swerdloff & Wang, 1998).

Implications for social neuropsychiatry

Biases and disturbances in social behavior are common in many psychiatric disorders. Difficulties and impairments in social interactions have a serious impact on patients' daily functioning and quality of life. As there is yet no pharmacological agent directly targeting social behavior, great interest in the translational potential of hormones, especially oxytocin, has arisen (Meyer-Lindenberg, 2008; Striepens, Kendrick, Maier, & Hurlemann, 2011). Regarding both diagnostic and therapeutic use, however, a number of issues are still unresolved.

Complementary to administration studies, endogenous hormone levels have been assessed as potential biomarkers for social competencies and behavior. The fact that peripheral and central oxytocin can be regulated independently (Neumann, et al., 1993) has led to an ongoing debate in how far plasma levels are informative for oxytocin's central effects. Although the exact nature and function of their connection is not fully investigated and likely to be complex, increased plasma concentrations have been found subsequent to intranasal oxytocin administration (Burri, Heinrichs, Schedlowski, & Kruger, 2008; Gossen et al., 2012), as well as in some psychiatric conditions that are discussed in this thesis. In patients with social anxiety disorder, symptom severity and dissatisfaction with social relationships were positively correlated with plasma oxytocin in one study (Hoge, et al., 2008), but when patients performed an interactive social task, oxytocin levels were reduced (Hoge et al., 2012). Similarly conflicting are the patterns for patients with major depression since elevations of oxytocin plasma levels (Cyranowski et al., 2008; Parker et al., 2010) as well as negative associations with symptom severity (Scantamburlo et al., 2007) have been reported. When assessing oxytocin in cerebrospinal fluid, levels did not differ between depressed patients and healthy individuals (Sasayama et al., 2012). In contrast, the association between higher testosterone levels and higher incidences of criminal behavior and psychopathy appear to be relatively robust (Dabbs Jr, et al.,

1995; Dabbs Jr, et al., 1988; Glenn, Raine, Schug, Gao, & Granger, 2011). Recently, lower testosterone levels were observed in patients with social anxiety disorder, patients with generalized anxiety disorder and patients with depression (all female; Giltay et al., 2012). The notion that external administration of hormones might compensate for a low endogenous level and some of the social deficits associated with it, particular social affective symptomatologies, remains to be investigated.

Moreover, in many administration studies, individual dispositions and social experiences moderate the effects of hormones on behavior. Particularly the link between parental attachment and oxytocin has recently gained attention as negative care-giving and childhood experiences are frequent in many psychiatric conditions (Bakermans-Kranenburg & van lizendoorn, 2013). In a series of studies, beneficial effects of oxytocin were found to be limited to participants from supportive family backgrounds, i.e., without harsh parental discipline or maternal love withdrawal (e.g., Bakermans-Kranenburg, van Ijzendoorn, Riem, Tops, & Alink, 2012; Riem, Bakermans-Kranenburg, Huffmeijer, & van lizendoorn, 2013; van lizendoorn, Huffmeijer, Alink, Bakermans-Kranenburg, & Tops, 2011). Similarly, only in healthy adults who did not feel lonely, oxytocin improved cardiac control (Norman, et al., 2011), and only in individuals with low rather than high attachment anxiety, oxytocin increased ratings of maternal care and closeness (Bartz, et al., 2010). The findings from chapter 2 of this thesis, i.e., social threat approach in low socially anxious participants after oxytocin administration, corroborate these findings. In individuals with high social anxiety, oxytocin may not provide sufficient anxiolysis to improve their social functioning (Hoge, et al., 2008), but they might need additional social support (Heinrichs, et al., 2003).

Closely related to the underlying mechanisms of hormonal effects on social behavior is the question for which deficits such a treatment may be most promising. Whereas several psychiatric conditions are associated with impairments in the social domain, the processes expected to be targeted by administration might be highly specific and dissimilar. For social anxiety, for example, attenuation of the stress response elicited by social encounters might be beneficial for improving self-centered perceptions and overcoming safety or avoidance behaviors. In one placebo-controlled clinical trial, oxytocin was given alongside with exposure therapy to patients with social anxiety disorder and promoted patients' ratings of their performance, but did not affect reported anxiety or symptom severity (Guastella, et al., 2009).

Encouraging emotional sensitivity and social concern could be the objective of administering oxytocin in psychopathy, but empirical studies have not been conducted until now. Here, it will be crucial to distinguish between cognitive and emotional aspects of empathy as there are indications that individuals with psychopathy exhibit specific deficits in making emotional, but not cognitive, inferences about others' affective states (Cima, et al., 2010; Shamay-Tsoory, et al.,

2010). There are, however, some intriguing behavioral parallels between individuals with psychopathy and healthy volunteers after oxytocin administration. For instance, the approach towards social threat observed in low socially anxious participants after oxytocin administration (**chapter 2**) was also displayed by psychopathic offenders (Von Borries, et al., 2012). Likewise, attenuated amygdala responses to distress cues have been related to anxiolytic properties of oxytocin (e.g., Domes, Heinrichs, Glascher, et al., 2007; Kirsch, et al., 2005) as well as to psychopathy (R. J. Blair, Peschardt, Budhani, Mitchell, & Pine, 2006). Given that psychopathy is often associated both with decreased anxiety and experiences of poor or inconsistent parenting (R. J. Blair, et al., 2006), caution should be undertaken when exploring the utility of oxytocin in clinical trials.

The inconsistent findings on endogenous oxytocin levels and depressive symptomatology preclude clear-cut deductions on oxytocin's therapeutic potential. One rationale for administration would be the influence of oxytocin on social motivation, with desired outcomes being increases in the interest in social interactions and the capacity for social approach. Indeed, unmedicated patients with depression showed enhanced recruitment of emotion-related brain circuits during mentalizing, i.e., the cingulate and the insula, after oxytocin administration (Pincus et al., 2010). In another recent clinical study (K. Macdonald et al., 2013), oxytocin reduced social avoidance behaviors in a psychotherapy setting, e.g., gaze avoidance, in (medicated) patients with high levels of depression. These first results may seem promising for beneficial effects of oxytocin on the affective involvement and rewarding value of social interactions in depression, but more research is needed to determine whether and through which pathways oxytocin can indeed tackle approach deficits and anhedonia. Due to the high comorbidity of depressive and anxiety disorders, such effects might partially be mediated via the hypothalamus-pituitary-adrenal (HPA) axis or the vagus (Porges, 2011).

Additional methodological considerations need to be addressed in fundamental research before translation into clinical applications. Genetic and prenatal factors appear to play a role in the susceptibility to hormone administration later in life. Variants in expression of the oxytocin receptor gene and prenatal exposure to androgens have lately been shown to moderate the effects of external oxytocin and testosterone, respectively (Marsh et al., 2012; Montoya, et al., 2013; Sauer, Montag, Worner, Kirsch, & Reuter, 2012; van Honk, Schutter, et al., 2011). Moreover, the endocrine system comprises a network of hormones interacting with each other as well as with other neurotransmitters. In the ventral striatum, oxytocin interacts with dopamine in the regulation of bonding and reward (K. A. Young, et al., 2011); and in the hypothalamus, cell bodies containing oxytocin are adjacent to serotonin terminals (Emiliano, Cruz, Pannoni, & Fudge, 2007). The latter findings might even indicate that the therapeutic effects of SSRIs could be partially driven by the oxytonergic system

(see also Marazziti et al., 2012). Testosterone regulates stress responses by inhibiting the HPA axis (Viau, 2002) and also influences the dopamine system (Hull, Du, Lorrain, & Matuszewich, 1997).

Besides, the majority of administration studies are still based on only one gender, i.e., males for oxytocin and females for testosterone research (for notable exceptions, see Bakermans-Kranenburg, et al., 2012; Domes et al., 2010; Lischke et al., 2012; Riem, et al., 2013; van Ijzendoorn, et al., 2011). Further differences in dosage, time-frame and procedure render direct comparisons difficult, so that the development of standardizations is desirable (see also Guastella et al., 2013). For clinical interventions, significant outcomes need to extend the period of experimental sessions and although the use of both oxytocin and testosterone seems safe in adults (E. MacDonald et al., 2011; Salehian et al., 1995), the 'natural' peripheral effects of oxytocin, i.e., stimulating uterine contractions and lactation, might limit its long-term clinical potential in females.

Frontiers and challenges

The title of this thesis *Acting social* raises the question "what is social?". The experiments reported in the preceding chapters established different social contexts by manipulating emotional expressions, motivational relevance and intentionality of interaction partners. As a recurrent finding, the most salient social contexts, e.g., faces with angry expressions or direct gaze, and unfair offers deliberately chosen over a fair alternative, elicited robust reactions. A limitation of some of the paradigms used in this thesis is the lack of a genuine non-social control condition in order to disentangle 'social' from other general, cognitive or task-related effects. Varying the nature or intensity of social affordances (e.g., by contrasting different gaze directions or emotional against neutral facial expressions) may be adequate depending on the research aim and time constraints of the experimental session. However, including non-social conditions or social conditions that do not engage the amygdala in pharmacological fMRI studies would be especially valuable for pinpointing and differentiating the effects of oxytocin on social and non-social processing.

Investigating social behavior in experimental and laboratory settings often yields the problem of external and ecological validity, i.e., the generalization to other individuals and other situations, preferably in real-life social interactions. Although all empirical chapters of this thesis used social stimuli, the extent to which genuine interactions took place, is limited. Whereas genuine social interactions involve a cycle of reciprocal (re)actions that mutually and directly influence each other (Schilbach et al., 2013), the paradigms used for this thesis usually probe just one reaction to a social stimulus before the next 'interaction', i.e., ostensibly unrelated trial, starts.

Along these lines, both for social approach and social decision-making, participants were put into the roles of responders and not initiators of an interaction, which might entail different foci in monitoring of outcomes and emotions (Schilbach, et al., 2013). The initiation of an interaction is particularly relevant for social approach, so that future studies would benefit from going beyond quantifying approach-avoidance movements that are based on instructions by assessing 'free' approach decisions. This might be of special interest in the light of the postulated approach-enhancing capacities of oxytocin. Closely related, the intrinsically hedonic value of social interactions would be an exciting research avenue with regard to neuroendocrine and clinical modulations. Patients with psychiatric disorders such as depression or schizophrenia often do not enjoy interacting with others, possibly due to a decreased salience of social rewards (Krach, Paulus, Bodden, & Kircher, 2010; McGregor & Bowen, 2012). Recent studies suggest that oxytocin might aid in priming social reward and in recruiting reward-related brain circuits (Groppe, et al., 2013; Sauer, Montag, Reuter, & Kirsch, 2013).

Conclusions

Acting social begins, after all, with one individual and its specific dispositions, traits and previous experiences. Being in a social situation introduces further characteristics and behavior of interaction partners that need to be assessed, compared and weighed. This processing of social affordances is probably supported by the amygdala and other subcortical structures shared across vertebrates. Depending on the outcome of the evaluation, motivational systems can be primed, e.g., fight-or-flight when confronted with threat, which may be evident in overt behavior such as approach-avoidance tendencies (chapter 2). Human social actions on a higher level, e.g., social decision-making, are more likely to be additionally shaped by goals, abstract representations and other cognitive constructs. For example, whereas non-human primates and young children favor equal allocations in sharing, the work presented in chapter 6-9 shows that there is more to the concept of 'fairness' than distributive (in-)equality. In particular, mental representations about alternative courses of action, both in time and in regard to the actions and choices of interaction partners crucially shape our social preferences.

Hormones, at least oxytocin and testosterone, appear to modulate the initial processing stage by improving emotion recognition, facilitating social discrimination (**chapter 7**) and tuning amygdala activity to the motivational affordances of the situation while frequently leaving prefrontal regions unaffected (as in **chapter 3** and **4**; but see e.g., Petrovic, et al., 2008). In a similar vein, processing and evaluation of social cues is influenced by alterations associated with psychiatric conditions, e.g.,

hypervigilance to socially threatening cues as often observed in social anxiety. Atypical experiences and anticipation of the rewarding nature of social interactions might further contribute to shifts in processing and motivational behavior, as underlined by anhedonia and approach deficits in depression (**chapter 5**) and a tendency to obtain reward through instrumental aggression in psychopathy.

In this manner, these two levels of action come together in several facets of social behavior. For instance, emotional actions, i.e., how we act on our emotions and the emotions conveved by others' facial expressions, can influence our social decisions. In a 'fight' mode, possibly reflected in increased threat approach (chapter 2 and von Borries et al., 2012), we might incorporate abstract representations to a lesser extent into our decision-making, as indicated by a decreased adherence to fairness norms (chapter 7), the absence of context adjustments in the offender group without psychopathy (chapter 8), and in the disappearance of the robust context effect when interacting with an angry proposer (chapter 9). Conversely, decisions to control lower-level approach-avoidance tendencies are relevant for the pursuit of higher, often long-term goals, e.g., approaching threatening stimuli in order to overcome fear (as in exposure therapy) or avoiding sexual temptations in order to maintain a stable relationship. Besides, these decisions may not always map onto immediate action. When encountering obstacles, we sometimes temporarily retreat and disengage with the purpose of "getting a bigger picture" of the new situation (Förster & Friedman, 2013). Coming back to an example from the introduction (chapter 1), we might also decide to postpone our share of household chores until a more suitable moment arises – or even until our partner takes them over. The latter reasoning denotes instrumental social decision-making and thereby alludes to the different connotations and normative judgments of the term 'social'. In human interactions, 'social' is frequently interpreted as synonymous with positive or prosocial. Yet, social behavior simply signifies behavior directed at another individual of the same species - may it be prosocial or antisocial. Judging certain behaviors as more 'social' and desirable than others becomes particularly apparent in the appraisal of oxytocin as a "prosocial neuropeptide" or "moral molecule" (Meyer-Lindenberg, 2008; Scheele, et al., 2012; Zak, 2012). In light of the wide range of social behavior on different levels of action and with different expressions in both humans and other animals, such an anthropomorphic framing of psychobiological mechanisms appears rather narrow. The work in this thesis contributes to and calls for viewing neuroendocrine and clinical modulations across the broad spectrum of acting social.





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Appendix

Publications

- Egger, J. Wingbermühle, E., Verhoeven, W., Dijkman, M., Radke, S., De Bruijn, E., deVries, B., Kessels, R., Koolen, D. (2013) Hypersociability in the behavioral phenotype of 17q21.31 microdeletion syndrome. *American Journal of Medical Genetics: Part A. 161.* 21-26.
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- Radke, S., Schäfer, I. C., Müller, B. W., & De Bruijn, E. R. A. (2013). Do different fairness contexts and facial emotions motivate 'irrational' social decision-making in major depression? An exploratory patient study. *Psychiatry Research*, 201, 438-443.

Manuscripts

- De Bruijn, E. R. A., Ruissen, M. I., Radke, S., (in prep). To err is... social: The effects of oxytocin on performance monitoring in a social context.
- Radke, S., Güths, F., André, J. A., Müller, B. W., & De Bruijn, E. R. A. (under review). In action or inaction? Social approach-avoidance tendencies in major depression.
- Radke, S., Volman, I., Kokal, I., Toni, I., Roelofs, K., & De Bruijn, E. R. A. (in prep). Neural regulation of social approach-avoidance behavior after oxytocin administration.
- Radke, S., Volman, I., Mehta, P. H., van Son, V., Toni, I., Sanfey, A. G., de Bruijn, E. R. A., Roelofs, K. (in prep). Ready to go! Testosterone prepares the amygdala for social threat approach.

Curriculum Vitae

Sina Radke was born on February 24th, 1984 in Gifhorn, Germany and left her home town on the turn of the century to spend one year at West Columbus High School in Cerro Gordo (NC, USA). After graduating from the Otto-Hahn-Gymnasium Gifhorn in 2003, Sina studied Cognitive Science at the University of Osnabrück for one year, and then decided to pursue a major in Psychology with a minor in Neurobiology. She completed research internships at the German Primate Center and the University Clinic Bonn where she conducted her first fMRI experiment. In 2009, Sina obtained her diploma degree and moved to Nijmegen to start a PhD under the supervision of Ellen de Bruijn and Roy Kessels at the Donders Center for Cognition. The results of some of her projects are described in this thesis. Since 2013, she works as a postdoctoral researcher at the University Hospital RWTH Aachen in the group of Birgit Derntl.

Nederlandse samenvatting

Ons alledaagse leven wordt gevormd door sociale acties en gedragingen. We wisselen van gedachten met vrienden, werken samen met collega's en ontmoeten vreemden op straat – we handelen sociaal. Elke situatie eist van ons dat we niet alleen rekening houden met de steeds wisselende randvoorwaarden van de situatie, maar ook met de handelingen van andere personen die erbij betrokken zijn. Bovendien dienen we op dit alles ook nog flexibel en adequaat te reageren. Het vermogen om dit alles uit te kunnen voeren is belangrijk voor zowel ons psychologisch als lichamelijk welzijn. Gepast toenaderingsgedrag, dat bijvoorbeeld van belang is tijdens paarvorming en hechting, zorgt ervoor dat een soort zich kan voortplanten en dus niet uitsterft. Bij het nemen van bepaalde beslissingen versterken gedeelde sociale waarden, zoals het delen van voedsel en plichten, het gevoel van saamhorigheid en daarmee de maatschappij. Deze twee facetten van sociaal gedrag - sociale toenadering (hoofdstuk 2-5) en het nemen van beslissingen (hoofdstuk 6-9) - vormen het zwaartepunt van onderhavig onderzoek.

Verschillende psychologische motivatietheorieën gaan ervan uit dat ons gedrag in twee tegenovergestelde motivationele richtingen ingedeeld kan worden: toenadering en vermijding. Het benaderen van iets positiefs en het vermijden van iets negatiefs wordt niet alleen aangetoond ten opzichte van basisbehoeftes (opzoeken van voedsel versus vermijden van pijn), maar ook in de omgang met andere personen, dus in sociale situaties. Gezichtsuitdrukkingen spelen hierbij een bijzondere rol omdat ze gevoelstoestanden en intenties onthullen en daarmee de waarnemer tot reacties aanzetten. Een manier om deze uitgelokte actietendensen te meten is de zogenoemde toenaderings-vermijdingstaak die veel in experimenteel onderzoek gebruikt wordt. Bij deze computertaak verschijnen emotionele gezichten op het scherm en afhankelijk van de getoonde gevoelstoestand duwen de proefpersonen een joystick van zich af of trekken deze naar zich toe. De gezichten worden herhaaldelijk gepresenteerd zodat aan de hand van de gemiddelde reactietijden toenaderings- en vermijdingstendensen op millisecondeniveau kunnen worden vastgesteld.

Sociale beslissingen worden vaak met behulp van beslissituaties uit de speltheorie in kaart gebracht, zoals met het zogenaamde *ultimatumspel*. Bij dit spel dient een bedrag tussen twee personen te worden verdeeld. De eerste persoon (aanbieder) stelt een verdeling voor, de tweede persoon (de ontvanger) kan deze accepteren of weigeren. Als de ontvanger het aanbod accepteert, wordt het bedrag volgens het aanbod verdeeld; als de ontvanger weigert, gaan beide personen met lege handen naar huis. Er is maar één ronde, geen communicatie tussen de spelers en de ontvanger heeft het laatste woord (vandaar de naam *ultimatum*spel). In deze op zich eenvoudige configuratie ontstaan wederzijdse verwachtingen en sociale

wisselwerkingen die doorwerken in de uiteindelijke beslissingen van de ontvangers. Zo accepteren de ontvangers niet zomaar elk aanbod, maar slaan ze een mogelijke winst bijvoorbeeld af als ze de voorgestelde verdeling oneerlijk vinden. De aangepaste versie van het *ultimatumspel* die in de artikelen uit hoofdstuk 6-9 wordt gebruikt, heeft dezelfde basis als het originele spel, maar kan bovendien nader inzicht bieden in welke aspecten het afwegen van eerlijkheid bëinvloeden. Door de keuzevrijheid voor de aanbieder te beperken tot twee mogelijke verdelingen, kan de ontvanger de gekozen verdeling met de niet gekozen verdeling vergelijken. Als een aanbieder bijvoorbeeld kiest voor een oneerlijke verdeling, terwijl deze ook had kunnen kiezen voor een eerlijke verdeling, zal de ontvanger een dergelijk aanbod sneller weigeren. Als gedragsmaat wordt doorgaans het percentage weigeringen van de ontvangers op oneerlijke aanbiedingen afhankelijk van de mogelijke alternatieven gebruikt.

In dit proefschrift werden door middel van empirische studies verschillende factoren van sociaal toenaderingsgedrag en beslissingen onderzocht. Hierbij waren enerzijds biologische en psychologische eigenschappen van de handelende persoon van belang, zoals hormonen of persoonlijkheidskenmerken. Anderzijds werd belicht in hoeverre de gezichtsuitdrukking of de intentie van de actiepartner onze reacties bëinvloeden. Om de verschillende onderzoeksvragen te bestuderen, werden diverse methoden toegepast zoals functionele beeldvorming (fMRI; hoofdstuk 3 en 4) waarmee hersenactiviteit tijdens het uitvoeren van een taak zichtbaar kan worden gemaakt. Door het toedienen van de hormonen oxytocine en testosteron en de vergelijking met het toedienen van een placebo (stof zonder specifieke werkzaamheid) konden conclusies over de effecten van deze hormonen getrokken worden (hoofdstuk 2-4 en 7). Bovendien zijn in alle studies ook gedragsmaten meegenomen, met name reactietijden in de toenaderings-vermijdingstaak (hoofdstuk 2-5) en het percentage van afwijzingen van een bepaald aanbod in het ultimatumspel (hoofdstuk 6-9).

Hoofdstukken 2-4 lieten zien dat de hormonen oxytocine en testosteron de sociale toenadering en diens neurale regulatie beïnvloeden. In het gedragsexperiment uit hoofdstuk 2 veroorzaakte oxytocine bij vrijwilligers met weinig sociale angst een toename van toenaderingsgedrag op boze gezichten waarvan de blik gericht was op de proefpersoon. Op basis van deze resultaten werden vervolgstudies uitgevoerd met behulp van functionele beeldvorming met specifieke aandacht op activiteit in de amgydala – een hersengebied dat een belangrijke rol speelt in de verwerking en beoordeling van emoties. Tijdens sociale toenadering verhoogde oxytocine de amygdala activiteit bij het zien van veilige sociale situaties (vrolijke gezichten) en verlaagde de activiteit van deze regio voor het observeren van sociale bedreigingen (boze gezichten, hoofdstuk 3). Testosteron daarentegen leidde tot sterkere amygdala activiteit bij het benaderen van sociaal bedreigende prikkels en tot zwakkere activiteit als men deze kon vermijden (hoofdstuk 4). In hoofdstuk 5 werd het toenaderings-

gedrag van patiënten met een depressie vergeleken met een groep gezonde mensen. In tegenstelling tot de gezonde proefpersonen lieten de depressieve patiënten geen specifieke toenaderings- of vermijdingstendensen zien, ofwel ze reageerden vergelijkbaar op alle soorten gezichten onafhankelijk van hun gezichtsuitdrukking of kijkrichting.

De studies over sociale beslissingen (hoofdstuk 6-9) hebben een aantal centrale aspecten van de beoordeling van eerlijkheid nader onderzocht. Uit eerder onderzoek was bekend dat oneerlijke aanbiedingen vooral worden afgewezen wanneer de aanbieder ook een eerlijk alternatief had kunnen kiezen (het zogenaamde context effect). Dit effect trad zowel op bij gezonde proefpersonen als bij geweldplegers met psychopathie en bij patiënten met depressie (hoofdstuk 6, 8 en 9). Bovendien was dit effect met name aanwezig wanneer het overduidelijk was dat de keuze voor het oneerlijke aanbod in plaats van het eerlijke aanbod intentioneel was (hoofdstuk 6). Bij geweldplegers zonder psychopathie en na toediening van oxytocine bij gezonde deelnemers daarentegen was er sprake van een afgenomen context effect (hoofdstuk 7 en 8). Tot slot, bleek uit de studie in hoofdstuk 9, dat onafhankelijk van het getoonde alternatief de mate van afwijzing van oneerlijke voorstellen toeneemt als deze door aanbieders werden gedaan die boos (maar niet vrolijk of verdrietig) keken. Hoewel er een grotendeels verglijkbaar patroon van beslissingen bij verschillende psychiatrische populaties en gezonde proefpersonen aanwezig was, blijft het mogelijk dat de verschillen in gedrag die wel aanwezig waren, zoals een algemeen toegenomen afwijzing bij depressieve patiënten, het gevolg kan zijn van verstoorde processen in de waarneming en inschatting van sociale informatie in deze patiëntpopulatie.

De verschillende studies uit dit proefschrift laten zien dat sociaal handelen begint bij het individu en diens specifieke eigenschappen en ervaringen. Vervolgens zorgt het gedrag van onze actiepartners voor bijkomende sociale factoren die verwerkt en geëvalueerd dienen te worden. Deze verwerking wordt vermoedelijk ondersteund door de amygdala en andere sub-corticale structuren waarvan de activiteit door hormonen beïnvloed kan worden. Ook is duidelijk geworden dat de benadering en beleving van sociale situaties door psychische aandoeningen vertekend kunnen worden. Hierbij is het van belang om zich bewust te zijn van de verschillende betekenissen en de normatieve waardering van het woord "sociaal". In de Nederlandse taal wordt het woord "sociaal" vaak gelijkgesteld aan iets positiefs. Sociaal gedrag is echter gedrag dat zich richt op een ander individu van dezelfde soort en dat gedrag kan meer of minder positief (prosociaal) of negatief (antisociaal) van aard zijn. Het indelen van gedragingen als "socialer" en wenselijker dan anderen komt overduidelijk naar voren in de vele recent verschenen lofliederen waarin oxytocine als "prosociaal hormoon" of het "molecuul van de moraal" wordt neergezet. Een dergelijke indeling lijkt gezien het grote repertoire van sociale gedragingen bij mens en dier zeer eenzijdig. Dit komt tot uitdrukking in de Engelse titel van het proefschrift Acting social,

omdat *acting* niet alleen de betekenis van handelen in zich heeft, maar ook de betekenis van toneelspelen of doen alsof. Het wordt geïllustreerd door de twee personen op de foto van de omslag van dit proefschrift die volledig conform de etiquette van de Britse theecultuur optreden. Op die manier benadrukt het huidige proefschrift zowel qua uiterlijk als qua inhoud het brede spectrum van handelwijzen en verschijningsvormen wanneer we *sociaal handelen*.

Deutsche Zusammenfassung

Unser Alltag ist geprägt von sozialen Taten und Verhaltensweisen. Wir tauschen uns mit Freunden aus, arbeiten mit Kollegen zusammen, und begegnen Fremden auf der Straße – wir handeln sozial. Jede Situationen erfordert, dass wir unterschiedliche Rahmenbedingungen sowie die Handlungen der anderen beteiligten Personen berücksichtigen und flexibel darauf reagieren. Diese Anpassung ist wichtig für sowohl unser psychologisches Wohlbefinden als auch für unsere biologische Fitness. Angemessenes Annäherungsverhalten, das sich in z.B. Paarung und Bindung äußert, begünstigt die Fortpflanzung einer Spezies. Beim Treffen sozialer Entscheidungen stärken gemeinsame soziale Werte, z.B. das Teilen von Nahrung und Pflichten, das Zusammengehörigkeitsgefühl und damit die Gemeinschaft. Diese zwei Facetten von sozialem Verhalten - soziales Annäherungsverhalten (Kapitel 2-5) und Entscheidungsverhalten (Kapitel 6-9) - bilden den Schwerpunkt der vorliegenden Arbeit.

Verschiedene motivationspsychologische Theorien gehen davon aus, dass sich unser Verhalten anhand zweier gegensätzlicher Handlungsrichtungen einordnen lässt: Annäherung und Vermeidung. Die Tendenz, sich etwas Positivem anzunähern und Negatives zu vermeiden, zeigt sich nicht nur im Hinblick auf Grundbedürfnisse (Aufnehmen von Nahrung vs. Vermeiden von Schmerz), sondern ebenfalls im Umgang mit anderen Personen, also in sozialen Situationen. Gesichtsausdrücke spielen hierbei eine besondere Rolle, da sie Gefühlszustände und Absichten vermitteln und damit den Betrachter zu Reaktionen auffordern. Als eine Möglichkeit zu messen, zu welcher der beiden Handlungsrichtungen man neigt, hat sich in der Forschung die sogenannte *Annäherungs-Vermeidungs-Aufgabe* etabliert. Bei dieser Computeraufgabe erscheinen emotionale Gesichter auf dem Bildschirm und abhängig von deren Gesichtsausdruck ziehen die Probanden einen Joystick entweder zu sich heran oder drücken ihn von sich weg. Die Bilder werden mehrfach gezeigt, sodass sich anhand der durchschnittlichen Reaktionszeit Annäherungs-und Vermeidungstendenzen im Millisekundenbereich ablesen lassen.

Soziale Entscheidungen werden häufig mithilfe von Entscheidungssituationen aus der Spieltheorie abgefragt, wie z.B. dem *Ultimatumspiel*. Bei diesem Spiel soll ein Betrag zwischen zwei Personen aufgeteilt werden. Die erste Person (der Anbieter) schlägt eine Verteilung vor, die zweite Person (der Empfänger) kann diese annehmen oder ablehnen. Wenn der Empfänger dem Angebot zustimmt, wird der Betrag entsprechend aufgeteilt; wenn der Empfänger es zurückweist, gehen beide leer aus. Es gibt nur eine Spielrunde, keine Kommunikation zwischen den Spielern und der Empfänger hat das letzte Wort (daher *Ultimatum*spiel). In dieser an sich simplen Aufgabe entstehen gegenseitige Erwartungen und soziale Wechselwirkungen, die sich auch in den Entscheidungen der Empfänger widerspiegeln. Mitunter nehmen diese nicht jedes Angebot eigennützig an, sondern verzichten auf einen Gewinn,

wenn sie die vorgeschlagene Aufteilung als unfair empfinden. Die abgewandelte Version des *Ultimatumspiels*, die in den Artikeln aus Kapitel 6-9 verwendet wird, behält die Grundidee des Spiels bei. Welche Aspekte das Abwägen von Fairness prägen, kann eingehender untersucht werden, indem die Auswahl des Anbieters auf zwei Möglichkeiten, von denen eine immer unfair ist, eingeschränkt wird. Als Empfänger kann man beide Optionen einsehen und miteinander vergleichen. Bei der Auswertung ist maßgeblich, wie häufig die Empfänger ein unfaires Angebot ablehnen, abhängig von den möglichen Alternativen, die der Anbieter gehabt hätte.

In dieser Doktorarbeit wurden anhand von empirischen Untersuchungen verschiedene Faktoren von sozialem Annäherungsverhalten und Entscheidungsverhalten studiert. Hierbei waren zum einen biologische und psychologische Charakteristika (Hormone, Persönlichkeitseigenschaften) der handelnden Person von Interesse. Zum anderen wurde beleuchtet, inwiefern der Gesichtsausdruck oder die Absicht eines anderen unsere Reaktionen beeinflussen. Um diesen Forschungsfragen nachzugehen, bedienten sich die einzelnen Studien verschiedener Methoden, wie beispielsweise der funktionellen Magnetresonanztomographie (fMRT; Kapitel 3 und 4), mittels derer die Hirnaktivität während des Ausführens einer Aufgabe dargestellt werden kann. Durch die Gabe der Hormone Oxytocin und Testosteron und den Vergleich mit der Gabe eines Placebos (Stoff ohne spezifische Wirksamkeit) konnten Rückschlüsse auf die Auswirkung dieser Hormone gezogen werden (Kapitel 2-4 sowie 7). Im Rahmen aller Studien wurde Verhalten gemessen, d.h. Reaktionszeiten in der Annäherungs-Vermeidungs-Aufgabe (Kapitel 2-5) und die Rate von Ablehnungen einer bestimmten Angebotsauswahl im abgewandelten Ultimatumspiel (Kapitel 6-9).

In den Kapiteln 2-4 zeigte sich, dass die Hormone Oxytocin und Testosteron die soziale Annäherung und deren neuronale Regulierung beeinflussen. Im Verhaltensexperiment (Kapitel 2) bewirkte Oxytocin bei Probanden mit geringer Ausprägung von sozialer Angst eine Zunahme der Annäherung auf wütende Gesichter mit direkter Blickrichtung. Basierend auf diesen Ergebnissen wurden Bildgebungsstudien durchgeführt, die den Fokus auf die Aktivität der Amygdala richten - ein Hirngebiet, das eine wichtige Rolle in der emotionalen Verarbeitung und Bewertung spielt. Während der sozialen Annäherung erhöhte Oxytocin die Amygdala-Aktivität bei der Darbietung von fröhlichen Gesichtern und reduzierte die Aktivität dieser Region für Anzeichen sozialer Bedrohung (wütende Gesichter; Kapitel 3). Testosteron hingegen führte zu verstärkter Amygdala-Aktivität bei der Annäherung von sozial bedrohlichen Reizen und zu verringerter Aktivität, wenn diese vermieden werden konnten (Kapitel 4). In Kapitel 5 wurden Patienten mit Depression hinsichtlich ihres Annäherungsverhaltens mit einer gesunden Kontrollgruppe verglichen. Im Gegensatz zu gesunden Probanden wiesen die Patienten keine ausgeprägten Annäherungs- oder Vermeidungstendenzen auf, das bedeutet sie reagierten gleichartig auf alle Gesichter, unabhängig von deren Gesichtsausdruck oder Blickrichtung.

Durch die Studien zu sozialen Entscheidungen (Kapitel 6-9) wurde eine Reihe von Einflüssen auf die Beurteilung von Fairness herausgearbeitet. So wurden unfaire Verteilungen besonders dann abgelehnt, wenn eine faire Alternative zur Wahl gestanden hatte, jedoch nicht gewählt wurde (sogenannter Kontext-Effekt). Diese Reaktion trat sowohl bei gesunden Probanden als auch bei Straftätern mit Psychopathie und bei Patienten mit Depression auf (Kapitel 6, 8 und 9). Außerdem war sie besonders ausgeprägt, wenn die Wahl zugunsten des unfairen statt des fairen Angebots mit Absicht getroffen wurde, genauer gesagt vom Anbieter selbst und nicht durch ein Computerprogramm (Kapitel 6). Nach Oxytocin-Gabe bei gesunden Versuchsteilnehmern sowie in der Gruppe der Straftäter ohne Psychopathie hingegen zeichnete sich nur ein verminderter Kontext-Effekt ab (Kapitel 7 und 8). Unabhängig von der möglichen Alternative stieg die Ablehnungsrate von unfairen Angeboten, wenn diese von Spielern unterbreitet wurden, die wütend (und nicht fröhlich oder traurig) aussahen (Kapitel 9). Obwohl sich bisweilen ähnliche Entscheidungsmuster in den psychiatrischen Stichproben wie bei gesunden Probanden zeigten, bleibt zu vermuten, dass auffällige Verhaltensunterschiede, wie z.B. eine höhere Ablehnungsrate bei depressiven Patienten, auf grundlegendere Prozesse in der Wahrnehmung und Einschätzung von sozialen Informationen zurückzuführen sind.

Sozial handeln beginnt mit dem Individuum und seinen persönlichen Eigenschaften und Erfahrungen. Vor allem das Verhalten unserer Handlungspartner bringt weitere soziale Faktoren ins Spiel, die verarbeitet und beurteilt werden müssen. An dieser Verarbeitung sind die Amygdala und andere Strukturen unterhalb der Großhirnrinde beteiligt, deren Aktivität durch Hormone beeinflusst werden kann. Gleichsam können die Herangehensweise und das Erleben von sozialen Situationen durch das Vorliegen von psychischen Störungen verzerrt werden. Hierbei ist es wichtig, sich der verschiedenen Bedeutungen und normativen Bewertungen des Wortes "sozial" bewusst zu sein. Im zwischenmenschlichen Umgang gilt "sozial" oft als positiv oder prosozial. Dabei umfasst soziales Verhalten jegliches Verhalten, das sich an ein anderes Individuum derselben Spezies richtet – gleich, ob prosozial oder antisozial. Die Einstufung von Verhaltensweisen als "sozialer" und wünschenswerter als andere wird besonders in den Lobeshymnen auf Oxytocin als "prosoziales Hormon" oder "Molekül der Moral" deutlich, welche in Anbetracht der großen Bandbreite von sozialen Verhaltensweisen bei Mensch und Tier einseitig wirken. Dies kommt im englischen Titel Acting social zum Ausdruck, da acting nicht nur handeln, sondern auch schauspielern oder vortäuschen bedeuten kann, und wird weitergesponnen durch die beiden Gestalten des Titelbildes, die sich der Etikette der britischen Teesitten entsprechend darstellen. So veranschaulicht die vorliegende Arbeit äußerlich wie inhaltlich das breite Spektrum an Verhaltensweisen und Erscheinungsformen, wenn wir sozial handeln.

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