GENDER, COMORBIDITY & AUTISM

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GENDER, COMORBIDITY
&
AUTISM

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General introduction

1. Background

This research was inspired by my observations, working as an addiction psychiatrist, that addiction and developmental psychopathology frequently co-occur. The group of developmental disorders consists of attention deficit (hyperactivity) disorder (AD(H)D) and autism spectrum disorders. The relationship between impulsiveness and thrill-seeking in attention deficit hyperactivity disorder (ADHD) and in substance-use-disorder (SUD) is well-known, but the relationship between autism spectrum disorders and addiction has barely been accounted for in the scientific literature. Yet, in our clinics we noticed that addiction is comorbid not only with ADHD but also with autism. It occurred to us that the group-treatment approach in addiction-care frequently revealed odd and socially awkward individuals who found it very difficult to function within a group. Most of these subjects were subsequently diagnosed with autism. Furthermore, this research fits well with the current trend, within the broader field of psychiatry, to recognise that developmental disorders are of interest not only during childhood, but evolve in clinically significant manners, well into adulthood.

Strikingly, in our first clinical study on comorbidity between substance use disorder (SUD) and developmental disorders, comorbid autism spectrum disorder (ASD) was identified only in men. I was very much puzzled by this finding until I came across an impressive patient. She was a young woman with complex symptoms along with a series of addictions. She had been given many
different diagnoses such as borderline personality disorder, posttraumatic
stress disorder (PTSD), ADHD, until she was finally diagnosed with autism.
Approaching her symptoms from the point of view of autism and thus offering
her adequate treatment led to a great clinical recovery and gave her far more
quality of life. The question that kept puzzling me was why it took so long to
make the correct diagnosis and acknowledge the fact that her autistic features
were expressed in a misleading variety of morbid expressions such as addiction,
anxiety, social fear and a rigid compulsivity. This particular case formed the
starting point for the present studies.

Before formulating the aims and research questions involved in this thesis, I
explain in short how autism is currently defined focussing too much on male
gender, how comorbidity in autism spectrum disorders is conceived and how
the role of gender needs re-considered. I shall therefore, describe in more
detail the patient that triggered my scientific interest in teasing out the issue of
developmental disorders and gender and indirectly lead to my thesis.

1.1. Autism Spectrum Disorders (ASD)

Autism spectrum disorder (ASD) represents a set of heterogeneous
developmental disorders that all have in common A) impairments in social
interaction, verbal and non-verbal communication and B) repetitive and
stereotyped behaviour (DSM-5; 2013). The disorder is traditionally thought to
have a substantially higher prevalence in males, with a male to female ratio of
4.3:1 (Fombonne, 2003) and a prevalence of 60-70/10,000 (Fombonne, 2009).
Subsequently research on ASD has predominantly been performed in males.
The assumption has mostly been that the etiology and presentation of ASD in
males is similar to that in females. There is, however, growing evidence that the clinical presentation is different in females as compared to males (Holtmann et al. 2007; McLennan et al. 1993; Tsai and Beisler 1983). Some authors argue that the phenotypic gender differences may cause delays in diagnosing (Rivet and Matson 2011b). Moreover, the gender difference in clinical presentation may lead to misdiagnoses and false negatives of the diagnosis autism all together (Rivet and Matson 2011b).

So far, only a small number of studies have investigated phenotypic gender differences in ASD and the findings on gender differences are inconsistent. While some authors reported girls to have more social problems and to be less able to engage in social play and social imitative play than boys (Holtmann et al. 2007; McLennan et al. 1993; Tsai and Beisler 1983), others did not observe gender differences in social behavior or instead observed better social behavior in girls than in boys (Banach et al. 2009; Carter et al. 2007; McLennan et al. 1993). Reports on communication patterns are also discrepant. In some studies, girls are found to have less expressive and less advanced receptive language skills (Carter et al. 2007; Holtmann et al. 2007), while other studies did not find any differences (McLennan et al. 1993). In addition, some studies found repetitive and stereotyped behaviors to be less common in females than in males (Bolte et al. 2011; Hartley & Sikora 2009; McLennan et al 1993), whereas three other studies did not find any gender differences in this domain (Banach et al. 2009; Carter et al. 2007; Holtmann et al. 2007).

All in all, it is fair to state that findings regarding gender differences in the core triad of impairments in ASD remain ambiguous. One of the reasons for this ambiguity could be due to the inclusion of participants with different age ranges across the studies. The age of participants may indeed influence
potential gender-related differences in the symptom presentation of ASD, as there is some evidence that age plays a gender-specific role in symptom severity. For example, two studies found that ASD is detected earlier in infant girls (with concurrent intellectual disability) than in infant boys (Ozonoff et al. 2010; Rivet and Matson 2011b). Whereas other studies found that mild autism is diagnosed far later in high functioning females than in males (Shattuck et al 2009; Begeer et al. 2013). Several studies suggest possible deviations in the specific presentation of social and verbal abilities in girls as compared to boys with ASD. Substantial variations in the frequency of reported additional problems also seem to play an important role in the longer delay between the start of parental concern and finally making the diagnosis in girls with Asperger’s syndrome (Kopp and Gilberg 2011; Dworzynski et al 2012; Lunégård et al 2011). These recent studies thus support the above-mentioned hypothesis that ASD is often diagnosed in an early stage in females presenting with classic symptoms and intellectual disability, whereas the diagnoses can be for long missed in females with a higher IQ or with less extreme stereotypies and clearly at a young age do not meet criteria as defined for boys.

In sum, there are indications that there are gender differences in presentation of core symptoms of ASD and that both age and IQ influence these gender differences in their symptomatic expression, also referred to as phenotypic gender differences. Yet, little is known about the development of the phenotypical presentation due to a lack of longitudinal studies taking into account girls that later in life were diagnosed with ASD. This was the reason for us to perform a systematic review and meta-analysis to investigate possible gender differences in the core symptoms of ASD from infancy to adulthood as
well as a follow up study on gender differences in phenotypical presentation of ASD in toddlers as they grow into childhood.

1.2. Comorbidity in ASD

As in many other psychiatric disorders, autism spectrum disorders are frequently comorbid with other psychiatric conditions. Lifetime psychiatric comorbidity may range up to be present in 70-100% of patients with ASD (Rosenberg et al. 2011). Psychopathological problems most commonly co-occurring with ASD include: both internalizing disorders such as anxiety, obsessive-compulsive, mood and externalizing disorders such as ADHD, aggressive behavior as well as disturbances in sleeping and eating patterns (Rosenberg et al, 2011).

Internalizing comorbidity:

Anxiety disorders, for instance co-exist with ASD in 30-50% of autistic subjects (Simonoff et al. 2008). This includes specific phobias (30%), obsessive-compulsive disorders (OCD) (17%), social anxiety disorder and agoraphobia (17%), generalized anxiety disorder (15%), persistent separation anxiety (9%), and panic disorder (2%) (van Steensel et al. 2008; Kanne et al. 2009). Diagnostic difficulties are associated with co-existence, overlap or false identification of symptoms of social anxiety and OCD in ASD subjects (Kanne et al. 2009)

The frequency of depressive episodes in children with ASD appears to be extremely variable, with estimates ranging from only 1.5% up to 38% (including up to 10% of major depressive episodes). In contrast, the variation in prevalence of bipolar disorders is estimated only to be 2.5-3.3% (Ragunath et al. 2011). As is the case for comorbid anxiety disorders, diagnostic difficulties
result from overlap of symptoms, inaccurate interpretation of the child’s
behavior and his/her communication dysfunction (Ragunath et al. 2011).

*Externalizing disorders:*

30% of children with ASD meet the diagnostic criteria for ADHD, and another
25% demonstrate subclinical symptoms of this disorder (Grzadzinski et al.
2011). Co-existing ADHD symptoms are associated with more severe problems
with verbal working memory, executive dysfunction, disturbances of
organization and planning skills, externalizing behaviors and more disabling
core symptoms of ASD (Grzadzinski et al. 2011; Sinzig et al 2008).

In conclusion comorbidity in ASD is thus rather common. The question is: are
the so called “comorbid” conditions separate or could they be different
expressions or understandable complications of the core disorder? In order to
address this question, it is important to discuss the different developmental
mechanisms that lead to phenotypical psychiatric disorders, and subsequently,
to consider how these developmental mechanisms provide insight into the
variation in clinical presentations across the autism spectrum.

1.3. The clinical perspective:

In our addiction psychiatry clinic we noticed that substance use disorder (SUD)
in ASD patients is not uncommon. We also noticed that in many instances, the
presence of SUD somehow withheld clinicians from diagnosing ASD. One of the
reasons is that ASD symptoms, such as rigidity and social impairment are easily
mistaken for consequences of severe SUD. However, what remained unexplained was why we didn’t immediately notice the combination of ASD
and SUD in women.
Mary was our first patient who, after a long period in which she had several diagnoses, and treatments, was finally diagnosed with ASD. In that respect she triggered me to start this study.

Clinical vignette

Mary was 22 years old when she was first referred to our clinic. She had already had several unsuccessful treatments in other addiction clinics before she was referred to our clinic for the treatment of SUD, PTSS and borderline personality disorder. She was addicted to heroin, cocaine and also used cannabis, XTC, speed and alcohol on a regular basis. She first started using drugs when she was 14 years old. Mary had been physically abused by her father. At the elementary school she had aggressive outbursts, which disappeared at the age of 10. At the same time a 16-year-old boy from the neighbourhood began sexually abusing her. Later, in high school, she also was sexually abused by one of her teachers.

After detox, Mary was a very anxious, shy, chaotic, restless and clumsy young woman who had difficulties expressing herself in the group. She didn’t interfere a lot with the group yet she was not a real loner. The group members instantly liked her.

One poignant habit of Mary’s was to take showers many times a day. Both her shyness as well as her frequent showering were interpreted as a consequence of her history of sexual abuse. During her treatment in our clinic, we did not observe any symptoms to confirm the diagnosis borderline personality disorder. Due to her chaotic and clumsy behaviour, added to a hetero-anamnestic confirmed history of lifelong concentration problems and hyperactivity, we first performed a standardised clinical assessment on ADHD, which confirmed the presence of ADHD. The ADHD
as well as the PTSD were treated according to the state of the art. Unfortunately, after a short period of improvement, her situation worsened: Mary became afraid of leaving the clinic and spent an great deal of time alone in her own apartment, that her parents had arranged for her, thus avoiding the necessary steps to build up a social life, or in fact any activities outside the clinic. She became more and more anxious, with increasing insomnia and nightmares and coincidentally she developed more compulsive behaviour such as showering even more often and for a longer time than before and did it according to a specific and strict ritual. She also started sticking to specific rituals for getting dressed or leaving the apartment. The staff observed these changes and felt increasingly concerned about how to turn this situation for the better. It was in the face of these concerns that I started to explore with Mary her anxiety, her shyness, her reservations about meaningful friendships and family bonds and why she had not succeeded in looking for let stand finding a job. It emerged that she simply didn’t know how to live her life. She had difficulties interpreting social situations and was afraid of new situations. Her lack of imagination made it impossible for her to anticipate correctly. It became clear why she was so vulnerable for sexual abuse: she had misinterpreted the intentions of that boy and her teacher. She did not dare to say “no” to the offenders because she thought that she had to comply to meet their expectations and was also afraid to lose their friendship.

At this point it first occurred to me that she could be autistic. Her early history revealed that all these problems already existed all her life and after a standardised assessment according to the Dutch Guidelines ASD diagnosis was confirmed.
This vignette highlights that shyness and a variety of psychiatric symptoms may mask the ASD in women. Intelligent females with ASD, (high functioning (HF) girls, appear to look carefully at what other girls their age do. They are eager to be accepted and to reach that goal they tend to copy the other girls behaviours and thus try their very best to fulfil the expectations they think others have of them and this makes them vulnerable to (sexual abuse). If they cannot manage to meet the supposed expectations because it causes too much anxiety, they disengage from social contact or start using drugs to help them overcome their fear.

As Mary appears to be by no means unique, this led us to look more closely at ASD in high functioning girls and women with ASD to find out why they are misdiagnosed with often such dramatic consequences.

1.4. Gender and (psycho)pathology

All (psycho)pathology can be considered to be developmental and the outcome of permanently ongoing nature (constitution: resilience and risk) - nurture (environment: protection and stress) interaction in other words an intricate “vulnerability – stress” interplay (Cicchetti & Toth 2009).

Several recent studies show the influence of sex on brain structure and functioning and consequently, on the susceptibility for, prevalence of and response to treatment of psychiatric disorders (Cahill, 2012; Fernandez-Guasti et al., 2012; Franconi et al., 2012; Hasson & Fine, 2012; Jogia et al., 2012; McCarthy et al., 2012; Nolen-Hoeksema, 2012; Simpson & Kelly, 2012; ter Horst et al., 2012; Valentino et al., 2013). So all levels (genetic, epigenetic, brain,
neurocognitive and behavioral) of functioning are not only influenced by the environment but also by gender (Joel & Yankelevitch-Yahav 2014).

In our study we explore gender-related differences in the way subjects with autism respond to stress, i.e. their coping style and the way in which this is related to their broader developmental context. Furthermore, we looked into the subsequent expression of (psycho)pathology wondering why addiction appeared so often in our exploration as comorbidity?

2. Aim and research questions

The aim of this thesis is to further our understanding of the different developmental mechanisms and the role of gender in psychiatric disorders focusing on autism spectrum disorders.

We address the following research questions:

1) Which developmental conditions are comorbid with addiction?
2) Which developmental mechanisms lead to phenotypical psychiatric disorders?
3) What is the influence of gender on the development of psychopathology?
   3.1) What is the role of gender in gene-environment interactions?
   3.2) Are there gender-related neurobiological differences in the development of stress regulation mechanisms, and if so, what are their consequences for the expression of (psycho)pathology?
   3.3) Can gender be considered as a “social cause” of (psycho)pathology?
3.3a How does gender impact the way subjects express their emotions?
3.3b What, if any, is the influence of gender-specific childrearing in the development of psychopathology?

4) What are the gender differences in the expression of the core symptoms of ASD?
5) Gender differences in preschool children
   5.1) What are the gender differences in ASD in very young children?
   5.2) How have these differences evolved when these children are followed up three years later?

3. Outline of the thesis

After a general introduction (chapter 1), we present the first study on the comorbidity between substance use disorders and ASD. We performed a literature study on the similarities between addiction and ASD (at a phenotypical and neurobiological level) as well as a case note review on a year cohort of 200 consecutive admissions in an adult addiction psychiatry unit (chapter 2).

We performed an extensive review of relevant literature to help us understand the nature of the complexity of diagnosis in relation to development, (chapter 3). This changed our view on psychopathology. In a broader scope developmental aspects and the relationship between clinical phenotype and underlying (epi)genetic phenomena should be taken into account.
Chapter 4 addresses the issue of the specific role of gender in this process.

Throughout the project, we became particularly interested in the poignant gender differences in autism. We start with a meta-analysis of all the studies exploring the gender differences in the expression of the core symptoms of ASD (chapter 5) in a study titled: “Gender and Age Differences in the core triad of impairments in ASD: a systematic review and Meta-analysis”.

Finally we zoom in on gender differences in developing subjects with ASD (Chapter 6). For this study we used a sample of male and female infants screened positive for ASD in a general population screening recruitment over two Dutch Provinces followed by a clinical assessment and a systematic follow-up three years later

In the final chapter (Chapter 7) the conclusions are discussed and translated into implications for clinical practice. In this general discussion we also reflect on directions for further research into the important relation between gender and developmental (psycho)pathology.
References


Chapter 2

Addiction and Autism: A Remarkable Comorbidity?

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A remarkable comorbidity: Addiction and Autism

Abstract

Objective

Autism spectrum disorders (ASD) are well known for high prevalences of comorbid conditions especially anxiety, obsessions, depression, challenging behaviours.

In this article we will consider the evidence for comorbidity between ASD and Addiction (Substance Use Disorders (SUD) and explore the possible underlying explanations.

Methods

A literature study on similarities between Addiction and ASD (at a phenotypical and neurobiological level) as well as a case note review on a year cohort of 200 consecutive admissions in an adult addiction psychiatry unit.

Results

In our survey 8 (men) on 118 patients were diagnosed with autism spectrum disorder. This is much higher than in the general population (1%)

Autism spectrum disorders and addiction can both be perceived as developmental disorders in which a genetic predisposition and vulnerability interact with environmental factors. They can be induced by early stress thus affecting the proper functioning of the cortico-striatal dopaminergic regulation systems (and also the HPA axis). In “pure” ADHD this is attributed to a deregulation in the cognitive loops and the “impulsivity” endophenotype.
Whereas in cases of ASD without an ADHD component the limbic and sensimotore cortico-striatal regulations loops are also involved.

**Conclusions**

There are clear indications that a possible comorbidity of substance abuse disorder should be considered in cases of individuals with autism spectrum disorders. This finding is important for clinicians to take into account in assessing patients with addiction problems and ASD.

Keywords: Addiction, SUD, ASD, autism, dual diagnosis,

**Introduction**

When one thinks of a person with addiction, a person with autism spectrum disorder (ASD) is not the first one that come to one’s mind. Conversely in autism substance use disorder (SUD) is not the comorbidity that is commonly considered. Yet these conditions have more commonalities than one would suspect. In this article we will consider the evidence for comorbiditiy between ASD and SUD and explore the possible underlying explanations. From a neurobiological point of view there are some stricking overlaps between both conditions that could account for the enhanced mutual vulnerability making it clear that the dual diagnosis ASD/SUD is not merely a matter of chance. First let us begin with some clinical vignettes to make our case.

Peter an overlooked case of marked autistic rigidity:

Peter was 20 years of age when he was admitted to a detox with a serious addiction to alcohol and features of a cluster B personality disorder. He was pretty aggressive and would express both verbal and physical aggression when
hindered by his parents or others to consume alcohol. The detox did not pose any problems. These occurred when at the start of the rehabilitation he was assigned tasks in the group. Thus he was asked to do the shopping that day. The therapeutic goal is to learn how to perform tasks within a certain time frame, and take responsibility for oneself and others. He managed to get the shopping done in time but was tidying them at the time he was expected to join a group therapy session. When one of the nurses confronted him, he went out of his mind, became very aggressive and bashed doors and broke windows whilst threatening the nurse verbally. Due to this unacceptable behaviour he was dismissed from the program immediately. A week later he came back to our outpatient clinic and was asked what had happened and had caused his extreme reaction. He said that he became very angry because the nurse had interrupted him. For him it was inconceivable that he should have joined the group leaving his task unfinished. In the clinical interview it became clear that these rigid patterns of behaviour, his incapacity to communicate and an impaired social sensitivity had been characteristics during his whole development. Alcohol helped him to ease the path towards encountering others. A thorough assessment including interviews with his parents and reading school reports conform a diagnosis of Asperger’s within ASD. Once approached as such this difficult to handle older adolescent, became compliant and well willing.

Sarah: a preoccupation run out of hand.
Sarah is a 14 year old adolescent diagnosed with Asperger’s. At the elementary school she was well accepted as a pedantic eloquent clumsy girl with a special interest for all that was related to nature. She collected leaves and feathers and always had a tame mouse under her pullover. She was left alone and no one
ventured to tease or bully her. She did well and went to the gymnasium the highest secondary school type in our country with latin, greek and sciences. Her interest shifted from nature to gaming. She would spend hours in a row, playing games and chatting with virtual friends. Once in a while these would organize meetings. There she met people who drank and blew. She liked it because it helped her overcome her shyness. The group went on and experimented with speed. Her parents are amazed to witness a metamorphosis from socially aloof towards suddenly, spending time with “friends”. One day they get a phone call from the police. Their daughter has been arrested for dealing drugs. She has been used and (sexually) abused by dealers, and used as a drugs courier. She confessed in a very naive manner, once in the detox, that she thought these were her first real friends and would do anything to be their friend. Once in detox she reappeared to be the socially isolated and clumsy intelligent young girl.

*Autism and addiction in the field of addiction psychiatry:*
It is well accepted that the prevalence of comorbid (developmental) psychopathology in addiction care units ranges from 60 up to 90% (Couwenbergh et al. 2006) have dual diagnosis. In addiction units group approaches are greatly favoured. After detox patients can support each other in order to help them cope with craving and relapse. They also share in anticipating which pressure they will have to face when returning to their own social environment where peers are still using drugs.

Yet within these clinical settings a number of patients were observed that did not seem to fit in the group model. These loners can disrupt the group processes. They miss the point, cannot enjoy jokes and humor. They stick in a rigid way to rules they take literally and get upset by all the exceptions that are
made. For this reason we performed a survey in our clinic on a random cohort of subsequent admissions over a period of a year years. To assess for developmental disorders we used the standard diagnostic tools recommended by our national guidelines. In this study 8 (men) on 118 patients were diagnosed with autism spectrum disorder (table 1). This is much higher than in the general population (Baird et al. 2008) and difficult to compare to the prevalence within psychiatric populations as no studies as such have been published to the best of our knowledge. Yet beyond our own research group (Sizoo et al. 2010) this dual comorbidity had not been reported until recently (Singh et al. 2012) The other dual diagnoses in our cohort are in line with what is reported elsewhere: mostly externalizing disorders (conduct disorder and anti social personality disorders and ADHD) and along with depressions and psychoses. Though it must be noted that ADHD and ASD present a clinical and genetic overlap up to 20 to 40 % (Schubiner 2005).

Table 1: Diagnoses and Types of SUD

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>Sex (%)</th>
<th>SUD per diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>ADHD</td>
<td>36</td>
<td>31</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>30,5%</td>
<td>35,7%</td>
<td>16,2%</td>
</tr>
<tr>
<td>ASD</td>
<td>8</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>6,7%</td>
<td>9,1%</td>
<td></td>
</tr>
<tr>
<td>Psychotic</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2,5%</td>
<td>3,4%</td>
<td></td>
</tr>
<tr>
<td>Internalizing Disorders</td>
<td>33</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>27,9%</td>
<td>25,3%</td>
<td>35,5%</td>
</tr>
<tr>
<td>Externalizing Disorders</td>
<td>38</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>33,2%</td>
<td>26,4%</td>
<td>48,8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>87</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>118</td>
<td>87</td>
<td>31</td>
</tr>
</tbody>
</table>
Addiction and Autism from the autistic perspective

Prior to 2005 apart from anecdotal reports like that by Kalat (1978) and heavy drinking in a couple of cases in a follow-up study (Tantam 1988) no mention is made of any comorbidity between autism and addiction. There are however a number of autobiographic accounts that illustrate the case. For example Gunilla Gerland in her book A Real Person: Life on the Outside 2035, describes her addictions an how she felt at ease in the drugs scene where contacts were functional and communication explicit with clues and prompts. Many of the behaviours she describes are reminiscent of preoccupations, trance like repetitive behaviours and obsessions as described in young children with autism (Nelson & Panksepp, 1998). When asked, clinicians working with people with autism confess that the possibility of a co-occurrence of autism and substance abuse, never crossed their mind and they thus never questioned in that direction.

Similarities between Autism and Addiction

At a phenotypical level:

In the domain of Perceptions: it appears that both ASD and Addiction are strongly dopamine related neurobiological brain disorders (de Lange et al. 2010). But also at a behavioural level there are similarities at the level of detailed perception and habits. In autism a different “central coherence” explained the extreme focus on (visual) details. Moreover they develop strong interests called preoccupations and rigidly stick to them. They help them regulate their hypersensitive state of arousal, as some of them also do by repetitive motor stereotypy’s that bring them in trance like conditions. Likewise one of the characteristics of substance abuse is the extreme preoccupation with the substance or habit (gambling, stalking, sex) they are
addicted to. They tend to focus on small details related to their using habits. For example the sight of aluminium foil that can activate craving in (ex)heroin addicts even after years of successful abstinence.

Problems in the domain of Social Sensitivity: obviously people with autism have problems with social reciprocity as from a very young age. In people with addiction behaviour these problems may emerge when the substance dependence and the loss of control impends on their ability to relate to others. In some individuals with addiction this problem may subsist after detox thus pointing towards a possible underlying ASD whereas in the majority of cases addicts recuperate their social skills after a successful detoxification.

Substances may facilitate social engagement. Many individuals were shy and used substances to help them cope with tension in social encounters. Likewise individuals with ASD may experience the benefits of using substances in order to help them in more complex social situations. In addition there appears to be a high association with affective disorders e.g. depression (Bolton et al. 1998). Depression appears to be far more prevalent in families with autism than in the general population and in families with substance abuse (Boden & Ferguson 2012; Cottencin 2009).

*Neurobiological similarities*: Are these behavioural similarities the expression of common neurobiological roots? Recently de Lange and her colleagues (de Lange et al. 2011 - 2012) showed an overlap in dysregulation of the limbic cortico-striatale circuits between individuals with addiction, and obsessive-compulsive disorder, and ADHD and autism, both in animal and human studies. From an evolutionary point of view both addiction and autism appear to be deviances of normal adaptive coping strategies for the individual and the species (Weiss et al. 2007). To illustrate this point some examples: Salience and
focalization on smell cues plays a core role in primary attachment a vital behavioural pattern that enables the child to survive by seeking food and comfort with his mother. This preponderance of focus on smell and oral exploration persists in people with autism and characterizes individuals with addictive behaviour (Goldstein & Volkow 2011). The so-called “autistic condition” (Baron –Cohen 2010) refers to the evolutionary advantages of “extreme male thinking” perseverance in scientist and engineers in digital thinking that gives them great reward. E.g. using drugs/doping to pursue one’s goals thus taking the risk of getting addicted in the process.

People with ASD have these hypersensitivities for which their normal arousal regulation is insufficient. In order to cope with these situations where they tend to get overwhelmed by stimuli, they develop strong hyperfocalisations and/or stereotypy’s, that give them a frontal dopamine depletion that gives them a pleasant relaxation and helps them to cope.

In addiction a genetic vulnerability (Le Merrer et al. 2009) implying a lower density of dopamine receptors in their central reward system makes them less sensitive to “typical” rewards, making them easily bored and dependant on stronger thrills to stronger stimulate and thrilling sensations. At a behavioural level the obsession with the substance or behaviours becomes more intense as the addiction progresses reducing their other activities and social life, to a point that they drop out from normal society.

In individuals with ASD a longing for social contacts, an urge for getting out of isolation emerges in adolescence. Yet they are hindered in this striving by their social awkwardness and lack of sensitivity as to how to tune into the intentions and needs of others. This process is often frustrating and many experiences
that alcohol, cannabis or stronger drugs ease the path into participating in social group activities. Moreover there are similarities at a genetic and en psychophysiological level that may contribute to explaining the high vulnerability for addiction in autism. A series of studies demonstrate that a strong dependence on endogene opioïds in individuals with ASD (Buitelaar e.a., 1990; Nelson & Panksepp, 1998) These morphine like substances produced in the brain to help coping with stress are also depleted by activities that induce “virtual stress” like running or repetitive movements (stereotypes and preoccupations in individuals with ASD – trance like activities as dancing). These effects have also been described with regard to the neuropeptid oxytocin in autism: detailed perception, rigidity obsessive preoccupations and lack of habituation (Gurreri et al 2009). Finally, a paucity of dopamine sensitivity appears to play a role in different characteristics in autism related to regulation problems at a cognitive and emotional level (Dawson e.a., 2005; Guilloteau, Chalon, 2005; Salgado-Pineda e.a., 2005) and involved in stereotypes and preoccupations (Lavolia e.a., 2004). This paucity predisposes to the search for stimuli and substances that favour dopamine depletion a mechanism well described in the development of addictive behaviour (Volkow 2005)!

Thus autism spectrum disorders and addiction can both be perceived as developmental disorders in which a genetic predisposition and vulnerability plays a role, that can be induced by early stress (not understanding the surrounding environment, traumatisation and bullying) and exacerbated by current stress (anxieties, social isolation) thus affecting the proper functioning of the cortico-striatal dopaminergic regulation systems (and also the HPA axis). In “pure” ADHD this is attributed to a deregulation in the cognitive loops and
the “impulsivity” endophenotype. Whereas in cases of ASD without an ADHD component the limbic and sensimotore cortico-striatal regulations loops are also involved (de Lange et al. 2011)

Conclusions and implications:
This preliminary report intends to raise awareness on an unexpected and remarkable comorbidity, namely that between autism spectrum disorder and addiction. Yet in clinical practice it is very well possible that the diagnosis autism spectrum could be missed in addiction psychiatry units. Conversely many addicted individuals with autism spectrum disorders may go unnoticed and thus ill treated within services for autism, because of a lack of knowledge
about this possible comorbidity and the implications for guidance and treatment.

There are obvious limits to the present report: we now have an estimate of the occurrence of autism as a dual diagnosis in addiction, but they need yet to be confirmed, let stand on the prevalence of addiction in the autism spectrum population (that may or may not exceed the prevalence of addictive behaviour in the general population as reported by ESPAD (10-15%). But there are good neurobiological grounds to expect the ASD SUD comorbidity to be high but obviously further studies will be necessary.

The implications of our findings are that specialized services in addiction and developmental disorders should be aware of the likelihood of this comorbidity. Thus educating professionals will be of uttermost importance as will be offering the assessment tools available to ensure accurate diagnoses. This will prove helpful too in clinical guidance. In addiction units patients with ASD will need individual programs and explicit and well structured communication. In all cases the patients and teams will need to take into account that addictive behaviour in individuals with ASD stems from a longing for social contacts, that should not be frustrated by detox and relapse prevention, but taken very seriously and addressed in a proper fashion with teaching skills and relaxation techniques that can replace in a fruitful manner the need for substances or detrimental habits to facilitate social contacts and ease communication.
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Chapter 3

A fresh look at psychiatric disorders

Changing views on morbidity and comorbidity in psychopathology

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A fresh look at psychiatric disorders
Changing views on morbidity and comorbidity in psychopathology

Abstract

Background

The a-theoretical approach to psychiatric disorders, introduced via DSM-III, has had a tremendous impact on the way in which we classify psychiatric disorders. It has stimulated a large body of research, facilitated by the concurrent development of new techniques in genetics, neuro-imaging and neuropsychology. However the research results of the last twenty years or so, have cast doubt on the validity of the clinical categories set out in DSM-III

Aim

To develop a new view on developmental pathways in psychopathology, clinical assessment and scientifically acceptable classification of psychopathology.

Method

In this article we review the state of the art with regard to underlying endophenotypes at the level of brain and neurotransmitter functioning and neuropsychology in psychopathology and we consider the effect of social determinants on the development of psychopathology
Results

Our results show that neither genotypes and endophenotypes, nor brain mechanism, nor neuropsychological deviances provide evidence for a one-to-one correlation with clinical categories in even the DSM-5.

Conclusion

DSM-5 provides a range of possibilities for classifying psychiatric disorders at a symptom level. But these categories seem to be less distinct than was at first assumed. Recent research has shown that there is a great deal of overlap at the genetic, epigenetic and endophenotype levels. This calls for more emphasis on individual assessment and diagnostics in both clinical practice and scientific research. More attention needs to be given to the dimension of emotions and behaviour, vulnerability and resilience. This type of approach, involving genotypes, endophenotypes, epigenetics and brain-functioning, could help elucidate the interaction between these various levels and/or explain the underlying mechanisms of psychiatric disorders.

Keywords: classification – development – genetics – neuro-imaging – neuropsychology, psychiatric disorders
Introduction

The revised DSM-5 (DSM-5; 2013) represents the state-of-the-art classification of psychopathology. This long-expected revision incorporates insights from the latest neurobiological and behavioral studies. The writers of DSM-5 have opted for an approach that is both categorical and dimensional. The dimensional approach assesses the severity of psychopathology, providing a valid and accurate measure of functional and social impairments. Pre-emption rules, which in earlier versions of the DSM ruled out certain combinations of diagnoses, have been abolished, so that any imaginable “comorbid” conditions can be taken into consideration. These changes may be considered beneficial for both clinical and research reasons. On the other hand, adhering to a categorical system based on observable symptoms without any constraints on the combination of diagnoses harbours disadvantages. The psychiatric diagnostic assessment threatens to be reduced to a mere listing of symptoms and “positive” criteria. This could forfeit our understanding of why these particular symptoms co-occur in a patient under these specific circumstances.

In this article, we investigate whether DSM-5 does indeed reflect the state-of-the-art of clinical psychiatric practice and whether it opens the way to research that will provide a better understanding of psychopathology. To this end, we review recent literature on insights into morbidity and comorbidity. Finally we discuss the implications of our findings for scientific research and clinical practice in the field of psychiatry.
Changing views on psychiatric disorders

The a-theoretical approach to psychopathology in the successive versions of the DSM (i.e. DSM-III, DSM-III-R, DSM-IV and DSM-IV-TR) is based on the description of observable symptoms as the defining criteria for psychiatric disorders. This approach has tremendously stimulated research over the past three decades. Yet, this raises an important question: has the DSM’s approach increased our understanding of psychopathology now? To a certain extent it certainly has: technological advances, such as the unraveling of the human genome, the development of neuroimaging, and the in vivo assessment of neurotransmitters, have provided unprecedented advances. Our insight into the understanding of psychiatric disorders, as described in earlier versions of DSM have been profoundly altered. How have these changes contributed to the development of DSM-5?

Craddock and Owen (2010) propose to replace the traditional descriptive classifications by introducing an approach through “clinical entities” (both categories and dimensions) that are more strongly related to underlying brain mechanisms. They formulated a hypothesis to describe the complex connection between biomarkers and big categories of psychiatric disorders. They argue that one specific genetic predisposition can lead to a large variety of clinical expressions and that this does not fit well with the current classificatory categories in DSM-5. This hypothesis finds strong support in the recent findings that different psychiatric (developmental) disorders such as autism, ADHD, affective disorders and schizophrenia, have a common genetic predisposition or appear to be different expressions of common underlying vulnerabilities (Cross-Disorder Group 2013). Van Os (2009a; 2009b) likewise proposes to drop the current classificatory system based on clustered categorical features and
instead focus on common connecting endophenotypes. In this vein he proposes to replace the notion of “schizophrenia” by “salience-syndrome”. The commonality is a distorted perception of reality due to insufficient correcting cognitions: an endophenotype within disorders of perception.

In this way psychiatric disorders stem from distortions at different functional and structural levels of explanation. Between the genotype and the phenotype (the clinical expression) there are different intermediate levels (endophenotypes), such as neurobiological and psychological factors. These factors interact, leading to various clinical expressions. However, these genetic, neurobiological, psychological, and environmental factors do not fit exclusively in one diagnostic (phenotypical) category. The phenotypical classifications as defined in DSM-III have tremendously stimulated research but also raised some new questions. The question is whether DSM-5 took this progress seriously into account?

In this article we discuss the different developmental mechanisms that lead to phenotypical psychiatric disorders, to subsequently consider how this insight impacts our understanding of the stratification of clinical pictures.

**Psychopathology: the outcome of interactive developmental processes**

In 1995, Morton and Frith introduced a tiered model to explain the development of psychopathology (see Fig 1).
They defined three tiers: the organic level (genes and brain), the cognitive level, and the behavioral level. The model assumes that there is a linear causality in which the organic component induces a cognitive style that is responsible for the behavioral manifestations. There are three variants within this model. First, a single cellular defect (e.g. a trinucleotide repeat on the X chromosome) can affect cognitions (figure 1A) and become manifest in different behavioral phenotypes and this cluster of findings at different explanatory levels amounts to a syndrome called “fragile X”. A second variant is that one single neurocognitive abnormality (e.g. executive functioning defects) may arise from different organic causes and be expressed in different behavioral phenotypes (figure 1B). Finally various “organic” defects may give rise to different cognitive disturbances, leading to one single behavioural phenotype.
The Morton and Frith model reflects a new approach to understanding the development of psychopathology but over the past fifteen years the insights in developmental mechanisms have evolved. At present a stratification in five levels is the most favoured model: (1) a genetic level, (2) an epigenetic level, (3) a brain level (substrate – connectivity - neurotransmission), (4) a neurocognitive level and (5) a behavioral level (Cicchetti & Toth 2009). Moreover at all levels the interaction with the biological- psychological- and social environment influences development (Cicchetti & Toth 2009). In return the individual has a strong impact on his/her direct environment. This leads to an ongoing interaction between “nature-nurture”. The notion of interaction is an important addition to the linear causality expressed in Morton and Frith’s model. Genetic make-up and epigenetic changes influence the structural and dynamic development of the brain. The connectivity within the brain and the repartition of neurotransmitters are a result of this dynamic. The individual’s neurocognitive capacities are likewise the consequence of the interaction between the developing brain and everyday experiences. The outcome of the processes, which is also influenced by gender (Nugent & McCarthy 2010), expresses itself in (psychopathological) cognitions, emotions and behaviours. In other words: genetic and epigenetic deviances lead to “different” brains, which result in “different” behaviours and vice versa!.

The actual view is that causal pathways are by no means unidirectional, but that that there are continuous interactions and that the neurobiological and cognitive development are continuously influenced by external factors like interpersonal relationships and stress (Lenroot & Giedd 2011). This complexity is reflected in Figure 2. We will now explain this in more detail with illustrations of recent scientific findings.
Genetics

Genetic factors have been identified for various psychiatric disorders (Sullivan et al. 2012). However, the genetic transmission of psychopathology is by no means Mendelian. It has recently become clear that psychiatric conditions as different as autism spectrum disorders, ADHD, bipolar disorder, depression, and schizophrenia have common genetic roots (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013).

Studies involving monozygotic twins show that the concordance for a large range of diseases including cardiovascular risk, psoriasis, diabetes, and psychiatric conditions (autism, schizophrenia, bipolar disorders) never reaches 100% (Gray et al. 2007). Rather, the concordance rates vary from 30-40%,
reaching about 90% for autism (Rutter 2000; Ronald & Hoekstra 2011). Kendler (2010) and Dick (Dick et al. 2010) proposed that genes encode the vulnerability/susceptibility to develop a form of pathology rather than a specific disorder. This sheds new light on genetic influences on (psychiatric) disorders/diseases.

**Epigenetics phenomena**

Epigenetics is the study of changes in gene expression or cellular phenotype caused by mechanisms other than changes in the DNA sequence itself. For example, such changes may be due to aberrations in genetic transmission under the influence of external factors in utero, such as viral infections (e.g. rubella) (Carter 2009), toxic agents (e.g. alcohol; Paintner et al. 2012 2x), or thalidomide (Stephens et al. 2000). These changes may remain confined to one individual or become heritable. Spontaneous mutations are also possible (Huguet et al. 2013).

How do these (epi)genetic mechanisms play a role in the development of psychopathology? Genes influence the development of the brain, for instance by directing cell migration during embryogenesis (Meyer 2007). Mutations may also lead to neural malformations. Genes are also involved in synaptogenesis (Duman 2012). Once activated, neurons seek each other and interconnect via synapses to form functional circuits that are strengthened by experience. During the second year of life and in adolescence superfluous circuits are pruned through a process called apoptosis (programmed cell death). This enhances the formation and functioning of more efficient connections, that are
essential in order to realize an optimal adaptation of the individual to changing circumstances.

Epigenetic phenomena play a role throughout life. Genes can be switched on and off under external circumstances, for instance: melatonin production is dependent on exposure to sunlight (Holliday 1989). Life events or experiences too can influence gene expression. For example, recent studies show that bullying influences the configuration of the –serotonin-transport gene. This induces changes in the cortisol-response to stress in victims of bullying (Ouellet-Morin et al. 2013). Thus changes in gene-expression can occur, throughout life, under a wide range of (internal and external) circumstances which influence processes at any of the above-mentioned levels.

The Brain: functional networks, connectivity and neurotransmission

The third level in the cascade of factors involved in the development of psychopathology is the brain. The explosive growth of neuroimaging techniques (both structural and functional) has revealed the different ways in which the brain is involved in the development of psychopathology. Structural abnormalities are mostly genetic and/or develop prenatally. Postnatal anomalies are caused by trauma, destruction or neo-formations, whereas functional abnormalities emerge as a result of interactions with the (rearing) environment. They can manifest as deviant patterns of connectivity within brain networks. For example, individuals with autism display intense “local” connectivity, whereas the general population has a much stronger “global” connectivity (Just 2007). Likewise shifts in neurotransmitter activity may be at play in (psychiatric) disorders. There is evidence suggesting that this is the case.
for dopamine in Parkinson’s disease, ADHD, autism, and schizophrenia (Langen et al. 2011), and for serotonin in depression (Hirschfeld 2012).

Nobel prizewinner Torsten Wiesel was the first to demonstrate that the brain develops in an interactive fashion (see Hubel & Wiesel 2012). He showed that even if a brain structure was in place at birth, it would not develop unless adequately stimulated. Visual stimulation is crucial in order to develop the occipital cortex and connect the visual pathways. The brain develops throughout life in a highly interactive way, stimulated by interactions with the environment, generating neural circuits that are strengthened by rewarding experiences and weakened by negative experiences. Thus, in normal and deviant development, certain areas and circuits in the brain will be stimulated (just as muscles may become bigger as a result of training) whereas others will be less developed and may even shrink. There are definitely sensitive periods for optimal stimulation during development. When these windows of opportunity are missed, it may have life-long consequences for the individual (Hubel & Wiesel 2012). On the other hand, the tremendous plasticity of the brain provides both developmental alternatives and second chances (Caroni et al 2012). These “adaptations” in the brain may temper disorders, not because they make them disappear, but because the brain develops an alternative scenario, for instance in dyslexia (Eicher & Gruen 2013).

Alterations in certain parts of the brain do not necessarily manifest in a unique fashion. The amygdala and fusiform gyrus are important cerebral regions. They are involved in processing visual information about the perception and recognition of faces, emotions, and intentions of the others. Amygdala function is abnormal in conditions as diverse as anxiety disorders (Etkin 2010), autism (Volkmar 2011), depression (Hamilton et al 2012), addiction (Morikawa et al. 2012), and Alzheimer’s disease (Jack et al. 2011).
2011; 10), and also in schizophrenia (Chen 2012). This diversity suggests that different functional abnormalities give rise to different clinical phenotypes.

Neurotransmitters strengthen the connectivity of neural circuits in the brain, but the consequences of neurotransmitter abnormalities depend on the neural circuit involved. In their review article, Langen et al.(2011) explored the role of dopamine and serotonin in three distinct functional and anatomical frontostriatal regulatory loops in the brain. They showed how each of these neuronal loops can be linked to different behavioural anomalies. For example, dysfunction of the “sensorimotor” circuit was found to be associated with the emergence of Parkinson’s disorder, whereas dysfunction of the “cognitive-attentional” circuit was associated with impulsivity and concentration weaknesses, as seen in ADHD, and dysfunction of the “limbic” circuit was linked with addictive disorders.

By clustering these behaviours, Langen et al. developed a model which can explain that dysfunction of distinct systems may lead to distinct forms of pathology, but that they can also co-occur leading to specific clinical phenomena. Thus abnormalities in all three regulatory loops are involved in autism spectrum disorders (figure 3). This model fits with other studies that employ *diffuse tensor imaging* to show that frontostriatal connectivity is significantly different in individuals with autism spectrum disorders than in controls (Langen et al 2012; Groen et al. 2011).
ADHD Attention Deficit Hyperactivity Disorder
OCD Obsessive Compulsive Disorder
PD Parkinson’s disease
HD Huntington’s disease

Figure 3 Overlap in dopaminergic circuitry

Langen et al. 2011
In other words: disruptions in anatomical development and the functioning of specific brain areas are suspected to play a role in different psychopathological diagnostic categories but there is (as yet) no one-to-one mapping of anatomical and functional disruptions and clinical profile.

**Neurocognitive profile and information processing (endophenotype)**

Functional pathways in the brain modulate behaviour. The potentials of these pathways can be evaluated in terms of neuropsychological parameters, such as intelligence level and profile, executive functioning, central coherence, and social empathy through the *theory of mind*. Significant differences between verbal IQ and performance IQ can increase susceptibility to not only learning disabilities and but also different forms of psychopathology (Aarnoudsen-Moens et al. 2012). Also, changes within the verbal or performance profile may reflect neurocognitive difficulties related to certain neuropsychological (dysfunctional) endophenotypes. For example, marked differences between visuospatial abilities and cognitive flexibility influence executive functioning, which is needed for planning and organizing behavior and for adaptation (Slaats-Willemse et al. 2005).

These dysfunctional patterns of executive functioning (Rommelse et al. 2008) or of central coherence (Frith 2012) are by no means specific for a particular clinical entity but can be found in clinically disparate syndromes such as ADHD, autism spectrum disorder, schizophrenia, and depression. Moreover a similar endophenotype can be found in a well-functioning unaffected sibling (Rommelse et al. 2008).
In short, dysfunctional neuropsychological endophenotypes play an intermediate role between the genotype and the behavioural phenotype. However, there is no exclusive association with a specific clinical entity.

**Environmental factors**

The role of the environment in the developmental and causal pathways of all psychiatric disorders is often underestimated (Marmot et al. 2012). As described before, this interaction begins in the intra-uterine milieu, expanding in the course of development via emotional attachment and child rearing to the broader social context (friends, school, work and culture). The environment shapes an individual’s behavior by rewarding or correcting behaviors, thereby influencing that individual’s emotional response (Jones et al. 2011). The language and behavior of individuals in a child’s environment can be mirrored, imitated, and integrated into play and imagination (Rizzaloti et al. 2008). Interactions with adults or their peers provide infants and children with the opportunity to experiment and practice social role-play and help them to develop a pallet of communicative tools preparing them for adulthood. These patterns are anchored in neural networks. The (mental) health of an individual will be strongly determined by his/her ability to adapt to circumstances in their psychosocial environment.

Genetically vulnerable individuals will develop less resilience and flexibility and are more likely to get trapped in dysfunctional emotional and behavioural patterns. How (psychiatric) disorders manifest is the result of the interplay between genetic-, gender- and environmental influences (see figure 2). Fortunately, besides these risk factors, there are also environmental and
constitutive protective factors (2006). As a consequence, the phenotypical expression will vary considerably from one individual to the other.

**Implications for clinical practice and research**

Technological progress and solid research based on the new a-theoretical approach introduced by DSM-III have opened new perspectives to a better understanding and insight in the underlying factors that play a role in healthy as well as in (psycho)pathological development. This insight involves not only genetic factors but also neurobiological and psychological causal factors. Unfortunately, there does not appear to be a one-to-one relationship between these factors and current (or previous) diagnostic categories. As a consequence one may question the scientific validity of these categories in the current classification systems and it raises the question of whether the approach to diagnostics and classification should not be profoundly reconsidered for the sake of scientific progress.

DSM-5 shows a prudent shift: besides its categorical approach, dimensions have been added in order to take into account the notion of disease burden and social dysfunctioning. The different DSM committees have deemed it too early to add to this neurobiological or psychological characteristics. On one hand this is understandable: the genetic and neurobiological and psychological markers are still neither sensitive nor specific enough. On the other hand, I claim that there are sufficient available biomarkers.

There are indications that fatty acid omega-3 supplements help decrease psychotic complaints for a subgroup of patients with schizophrenia. This subgroup appears to have a genetic defect that is related to the transformation
of these fatty acids. This genetic defect could be employed as a biomarker that divides the group of people that we regard as suffering from schizophrenia into subgroups based on their genetic make-up (Akter et al. 2012). Likewise eye-tracking data in young children with autism predicts better outcome at follow-up on the Autism Diagnostic Observation Schedule (ADOS-G) (Falck-Ytter et al. 2013). In other words, there are (promising) indications of biomarkers, but these do not follow the divides between classificatory categories in the current DSM which are based solely on clinical observation.

DSM-5 has opted for a hybrid solution. Based on this review we call for a reconsideration of this approach to psychiatric disorders. We suggest focusing more on individualized diagnostics (van Os et al. 2013). This would allow for more attention for dimensions of emotions and behaviour and take into account central factors such as vulnerability and resilience. Such an approach via genotypes, endophenotypes, epigenetics and brain functionality, could contribute to understanding the interactions at different levels of explanation, in other words help to elucidate the underlying mechanisms of psychiatric disorders.

Research could then focus more on groups defined by common genotypes/endophenotypes instead of adhering to the current clinical syndromes. Clinicians should be more aware of developmental- and interactional-features of psychiatric disorders and include them in their assessment of their patients. They could enrich their diagnostic assessment by an ongoing process of evaluating strengths and weaknesses in each individual patient at the level of 1) symptoms, behavioural- and emotional responses, 2) the psychological and social environment characteristics, 3) the neuropsychological profile of the patient, 4) aspects of brain physiology and 5)
the genetic constitution of the individual. Admittedly any biomarkers at level 4 and 5 will not become available to clinicians in the short term. Yet, we would like to motivate clinicians to look more closely into the interrelationships between various aspects of psychiatric disorders in their patients and urge them to be aware of the possibility that many of the comorbidities according to DSM could in fact be expressions of a single abnormality at the third, fourth or fifth level mentioned above.
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Chapter 4

Gender Differences and Health: Development and (Psycho)pathology

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Submitted
Gender Differences and Health:
Development and (Psycho)pathology

Abstract

Background

According to a proposal for a new definition of health (Huber et al 2011), health is not as the WHO definition still stipulates absence of disease and a state of complete mental, physical and social wellbeing, but the capacity to adapt under different circumstances, including the burden of disease.

Goal

In this article life and the burden of disease is considered in relation to gender. The question is whether women are more vulnerable to ill/health for a series of gender/bound reasons.

Methods

The scientific literature was searched and questioned on various relevant issues: What is the role of gender in gene-environment interactions? Are there gender related neurobiological differences in the development of stress regulation? Can gender be considered as a social determinant? Is gender a risk factor for (psycho)pathology? What is the role of childrearing and of social/economic circumstances?
Results

Gender is an essential intermediate factor between genetic predisposition that influences brain and psychological development leading to behaviours and coping mechanisms that are different across sexes. Stress regulation is different in men as compared to women. The much shorter but far more intense reaction of the hypothalamus-pituitary-adrenergic system in women has impact on immune-reactions but especially on vulnerability for psychopathology. This tendency appears to have been strengthened by the different way in which in childrearing parents react to girls as compared to boys. Finally Socio-economic-status (SES) has impact through the so-called Subjective Social Status (SSS) leading to marked gender-related health inequities.

Conclusions

Healthcare is no longer a matter of treating diseases. Health education and stimulation of the development of coping skills are essential. Along with socio-economic factors, genetic predisposition and gender play a key role in health perspectives. Women are different and tend to react to stress along different pathways. This should be acknowledged in healthcare. Serious efforts should be made to realize parity of esteem between mental- and general health, as women will react more often with mental health problems to stress than men. But healthcare is only the final pathway. Prevention should focus on educating parents. School should include gender specific health education in their curricula.

Keywords: gender - health – stress regulation – coping – health inequity
Introduction:

Recently Huber et al. (2011) proposed a new definition of health. In contrast with the old and still in use WHO formulation, this definition encompasses the capacity to adapt to circumstances of life as the main characteristic of health and not merely the absence of disease. This new approach makes it clear that individuals with (a series of) chronic diseases can live a relatively healthy life as they are able to participate, merely fully in every day. They thus manage to adapt to the limitations imposed by their disease in a productive fashion as medical treatments and technology have greatly progressed. As such health is strongly determined by one’s resilience. Yet our concern is, that the perspectives both of social determinants and that of gender as important factors for resilience, are still underestimated. Men and women do not react in the same way. Moreover the positions of women and men in society are, worldwide, still quite different. Everyday life stress and also traumatization have a major impact on one’s potential to adapt and thus live a healthy life. The outcome in terms of health is worse in women than in men under the same circumstances (Mackenbach, 2013), let stand under circumstances where women are culturally and economically disadvantaged. The reason for this is that pathways to the expression of (psycho)pathology related to environmental stress are different across gender. Though both sexes react to stress similarly by developing immune and metabolic disorders and diseases such as adiposity, diabetes type 2, cardiovascular problems and (auto)immune problems as a result of exposure to (societal) stress, men tend to be more vulnerable for inflammatory disorders, whereas women are moreover likely to react also with mental conditions like anxiety, fatigue and depression (Vitaliano et al. 2002). In other words, if health is defined as the ability to adapt to the circumstances of
life and to the burden of disease, the question is whether women are more vulnerable to ill-health for a series of gender related reasons?

Many studies have underscored the gender related impact of social determinants of health (Marmot & Allen 2014). It then becomes even more clear that gender influences on stress regulation are not only linked to gender in se, but are also conveyed through differences in child rearing, education, social status and the position of women in society (Rasing et al. 2013).

In this article we look into gender differences in various ways: are there differences in terms of adaptive mechanisms such as development of reaction to stress. We also wonder if there are differences in adaptive/coping styles related to rearing style differences in girls as compared to boys and the subsequent expression of (psycho)pathology.

In order to do so we looked into the recent literature for differences with regard to the development and functioning of stress regulation systems in men and women and tried to find out which consequences this could have on the subsequent occurrence of (psycho)pathology. We also searched for the most current knowledge of the impact of gender specific child rearing on the development of coping styles in men and women.

Consequently we will reflect on how these differences should be taken account in healthcare approach and how to prevent and bridge these detrimental gaps.

The questions we want to address in this article are:

1) What is the role of gender in gene-environment interactions?
2) Are there gender related neurobiological differences in the development of stress regulation. And if so what are the consequences for the expression of (psycho)pathology?

3) Can gender be considered as a risk factor for “socially determined forms of (psycho)pathology?

   3a) What causes gender differences in expressed emotions?
   3b) What is the influence of gender specific childrearing on development of psychopathology. In other words what is the role of parental response to emotions and (psycho)pathology in girls as compared to boys?
   3c) Does socioeconomic status (SES) have an different impact on men and women in terms of health outcome?

After summing and discussing the answers to these questions, we will elaborate on the consequences of these findings in terms of health care approach.

(1) The role of gender in gene-environment interaction:

In 1995 Morton and Frith introduced a layered model to explain the development of psychopathology. They defined three levels: the Organic (Genes & Brain), the Cognitive and the Behavioural level. Their assumption was that there is a linear causality in which the organic component induces a cognitive style that is responsible for the behavioural manifestation of the deregulation.

The Morton & Frith model reflected a novel approach to understanding the development of (psycho)pathology. But the “unidirectional – causal” model has
been dropped (Cicchetti & Toth 2009) to make place for a more interrelated model of interactive processes. All factors in play may bring along enhanced risk and vulnerability to develop illness and diseases, but can also be promotive by enhancing protection and fostering resilience.

Thus firstly, nowadays at least five –instead of three- levels can be discerned in human development: (1) the genetic level – (2) the epigenetics – (3) the brain circuitry and transmission mechanisms} – (4) the neurocognition – (5) and finally the behavioural level. All these levels are subject to influences form the environment (biological, psychological and social). Yet the environment in return is strongly influenced by the individual. These nature-nurture interactions start as from conception in the milieu intern of the womb. Later as from birth experience shapes the configuration of the brain and brain circuitry as well as and neuropsychological faculties.

Secondly the causal pathways are no longer perceived as unidirectional but should be conceived as permanent interactions.

And thirdly all these interactions are influenced by environmental factors (external agents) (Lenroot & Giedd 2011) such as psychological relations and stressors at every level.

Thus all forms of (psycho)pathology can be considered to be developmental. They result from the outcome of permanently ongoing nature (resilience and risk) - nurture (protection and stress) interactions, in other words intricate “vulnerability – stress” interplay.

Several recent studies showed that another factor could be in play, namely gender (Kessler et al. 2005). There is strong evidence that developmental pathways are different in females as compared to males. For example
Nugent & McCarthy (2011) found evidence that gonadal hormones in the neonatal brain influence epigenetic processes such as DNA methylation and histone acetylation, which is important for the sexual differentiation of the brain. In several animal and human studies, sex-dependent physiological, gene expression, and behavioral responses to prenatal stress have been identified (Tibu et al., 2014; Katjantie & Raikkonen, 2010; Kolb & Gibb 2011; Zohar & Weinstock, 2011). Other studies reported that prenatal risks are associated with elevated internalizing disorders in females but not in males (Costello et al., 2007; Van den Berg et al., 2008; Van Lieshout & Boylan, 2010).

This implies that development at all levels is not only influenced by the environment but also by gender.

(fig 1)
(2) Neurobiological differences in the development of stress regulation and it’s consequences for the expression of (psycho)pathology.

The hypothalamic–pituitary–adrenal axis (HPA) is the main stress regulating system in both animals and humans. Sex differences have consistently been reported in rodent studies and there is reliable evidence that this holds true for humans too (Goel et al. 2014). In response to both physical and psychological stress, females produce higher concentrations of corticosterone than males, in mice. In humans the findings are less consistent due to a diversity of the methods used. But it appears that women, as from puberty, show far higher but also shorter corticosterone secretion in response to acute and chronic stress. In this process testosterone plays an inhibitory role (Viau et al. 2005; Viau et al. 2003; Viau et al. 1996) which in part explains the milder and more protracted response to stress in men. Estrogen and progesterone play a mediating role. During pregnancy corticosterone concentrations rise (Allolio et al. 1990; Neumann et al. 1998, Ogle & Kitay 1977) and remain high during lactation (Fischer et al. 1995). This explains the greater resilience in face of stress during pregnancy and breastfeeding (Carter et al. 2001). But the aptitude of the HPA to help alleviate stress in men and women is not only sex but also hormone driven. In fact the HPA-axis is subject to the influence of maternal stress as from early intrauterine experiences (Tibu et al, 2014). This maternal stress influences the development of the HPA-axis but also that of the hippocampus where memories are stored (Wei et al., 2014; Richetto et al., 2014). In that early stage of life gender differences emerge pointing out that girls are more sensitive to intrauterine perceived stress than boys. The state of the HPA axis at birth will be of great influence on the way the child will learn to cope with adversity and stress. The sex differences in HPA axis activity begin to
emerge at puberty. Pubertal maturation which is associated with rising levels of estrogens and androgens, activates maturational processes that contribute to the development of adult HPA-axis stress responsivity (Goel et al. 2014).

Social environment also plays an important role as it appears that women are far more sensitive to rejection (Stroud et al. 2002) and absence of social support (Kendler et al. 2005) or social structure (Haller et al. 1999) whereas defeat has a greater impact on stress regulation in men.

But the most important difference between genders with regard to stress regulation is its consequences, in other words how stress affects health in men and women. Several studies suggest that stress has a greater negative impact on the psychological health of women (Goel et al. 2014). For instance stress-related mood disorders (depression, general anxiety) are two times more prevalent in woman than man (Kessler et al. 1993, Kessler et al. 2005).

Moreover, women are more likely to develop psychopathology (for instance posttraumatic stress disorder, Breslau 2009, Iteke et al. 2011) or autoimmune diseases when facing the same stressful events than men.

Stress appears to potentiate sex differences in HPA axis responses, resulting in greater divergence in inflammatory profiles between the sexes. These diverging inflammatory profiles may be partially responsible for the differences we see in susceptibility to disease, with men and post-menopausal women more vulnerable to infection and pre-menopausal women more vulnerable to autoimmune disorders (Yang and Kozloski, 2011). Females generally show greater immune reactivity than males, leaving males more susceptible to bacterial and viral infections while females are more prone to autoimmune inflammatory disease, such as e.g. rheumatoid arthritis (Ahmed and Talal, 1990, Da Silva,
1999 and Rohleder et al., 2001). The severity of these diseases is modulated by menstrual status and sex differences are maximal during the reproductive years (Da Silva, 1999). In addition, sex steroids have been shown to have direct modulatory roles on immune cells. For instance, progesterone inhibits dendritic cell function in female rodents to a greater extent than in male rodents (Butts et al., 2008). Evidence suggests that sex differences in immune function are influenced by stress and glucocorticoids. A recent study found that the association between social isolation and inflammation existed in males only, suggesting that females are less prone to glucocorticoid modulation of inflammation (Hafner et al., 2011).

Inflammation, in turn, can also lead to increased risk of cardiovascular disease (Yudkin et al., 2000). The sexually dimorphic effects of stress on the immune system may only partially explain sex differences in cardiovascular disease, but sex differences in stress and metabolic function extend beyond inflammation (Kautzky-Willer A, Handisurya 2009).

But there is also some evidence for gender-related differences in risk factors, and comorbidity with metabolic diseases. For instance the review article by Kautzky-Willer (2014) pointed out that impaired glucose and lipid metabolism as well as dysregulation of energy balance and body fat distribution have a great impact on overall health via neuroendocrine changes and inflammatory pathways and deteriorate the course of many diseases in both sexes but with particular harm in women.

So in sum, stress seems to have a greater negative impact on the psychological health of (pre-menopausal) women. Whilst men appear to be more protected for developing psychopathology, they are more prone to respond only with
metabolic disease in relation to acute and chronic stress. On the other hand psychosocial factors such as mental stress, depression, anxiety, and work and marital stress play an important role in ischemic heart diseases and metabolic diseases in women (Metha et al., 2014).

But though there seems to be a direct relationship between stress, (psycho)pathology, (psychiatric)disorder and gender, it seems more likely that there are intermediate factors that are sex related namely for instance the psychological processing and expression of emotions.

(3) Gender as a “Social Determinant” of (psycho)pathology?

One of the key features of a healthy social-emotional development is learning to know and to express one’s emotions. In the early years of life, children learn the rules of emotional expression. They learn the aptitudes necessary for appropriate and effective expression and regulation of emotions, through their daily interactions with their parents. They learn which emotions to express and when to express them. They also learn the most effective way to communicate their needs to others as well as how to respond to other’s requests and needs. In this way, they learn socially appropriate behaviours that enable them to express a range of emotions, which is considered to be essential for the development of emotional competence (Denham, 2007).

The ability to be emotionally aware and appropriately communicative of feelings, is not only an indication of socio-emotional functioning but also of mental health (Cicchetti et al., 1995; Gross, 1999). There is some evidence that, when a person is limited in the range of emotions he can express or is encouraged to express particular emotions to the exclusion of others, there is a
risk for developing psychopathology (Aldao et al., 2010; Chaplin et al. & Cole, 2005; Zahn-Waxler, Shirtcliff, & Marceau, 2008).

In line with the new definition of Health (the capacity to adapt to circumstances of life as the main characteristic of health and not merely the absence of disease) the capacity of appropriate and effective expression and regulation of emotion is also an important factor.

Because of the importance of the expression of emotions for healthy development, it is important to know if it is also influenced by gender. Several studies have addressed the issue of gender differences in the expression of some emotions. For instance in childhood, boys are more likely to show conduct problems such as defiance and aggression, which are often associated with high levels of anger (Cole, Michel, & Teti, 1994; Chaplin & Aldao 2013), whereas (by adolescence) girls are more likely than boys to demonstration symptoms of depression and anxiety (Hankin et al., 1998; Ollendick & Yule, 1990). Chaplin & Aldao (2013) suggest that there are small but significant gender differences in emotion-expressions, with larger gender differences emerging at certain ages and in certain contexts. They found that girls showed greater positive emotion-expressions than boys. This gender difference became increasingly evident as the age of the research participants progressed into adolescence and also in situations with an unfamiliar adult and in which there was social pressure to mask negative emotions and appear cheery. This way of internalizing rather than express feelings of distress could increase the likelihood of developing symptoms of depression and anxiety.

The question then arises if these gender differences in childrearing and developing fit in a bigger issue namely the question whether gender has to be considered as a risk factor for socially determined forms of (psycho)pathology.
What causes gender differences in expressed emotions?

Brody (1999) introduced a theory in which gender differences in emotional expression are perceived as the result of a combination of biologically based temperamental predisposition and the socialization processes in boys and girls go through in order to adopt gender-related rules for expressing emotions. In western cultures girls are expected to display greater levels of most emotions, particularly happiness and internalizing (or “intropunitive”) negative emotions, such as sadness, fear, anxiety, shame, and guilt than boys (Brody & Hall, 2008). Girls are also expected to show more empathy and sympathy both by facial expressions and/or by empathic behaviors (Zahn-Waxler, 2001; Zahn-Waxler, Cole, & Barrett, 1991). This is in line with woman’s traditional role as caregivers as to be more relationally oriented, nurturing, and helpful than males. Happiness and internalizing emotions, facilitates relationships and closeness with others (Barrett & Campos, 1987; Izard & Ackerman, 2000; Zahn-Waxler et al. 1992). In contrast boys are expected to show less of these tender emotions and are more allowed to express “externalizing” emotions such as anger, contempt, and disgust more than girls. This kind of emotion expressions serves the goal of overcoming obstacles, which involve externalizing “pushing outward”, rather than internalizing, of distress (Brody, 1999, 2000; Brody & Hall, 2008) To be assertive, individualistic, independent, and even aggressive is in line with the traditional roles for man to protect their families and overcome dangers that could interfere with their ability to provide food and security for their families (Brody, 1999). This implicates that the written rules for the expression of emotions are different for boys than for girls. It appears that children understand these rules perfectly as from early in life (Birnbaum et al., 1980; Zeman & Shipman, 1996; Root & Kenneth, 2010). So these
different implicit rules for males and females which may be rooted in biologically based different temperamental predispositions, may lead to differences in the development of the capacity of expressing emotions. But parents also seem to play an important role in continuity and discontinuity of dispositional traits (Crockenberg, 1987).

3.b What is the influence of gender specific childrearing on differences between gender in development of psychopathology?

For instance, in preschool children mothers tend to match better with male infant emotional expressions more than with female infant emotional expressions. They tend to respond more to their sons’ positive affect than to their daughters’ because of gender differences in irritability during infancy as males displaying more irritable and negative affect than females, (Malatesta & Haviland, 1982; Kennedy Root & Rubin, 2010). In their conversations, both fathers and mothers, refer to emotions more often when talking to their preschool-aged daughters than in discussions with their preschool-aged sons. They also tend to discuss sadness and dislike more often with their daughters than with their sons (Adams et al., 1995; Fivush Brotman, Buckner, & Goodman, 2000; Kennedy Root & Rubin, 2010). Kennedy Root & Rubin (2010) also found that mothers of daughters and fathers of sons reported significantly more disgust in response to their children’s displays of disappointment than mothers of sons and fathers of daughters. This is in line with the suggestion that the same-gendered parent may be the best socializer for the development of altruistic behavior (Eisenberg, Fabes, Carlo, & Karbon, 1992; Hastings, Rubin, & DeRose, 2005).

The parental responses are also influenced by age. With increasing child age parents expect more emotionally competent behavior, and therefore alter their
expectations (Cassano, Perry-Parrish, & Zeman, 2007; Dix, 1991; O’Neal & Malatesta-Magai, 2005). They may be less supportive or more punitive with older children than younger children. There are biological changes, including reorganization of the frontal-limbic neurocircuitry and neurobiological stress systems (implicated in emotional processing), in adolescents which affects the ways of parenting. (Zeman et al., 2007). Adolescents face new social challenges such as rising importance of the influence of peers and romantic relationships (Larson et al., 1996; Steinberg & Silk, 2002). At the same time, the pressure to abide to cultural norms and standards also increase. (Dix, 1991; Klimes-Dougan et al., 2007; Lukenheimer, Sheilds, & Cortina, 2007). The strong emotions that typically accompany adolescence provide important opportunities for parents to help their adolescent child to develop strategies for managing these emotions. Mothers and fathers alike express both types of emotions but more positive than negative emotions within the family (Garside, 2004; Halberstadt, 1991). But there are also potentially important differences in way parents show their own social-emotional behaviors. Despite of the changes in family structure over the past several decades mothers continue to be primarily responsible for child rearing and are more involved than fathers in parenting their adolescent children (Paulson & Sputa, 1996; Brand & Klimes-Dougan, 2010). Research on adolescents and young adults (Garside, 2004; Garside & Klimes-Dougan, 2002; Klimes-Dougan et al., 2007) showed that mothers reward and magnify of the expression of sadness, fear, and anger were as fathers were more likely to overlook negative emotions. Other studies pointed out that the father’s emotion-socialization practice style s predicted their child’s emotional competence (McDowell & Parke, 2005) and psychological distress (Garside, 2004). Fathers are often more punitive in response to their children’s emotional expressions (Cassano et al., 2007;
Eisenburg, Fabes, & Murphy, 1996) and more likely than mothers to use dismissive or distracting strategies to respond to their child’s expression of fear or sadness (Klimes-Dougan et al., 2007). In another study fathers reported that they rewarded their daughters and punished their sons for expressing sadness and fear (Garside & Klimes-Dougan, 2002).

Taken together, it appears that there are similarities and differences in the way that mothers and fathers respond to their children’s emotions, which are influenced by both the child’s gender and the type of emotion. It appears that mothers and fathers are particularly invest in teaching their same-gendered child what they perceive as gender-appropriate expression and regulation of emotions. There is growing evidence that links parental emotion-socialization-practices with various aspects of child adaptation and maladaptation (Cicchetti et al., 1995; Denham, 1993; Denham et al., 2000; Eisenberg et al., 1998; Gottman et al., 1997; Katz et al, 1999; O’Neal & Malatesta-Magai, 2005; Saarni, 1993; Shipman et al., 2005; Yap et al., 2008; Zahn-Waxler et al., 2000).

Although parental emotion-socialization-practices may influence child developmental outcomes, it is important to realize that the impact of contentious, challenging behavior of adolescents is equally likely to change the ways in which even the most capable parent will respond (Ge et al., 1995; Yap et al., 2008). In others words the causal pathway of the child’s outcome is not unidirectional but should be conceived as permanent interaction between the environment (parents), gender and the phenotype / behavioural expression of the child itself. The psychological environment has, as shown, an important impact on the development of coping styles and adaptive behaviour over the sexes, but the question is whether this is a universal phenomenon or if broader circumstances impact differently on women and men?
(3c) Does socioeconomic status (SES) have a different impact on man and woman in terms of health outcome?

Socio-economic inequalities are a key public health problem (Siegrist & Marmot 2004). Despite of extensive arrangements aiming at reducing socioeconomic inequality and its various consequences, health inequalities have not only persisted while welfare states were being built up, but in some aspects have even widened and enhanced (Mackenbach 2012). This hold particular true for lifetime expectancy in high and low social-economical classes. There is also some evidence to show that this could affect men and women in a different way. For instance recent studies suggests that there are gender differences the distribution of related risk factors (i.e. in coronary heart disease and hypertension and diabetes) (Dalstra et al., 2005; Thurston, Kubzansky, Kawachi, & Berkman, 2005) and that different socioeconomic status (SES) dimensions might relate in a differential way to men’s and women’s health outcomes (Sacker, Firth, Fitzpatrick, Lynch, & Bartley, 2000). In the Women’s Health Study, educated women were less likely to smoke and have hypertension, diabetes, or obesity. Albert et al. (2006) observed a decrease in of prevalence of cardio vascular events with an increase of the level of education and income. Low socioeconomic status and work stress were also related to an higher risk for developing ischemic heart disease in the Fem.Cor.Risk study (Wamala et al.,2000).

The question is whether socio-economic status in se has in impact on health or if the influence is mediated by related factors.

To address this issue some studies examined the Subjective Social Status (SSS) as a health correlate and explored its role as a potential mediator of the associations between objective indicators of SES (education, occupational class,
and wealth) and health outcome measure. SSS refers to “the individual’s perception of his/her own position in the social hierarchy” (Jackman & Jackman, 1973) and relates to objective SES in as much as their economic resources form the basis for their appreciation of their social standing in a given society or community. For example Demakakos (2008) found that, irrespective of sex, SSS is related to the own perception of health as self-rated depression, and longstanding illness or disability over and above education, occupational status, wealth, age, and marital status. This was also the case for diabetes and HDL-cholesterol in women. These findings are in line with the existing literature suggesting that SSS is related to self-rated health (Franzini & Fernandez-Esquer, 2006; Hu et al., 2005; Ostrove et al., 2000; Singh-Manoux et al., 2005) and mental health (Franzini & Fernandez-Esquer, 2006; Singh-Manoux et al., 2005). The influence of economical wealth on the associations between SSS and health outcomes appeared to be stronger in men than in women. Associations in women more than in men were significant after adjusting for objective indicators of SES. These differences may reflect gender differences in terms of life’s achievements and perspectives. Thus they need to be considered in the light of the different ways that men and women perceive the world and evaluate their own life-time successfulness. This is in line with the results of the Swedish study of Myakawa (2012) who found that when ranking their SSS, women put more weight on household financial situation and men on their personal income.

**Consequences for a gender approach to healthcare**

Huber et al. (2011) proposed a new definition of health as one’s capacity to adapt to circumstances of life. They pointed out that the limitations of the
current definition are increasingly affecting health policy. For example, in prevention programs and healthcare the definition of health determines the outcome measures: health gain in survival years may be less relevant than societal participation, and an increase in the ability to adapt and coping capacity may be more relevant and realistic than complete recovery. They pointed out that first step towards using the renewed concept of “health, as the ability to adapt and to self-manage”, is to identify and characterize it within the three main domains of health: physical, mental, and social.

In this study we pointed out that gender plays a role in not only in the vulnerability to develop certain physical and/or mental diseases but also influences the way how to cope with them. In other words gender influences physical, mental as well as social health. This implies that interventions need to be gender-responsive in order to be successful. Therefore “gender sensitive” actions will be necessary at various levels aiming at cross-sector policies, in families and communities, and the way services are provided in health care.

So in order to improve health for all, we need to raise awareness for gender issues and improve gender sensitivity into healthcare practice, society and policy makers. Finally it should be noted that gender in relation to health is not only a question of women versus men. In women there are important differences between girls, pre- and postmenopausal women. The girls are vulnerable to environmental factors that shape their psychological responses and coping behaviours. Women in their second phase in live are far more different than men in immune reactivity, which difference fades out after menopause. Clinicians should be advised that it is not only important to focus on good
diagnostics and treatment of diseases but also to be aware of gender influences on health and how gender plays a role in the patient’s ability to cope and adapt. This implies that they have to understand the different factors that are of influence on the development of (psycho)pathology and how gender plays an important role in these interactions. Healthcare workers should realize that women are biologically more vulnerable to stress because of differences at the level of HPA axis activity and subsequently are more likely to develop psychopathology (affective disorders) when facing the same stressful events as man. They should also bear in mind that the social environment plays a different role in men and women. There is growing evidence that links inadequate parental emotion-socialization in upbringing with bader outcome in terms of adaptability later in life. Finally it is apparent that the impact of both the social environment as of the social economic status is different in men as compared to women. But it is also clear that this impact is not static, but is conveyed through psychological processes (SSS) that are in turn strongly related to the larger social (economic) context as well as the narrower social context within the rearing environment. This is illustrated by the fact that women are far more sensitive to rejection, absence of social support or social structure, whereas defeat has a greater impact on stress dysregulation in men. In prevention programs it is important to take gender into account when tailoring programs to help women improve their coping skills in order to become more resilient when facing adversity.

In conclusion: healthcare can no longer merely be a matter of treating diseases. Health education and stimulation of the development of coping skills are essential in order to promote healthy adaptation to illness and adverse circumstances. Along with socio-economic factors, gender plays a key role in
outcome and health perspectives. Women are different and react in a different way to stress. Healthcare should take this in to account. No longer should researcher consider that “one size fits all” and disregard gender as an important modulating factor. The personalized approach in medicine should take gender specific reactions of women into serious consideration. As women will tend to react more often with psychopathology, this should be acknowledged for as of equal importance as compared to the physical reactions (that men and women share although the causal pathways may differ).

This implies that at a health governance level serious efforts should be made to truly realize parity of esteem and funding between mental- and general health.

But health-care is only the final pathway. Prevention should focus on educating parents to respond differently to their daughters and to become more sensitive to their signals of distress. School should include gender specific health education in their curricula, with a focus on promoting healthy coping styles to strengthen resilience in girls as well as in boys.
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Chapter 5

Gender and Age Differences in the Core Triad in Autism of Impairments in Autism Spectrum Disorders: A Systematic Review and Meta-Analysis

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Gender and Age Differences in the Core Triad of Impairments in Autism Spectrum Disorders: A Systematic Review and Meta-analysis

Abstract

Autism is an extensively studied disorder in which the gender disparity in prevalence has received much attention. In contrast, only a few studies examine gender differences in symptomatology. This systematic review and meta-analysis of 22 peer-reviewed original publications examines gender differences in the core triad of impairments in autism. Gender differences were transformed and concatenated using standardized mean differences, and analyses were stratified in five age categories (toddlerhood, preschool children, childhood, adolescence, young adulthood).

Boys showed more repetitive and stereotyped behavior as from the age of six, but not below the age of six. Males and females did not differ in the domain of social behavior and communication. There is an underrepresentation of females with ASD an average to high intelligence. Females could present another autistic phenotype than males. As ASD is now defined according to the male phenotype this could imply that there is an ascertainment bias. More research is needed into the female phenotype of ASD with development of appropriate instruments to detect and ascertain them.
Introduction

Autism spectrum disorder (ASD) is a collective term for a group of heterogeneous disorders characterized by impairments in social interaction and verbal and non-verbal communication, and repetitive and stereotyped behaviors. ASD is more common in males than in females, with a male to female ratio of 4.3:1 (Fombonne 2003) and a prevalence of 60–70/10,000 (Fombonne 2009). As a consequence, most research has involved male patients. However, there is some evidence that the clinical presentation is different in males and females (Holtmann et al. 2007; McLennan et al. 1993; Tsai and Beisler 1983), and it is argued that phenotypic gender differences might lead to delayed diagnosis or even missed diagnosis in girls and women with autism (Rivet and Matson 2011b). For instance, girls and women with relevant symptoms may be diagnosed with other disorders, such as social phobia or borderline personality disorder, instead of ASD (Attwood 2007). As yet, there have been relatively few studies of gender differences in symptoms, and available findings are inconsistent. While some studies have reported girls to have more social problems and to be less able to perform social play and social imitative play than boys (Holtmann et al. 2007; McLennan et al. 1993; Tsai and Beisler 1983) others have not found gender differences in social behavior or have reported that social behavior is better in girls than in boys (Banach et al. 2009; Carter et al. 2007; Holtmann et al. 2007; McLennan et al. 1993). Findings about communication patterns are also discrepant. Some studies found girls to have less expressive and advanced receptive language skills (Carter et al. 2007; Holtmann et al. 2007), while others did not find any differences (McLennan et al. 1993). One study found repetitive and stereotyped behaviors to be less common in females than in males (Bolte et al.
2011), whereas three other studies did not find any gender differences in this domain (Banach et al. 2009; Carter et al. 2007; Holtmann et al. 2007). Thus, findings regarding gender differences in the core triad of impairments seen in ASD remain ambiguous. In addition, age may influence potential gender-related differences in the symptoms of ASD, as there is some evidence that age has a gender-specific role in symptom severity. For example, two studies found that ASD was detected earlier in infant girls than in infant boys (Ozonoff et al. 2010; Rivet and Matson 2011b) however, other studies found that mild autism was diagnosed far later in high functioning females than in males (Begeer et al. 2013; Lugnegård et al. 2011).

Because ASD is far more prevalent in males than in females, relatively little attention has been paid to how the disorder manifests in females, despite there being some evidence that core symptoms of ASD differ by gender and that age influences these gender differences in symptomatology. For this reason, we performed a systematic review and meta-analysis to investigate possible gender differences in the core symptoms of ASD from infancy to adulthood, because a better understanding of gender differences may lead to an earlier diagnosis and better treatment of ASD in girls and women.

Method

Literature Search

Multiple electronic databases (PubMed, Scopus, Medline, Web of Science Direct) were searched for relevant articles, published between 1943 and June 2013, on gender differences in the core triad of impairments seen in ASD (impaired social interaction, impaired (non)verbal communication, and restricted patterns of behavior and interest), using the following keywords:
‘autism spectrum disorder’, ‘ASD’, ‘pervasive development disorder’, ‘PDD’, or ‘autism’ in combination with ‘gender, ‘gender differences’, ‘sex’, or ‘sex differences’. Inclusion criteria were comparison of core symptoms of ASD in males and females and availability of test scores for males and females.

**Procedure**

The initial database search identified 504 articles. The title and abstract of these articles were screened for inclusion criteria by two researchers (a third researcher was consulted in case of doubt), which resulted in 70 potentially relevant articles. The full-text documents were retrieved and screened for inclusion. The reference lists of these articles were checked to identify additional relevant articles. Decisions made at this stage were discussed in a research team including psychiatrists, a psychologist, and an epidemiologist.

Articles were excluded if no distinction was made between the core symptoms in the triad of impairments in ASD ($n=16$), if the article was a review and did not include new data ($n=8$), if the information provided was unclear ($n=1$), if gender differences in ASD were not explicitly investigated ($n=6$), or if the study merely included gross epidemiological data ($n=2$). Of the remaining 37 articles, 15 were excluded after a thorough examination of the data provided (11 articles did not provide scores for core symptoms of ASD and 4 did not distinguish between the three core impairments). Of the 22 remaining articles, 20 reported on social impairments, 18 reported on communication deficits, and 15 reported on repetitive and stereotyped behavior. Figure 1 provides an overview of this selection procedure.
Funnel plots (appendix III) of the standardized mean differences were made for each core symptom using Review Manager 5.1 (Nordic Cochrane Centre, 2011) to check for outliers. If there were outliers (n=2), two independent authors (RG and PW) checked the research method, sample size, reproducibility, and possible bias of these studies. None of the articles were excluded.

Data selection and extraction
The following information was extracted from the articles: (1) sample size, (2) gender distribution, (3) age, (4) autism diagnostic criteria used, (5) test instrument used, (6) scorer (for example, self-report, parental report, observer...
report), and (7) test scores for the impairments investigated. The latter data were entered into Review Manager 5.1. The main characteristics and results of the included studies are presented in Appendix I. In total, the analysis included 4195 patients with an ASD, 3207 males and 988 females. Some participants were included in more than one analysis of core symptoms because symptom severity was assessed with different test instruments. Thus for social behavior, 4783 test scores for males and 1277 test scores for females were analyzed; for communication, 2781 and 992 test scores, respectively; and for repetitive and stereotyped behaviors, 2093 and 781 test scores, respectively. Post-hoc analyses showed that the multiple inclusions of some participants did not affect the results.

**Data analysis**

Data were standardized using the Standardized Mean Difference (SMD), to account for the use of different instruments, such as the Vineland Adaptive Behavior Scales (VABS) (Sparrow et al. 1984), Autism Diagnostic Observation Schedule-Generic (ADOS-G) (Lord et al. 2000), Autism-Spectrum Quotient (AQ) (Baron-Cohen et al. 2001) and Autism Diagnostic Interview-Revised (ADI-R) (Le Couteur et al. 1989) The SMD and 95% confidence intervals (95% CI) were calculated using Review Manager 5.1. If no standard deviation (SD) was provided (Sipes et al. 2011), the mean SD of all studies was used as an approximation. A SMD above zero indicates that males are more affected and a SMD below zero indicates that females are more affected.
Heterogeneity was calculated using Chi-squared ($\chi^2$) and I-squared ($I^2$) tests. If the mean scores of different samples differ, then the samples may originate from different populations (heterogeneity). Heterogeneity was found for social impairments ($I^2=81\%$), communication impairments ($I^2=89\%$), and repetitive and stereotyped behaviors ($I^2=91\%$). This necessitated the use of random effects models, which correct for heterogeneity, to test for gender differences.

To determine whether age was a cause of heterogeneity, a stratified sensitivity analysis based on age was performed, using the following age strata: toddlers (0–3 years), preschoolers (0–6 years), children (6–12 years), adolescents (12–18 years), and adults (18 years and older). ‘Toddlers’ was selected as age category because of evidence that there are gender differences in symptoms in toddlerhood (Rivet and Matson 2011a). Further, sensitivity analyses were performed post hoc to evaluate whether the choice of test instrument and the Intelligence Quotient (IQ) and the Development Quotient (DQ) of the participants affected the results.

Instruments used to measure core symptoms
Fifteen different instruments were used to score symptoms of ASD; two instruments had two versions (i.e., the ADI and ADI-R, the ADOS and ADOS-G). The ADOS and ADI-R were used most frequently (23.9% and 15.9%, respectively). All instruments were based on parent report, except for ADOS and ADOS-G (observer report) and Autism Quotient (patient report) (Appendix II). In total, 14 instruments assessed current symptoms and 4 articles assessed (partial) retrospective symptoms (Appendix II).
Results

Meta-analysis

To examine whether there are gender differences in the core symptoms of ASD, differences in symptom severity between males and females were determined overall and then in the specific age groups. Overall, females with ASD exhibited less severe symptoms of repetitive and stereotyped behaviors than did males with ASD (SMD 0.51, 95% CI 0.22–0.80) (Figure 4), but there were no gender differences in social behavior (SMD –0.4, 95% CI –0.20 to 0.13) or communication (SMD –0.03, 95% CI –0.26 to 0.21). The gender difference in the severity of repetitive and stereotyped impairments was seen from 6 years onwards but not in the younger children (Table 1).

<table>
<thead>
<tr>
<th>Age</th>
<th>Social SMD (95% CI)</th>
<th>Communication SMD (95% CI)</th>
<th>Repetitive and stereotyped behaviour SMD (95% CI)</th>
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<tr>
<td>0-6</td>
<td>-0.05 (-0.72 to 0.62) p= 0.89</td>
<td>-0.54 (-1.94 to 0.86) p= 0.45</td>
<td>1.05 (-0.39 to 2.49) p= 0.15</td>
</tr>
<tr>
<td>6-12</td>
<td>0.02 (-0.08 to 0.11) p= 0.74</td>
<td>0.10 (-0.03 to 0.23) p= 0.14</td>
<td>0.19 (0.06 to 0.32) * p= 0.004</td>
</tr>
<tr>
<td>12-18</td>
<td>-0.29 (-0.74 to 0.16) p= 0.21</td>
<td>-0.01 (-0.28 to 0.27) p= 0.97</td>
<td>0.64 (0.34 to 0.94) * p&lt; 0.0001</td>
</tr>
<tr>
<td>&gt; 18</td>
<td>0.13 (-0.05 to 0.32) p= 0.15</td>
<td>0.12 (-0.06 to 0.31) p= 0.20</td>
<td>0.47 (0.03 to 0.92) * p= 0.04</td>
</tr>
</tbody>
</table>

Table 1. Gender differences in age categories, * p < 0.05

Thus, female children, adolescents, and young adults had less severe symptoms of repetitive and stereotyped behaviors than males of the same age.
Analysis indicated that the data heterogeneity was mainly due to the large variance in the toddler group (see Figures 2-4), because exclusion of the toddler group drastically reduced heterogeneity in all three core domains (to $I^2=60\%$, $I^2=24\%$ and $I^2=61\%$, respectively).
Fig. 4. Scatterplot of repetitive and stereotyped behavior.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Male</th>
<th>Female</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
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<th>Total</th>
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<tr>
<td>Toddlers and pre-schoolers</td>
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<tr>
<td>Carter 2007</td>
<td>3.6</td>
<td>0.5</td>
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<tr>
<td>Harlow 2009</td>
<td>3.4</td>
<td>0.5</td>
<td>20.0</td>
<td>20.0</td>
<td>4.5</td>
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<td>Total</td>
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<td>0.5</td>
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<td>Subtotal (%C)</td>
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<td>20.0</td>
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Fig. 3. For example, communication.

<table>
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<tr>
<th>Subgroup</th>
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<th>SD</th>
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<tr>
<td>Total</td>
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<td>Total (%C)</td>
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<td>20.0</td>
<td>4.5</td>
<td>2.0</td>
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Funnel plot analysis identified three outliers (Hartley and Sikora 2009; McLennan et al. 1993; Sipes et al. 2011), and these studies involved the toddlers responsible for the data heterogeneity. However, there were no valid reasons to exclude these studies, based on research method, sample size, reproducibility, and possible bias. Thus, the variance in gender differences was largest at a very young age. Lastly, the results of the studies that used the ADI-R and the ADOS, the most frequently used instruments, were compared. Heterogeneity was low when only studies using the ADI-R and the ADOS were included (social $I^2=0\%$, communication $I^2=39\%$, repetitive and stereotyped behavior $I^2=0\%$), indicating that the results of these studies were homogeneous, but that the other studies that used other instruments might have contributed to heterogeneity. Furthermore, a post hoc sensitivity analysis was conducted to check whether DQ and IQ influence the results. Only one study (Sipes et al. 2011) included patients with a low DQ, excluding these results did not change the SMD of social behavior (-0.05, 95\% CI -0.22 to 0.13), communication (-0.03, 95\% CI -0.28 to 0.22) or repetitive and stereotyped behavior (0.54 95\% CI 0.23 to 0.85). Two studies included patients with an IQ below 70 (Tsai and Beisler, 1983; Volkmar et al. 1993). When these results are excluded no change in SMD of social behavior (-0.07, 95\% CI -0.25 to 0.11) or communication (-0.04, 95\% CI -0.29 to 0.21) was observed. Repetitive and stereotyped behavior was not measured in both studies.

**Discussion**

This meta-analysis of 20 studies investigated gender differences in ASD symptoms. Overall, there were few differences in symptom severity between males and females. Males and females with ASD showed similar symptom
severity on communication and social behavior, but girls showed less restricted interests and behaviors and stereotypes than boys.

These results can be discussed from three perspectives. The first perspective hypothesizes that girls with ASD truly show less restricted interests and behaviors and stereotypes than boys. In other words, females present another autistic phenotype than males. This dimorphic phenotype may be the result of sexually dimorphic underlying causal mechanisms. ASD risk is likely to be multifactorial, with many different genetic variants and environmental factors contributing to liability. Sex chromosomal gene dosage and sex hormone levels may be involved. Biological theories for the sex difference in ASD prevalence propose that females have a higher threshold for reaching affectation status than males and genetic studies hypothesize that females with ASD are likely to be carrying a higher heritable load than affected males (Werling and Geschwind 2013). But so far, the male-skewed bias towards restricted interests and behaviors and stereotypes has not been precisely elucidated by biological theories. The underlying mechanisms are yet to be identified.

If this perspective of a sexually dimorphic phenotype would be true, the formal diagnostic criteria of ASD could be unjustly biased towards males. It should be borne in mind that the diagnostic criteria were formulated on basis of behaviors and features found in boys. As early as 1943, Kanner described ASD as being predominantly found in severely impaired boys with comorbid mild intellectual disability. It has recently indeed been recognized that the behavioral phenotype of ASD is different in girls and women than in boys and men, whereas diagnostic criteria are based on the symptoms seen in boys (Kirkovski et al. 2013). Dworzynski and her colleagues (2012) recognized this difference and hypothesized that an unknown mechanism helps girls with ASD
to cope in such a way that their symptoms do not reach the diagnostic threshold. Thus it appears that there is a male bias in the clinical diagnosis of ASD. The specific features that accompany girls with ASD and that differ from boys are increasingly recognized. Girls with ASD have better imaginative play than affected boys (Knickmeyer, et al. 2008), show more interest in social relations (Attwood 2007) and may have more socially accepted special interests (horses, dolls, pop stars), characteristics which might mask their ASD (Kopp and Gillberg 1992). Further, parents report that their daughters with ASD have problems establishing and maintaining adequate peer relationships (Holtmann et al. 2007). In an effort to facilitate the screening and detection of ASD in girls, a new screening tool ‘The Autism Spectrum Screening Questionnaire-Revised Extended Version (ASSQ-REV)’ is in development (Kopp and Gillberg 2011). The ASSQ-REV is sensitive to female features of ASD.

A second perspective on the results of the present meta-analysis incorporates the influence of intellectual disability. It is known that if ASD is accompanied by intellectual disability the female / male ratio is 1: 2. Furthermore, in ASD patients without intellectual disability, males are overrepresented 9-10: 1(Fombonne , 2009; Banach et al. 2009; Lord et al. 1982; Tsai and Beisler 1983; Volkmar et al. 1993). This is relevant in light of the present results, because in the included studies, female ASD patients with low IQ may be overrepresented compared to male ASD patients with low IQ. Moreover restricted interests and behaviors and stereotypes are not only a core symptom of ASD, but also highly related to general intellectual disability (Matson et al. 1997; Matson et al. 2010; Wilkins and Matson 2009). More over, restricted interests and behaviors and stereotypes are not specific for ASD and are also seen in children with an intellectual disability (Muthugovindan and Singer 2009). A consequence could
be that a part of the females who are included in this meta-analysis show problems on these core symptoms primarily due to the intellectual disability, not to ASD. If that would be true, intellectual disability could be considered a confounding factor, leading to an overestimation of problems in the domain of communication, social behavior and restricted interests and behaviors and stereotypes, especially in females. Regrettfully, we were not able to include intellectual disability as a confounder in the meta-analysis due to lack of specific data in the original articles. The only means we had to examine the potential influence of IQ or DQ on the present meta-analysis was a sensitivity analysis, in which the exclusion of studies with patients with low IQ or DQ did not change the final results. This indicates that the results of this meta-analysis were robust to the potential influence of IQ or DQ.

Another possibility is that intellectual disability is not a real but an artefactual confounding factor. That would be the case if in the true ASD population, IQ levels of males and females would be similar, but in the same time high functioning females with ASD are less likely to be referred and diagnosed than high functioning males with ASD. Indeed, recent studies support the hypothesis that ASD is only diagnosed in females presenting with classic symptoms and intellectual disability, with the diagnosis being missed in females with a higher IQ or with less extreme stereotypies (Baird et al. 2011; Begeer et al. 2013). Intellectual disability as an artefactual confounding factor may have influenced the studies that were included in the present meta-analysis. The studies that were included in the present meta-analysis may have missed the females with a higher IQ. If that were true, the present meta-analysis would in contrast overestimate problems in females in the domain of communication, social behavior and restricted interests and behaviors and stereotypes.
A third perspective on the results of the present meta-analysis considers the ascertainment bias. Several studies have shown that girls with milder symptoms and a normal IQ tend to be diagnosed at a later age than boys (Kopp and Gillberg 1992; Goin-Kochel et al. 2006; Siklos and Kerns 2007; Begeer et al. 2013; Russell et al. 2011; Giarelli et al. 2010) or are misdiagnosed (Kopp and Gillberg 1992; Nilsson et al. 1999; Begeer et al. 2013). It has been argued that girls with ASD show different and less severe social and communicative impairments than boys do, and parents, relatives, and health professionals may consider these impairments as being due to shyness or anxiety. This misinterpretation of symptoms could lead to misreferral and misdiagnosis (Holtmann et al. 2007). Autistic girls might be diagnosed as having anxiety disorder, avoidant personality disorder, etc, which means that ASD is potentially underdiagnosed in girls and women (Mandy et al. 2011). Moreover, girls with “internalizing’ problems are referred to professionals less often than boys with similar problems, probably because these behaviors are considered normal in females (Rucklidge 2010). However, once the diagnosis has been established, studies have shown that there are no differences in the type or severity of comorbid conditions accompanying ASD in girls and boys (Lugnegård et al. 2011). This indicates that the ascertainment bias is a real problem in the identification of females with ASD. ASD may show a bimodal distribution in females, with there being a group of severely impaired girls in whom the disorder is diagnosed and a group of girls with milder symptoms in whom the disorder is not or only later diagnosed.

The ascertainment bias may also have affected the present meta-analysis. The studies that were included in the present meta-analysis could have missed these high functioning girls. If that is true, the conclusion that females and
males do not differ on communication a social behavior would be false, and only an artifact of the missing of a specific group of girls. As a consequence, the true conclusion would then be that females with ASD show better communication and social behavior than males with ASD. 

A final thought from the perspective of the ascertainment bias is that it may not only affect referral and diagnosis of females, but also of males. The main result of the present meta-analysis is that boys with ASD show more restricted interests and behaviors and stereotypes than girls with ASD. It is important to realize that restricted interests and behaviors and stereotypes are not specific for ASD and are seen in both children with an intellectual disability and severe deprivation and in typically developing children with normal intelligence (Muthugovindan and Singer 2009). It should be considered that there might be false-positive ASDs among the patients with restricted interests and behaviors and stereotypes. This may primarily be the case in boys. More research on this issue is warranted.

In sum the main result of the present meta-analysis is that females with ASD show less repetitive and stereotyped behavior than males, whereas there appear to be no gender differences in the domain of social behavior and communication. These findings imply that according to the studies analyzed to date there are no major differences in the core symptoms of ASD between males and females according to the defining criteria thus far.

But in the discussion we raised the question why men would have more stereotype movements. This is biologically yet unclear and definitely needs more investigation. Other possible confounding factors are intellectual disability and the ascertainment bias. So it could be that many females with
normal to high intelligence could be overlooked or misdiagnosed because they do not present the male phenotype of autism. Therefore more research is will be needed with instruments better adapted or more fit to help defining and identifying a female phenotype of ASD.
References


Chapter 6

Gender differences in Autism Spectrum Disorder as Toddlers grow into Childhood

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Groen, Wouter \textsuperscript{2 \&4}
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submitted
Gender differences in Autism Spectrum Disorder
as Toddlers grow into Childhood

Abstract

Background

Autism Spectrum Disorders (ASD) seem more common in males than in females (average ratio 4:1). Subsequently, ASD is studied more frequently in males than in females. Especially in early childhood, little is known about gender differences in the ASD phenotype. The current study focusses on similarities and differences between boys and girls in an at-risk population of toddlers, who were followed-up into childhood. It addresses two research questions 1) what are the gender differences in ASD in toddlers?; and 2) how do these differences evolve at follow-up about 3 years later?

Methods

The study sample is part of the Diagnosis and Intervention study on Autism in the Netherlands [DIANE-study, Oosterling et al. 2010) including 252 children [(56 girls/ 196 boys ; mean age = 32,5 months, SD = 5,0] identified as at high risk for ASD after a systematic two-stage screening procedure using the Early Screening of Autistic Traits questionnaire (ESAT). We studied gender differences at the level of screening results and phenotypic expression (ASD core symptoms, cognition, and co-morbid problems) for those toddlers with a
confirmed ASD diagnosis after thorough clinical assessment (n = 163; 34 girls / 129 boys). In addition, for a subgroup of children with a stable ASD diagnosis that participated in a follow-up assessment three years later (n=138; 24 girls / 114 boys), gender differences were studied again.

**Results**

No gender differences in screening results were found, but females had significantly higher scores on all core symptoms of ASD and on comorbid problem “withdrawn” but lower scores on “attention problems” and “rule-breaking behavior”. Girls did show a more pronounced developmental delay than boys. The findings on social interaction appeared stable over time but disappeared after controlling for IQ. All other gender differences faded out at follow-up.

**Conclusions**

At a very young age, girls that were identified with ASD are different from boys in that they show more severe ASD symptoms, and more often a developmental delay. It is open for discussion why milder cases of ASD girls are hardly detected in toddlerhood.

**Keywords**

Autism spectrum disorder – gender – developmental disorder in girls and women – comorbidity – early detection- follow up
Introduction

The term autism spectrum disorder (ASD) is used to describe a heterogeneous group of developmental disorders characterized by impairments in social interaction, verbal and non-verbal communication, and repetitive and stereotyped behaviors (DSM 5, 2013). The prevalence is approximately 1% in the general population (Fombonne, 2009). The overall sex ratio is 4-5 males versus 1 woman (Baird et al. 2006). In individuals with co-occurring intellectual disability the sex ratio drops to 2:1 or tends to be equal, whereas women are underrepresented in high-functioning individuals with ASD. Defined (DSMIV?) criteria are mainly based on male behavior (qualitative approach) and so are the thresholds for qualifying to the diagnosis (Holtmann et al. 2007; Lai et al. 2015; McLennan et al. 1993; Tsai and Beisler 1983). Whereas in fact, the syndrome may appear differently in males as compared to females. This may result in delays in ASD diagnosis and missed or wrong diagnoses in milder cases, especially in females (Rivet and Matson 2011). In research, this may have led to an obvious male bias: Boys and men are overrepresented, but results are commonly generalized to both sexes (Lai et al. 2015).

When looking at literature that focusses on gender differences in ASD, findings seem not always easy to relate to each other and conclusions can be ambiguous (Lai et al. 2015). However, in a meta-analysis and using the current or immediate past criteria of the DSM IV, we found only small differences in symptom expression in males versus females (van Wijngaarden-Cremers et al. 2014). In fact, in our review including 22 studies, no significant differences at symptom level between males and females were found, except for the finding that boys and men have more “repetitive and stereotype” behavior as from childhood. In the few studies that did include infants and toddlers, this
exception (based on the meta-analysis) was not observed. In order to gain more insight into the nature of differences in the phenotypic expression of ASD in boys compared to girls from an early age onwards and applying a longitudinal design, the current study aims to compare the development of a relatively large group (N = 163 ) of boys and girls diagnosed with ASD in toddlerhood and followed up in early childhood.

To our knowledge, thus far, only a handful of studies specifically report on gender differences in children with ASD in the preschool years. Some of them indeed found gender differences and report that girls have significantly greater communication problems, but less restricted and repetitive behaviors than boys (Carter et al., 2007; Hartley & Sikora, 2009 ; Sipes et al., 2011), whereas others did not find any gender differences (Andersson et al. 2013; Rivet and Matson 2011b). There is also confusing findings on the age of recognition as two studies showed that ASD was detected earlier in infant girls than in infant boys (Ozonoff et al. 2010; Rivet and Matson 2011b) whilst on the other hand studies showed that mild autism was diagnosed far later in high functioning females than in males (Shattuck et al 2009; Begeer et al. 2013).

Given the rapidly increasing interest in the subject of linking ASD and gender, only very recently, Lai and colleagues (2015) have proposed a four-level framework to clarify different but interlinked research themes. The first level being that of the “Nosological and Diagnostic” challenge, in other words: defining appropriate criteria and thresholds for both sexes. The second level aims at comparing males and females with ASD in order to look for similarities and differences, and how the findings are influenced by intellectual level and co-occurring conditions. The third level is meant to elucidate the question of underlying etiological features, specially focusing on why high-functioning women have cognitions that protect and alleviate the ASD symptoms (Baron-
Cohen et al. 2013). Finally, the fourth level approach looks into the etiological pathways in order to find out whether there are genetic-epigenetic and environmental aspects.

The subject of focus of our study wants to add to research topics as defined for level 2 (sex/gender-independent and sex/gender dependent characteristics). I.e.: in order to gain more insight into gender differences in young children with an ASD diagnosis, we examined gender differences at the level of screening results as well as in phenotypic expression for those toddlers with a confirmed ASD diagnosis after thorough clinical assessment. As diagnosing ASD at a very young age is clinically hazardous (Oosterling et al. 2010) we also studied eventual gender differences within a subgroup of children with a stable ASD diagnosis that participated in a follow-up assessment three years after initial diagnosis.

We specifically address the following two research questions:

1) What are the gender differences in screening results and phenotypical presentation of ASD (core symptoms, cognition, and co-morbid problems) in very young children with an ASD diagnosis; and

2) How did observed gender differences evolve as these early ASD diagnosed children grow into childhood, three years after initial diagnosis.

Methods

Participants and procedure

This study sample is part of the Diagnosis and Intervention study on Autism in the Netherlands (DIANE study, see Oosterling et al., 2010), which was approved by the regional Medical Ethical Committee. All 252 participants (56 girls / 196 boys; mean age = 32.5 months, SD = 5.0 months) were clinically
referred to our child psychiatry outpatient unit in Nijmegen between October 2003 and April 2007 and considered at risk for ASD, because of either screen positive results (87%) on the Early Screening of Autistic Traits Questionnaire (ESAT; Dietz et al., 2006), or when screen negative (13%) on the ESAT, because of sufficient clinical concern. After referral, children were included in a research program. Initial clinical diagnosis (T1) was established by a multidisciplinary team (a psychiatrist and a psychologist) based on all information available and gathered during a six-week diagnostic assessment program consisting of the following: (a) Questionnaires asking about demographic information, developmental milestones and amongst others the Childhood Behavior Checklist (CBCL; Achenbach and Rescorla 2000); (b) a psychiatric evaluation and a parent-child play observation by a psychiatrist; (c) testing with the Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore, & Risi, 2001); (d) psychometric testing (cognition); (e) psychometric testing (language); and (f) interviewing with the Autism Diagnostic Interview-Revised (ADI-R; Rutter, LeCouteur, & Lord, 2003). Shortly after diagnosis, specific care was organized for all children and their parents. Clinical psychologists who met standard requirements for research reliability administered the ADOS and ADI-R.

About three years later all participants included in the initial sample were approached for a follow up assessment (T2). The diagnostic assessment program at T2 included mostly the same methods and instruments as at T1, with the exception of cognitive and language testing as not all measures were applicable to an older age group. At T2 182 (38 girls/144 boys) children from the initial sample participated (see Figure 1, drop out = 28%), and 112 (21 girls / 91 boys) of them had a stable diagnosis of ASD and could thus be further analyzed for purposes of this study.
Ninety percent of the children included in this study had a Dutch Caucasian background, while 10 percent came from non-western ethnic minorities. Parental education level was more or less normally distributed.

**Measures**

**Screening instrument**

The *Early Screening of Autistic Traits* (ESAT; Dietz et al., 2006; Swinkels et al., 2006) consists of 14 easy-to-administer items measuring early social-communication skills, play and restricted and repetitive behavior focusing for instance on eye-contact, facial expressions, interest in others, varied play and sensory interest, to be answered with yes or no. Children failing three or more items were considered to be at risk for ASD.

**ASD core symptoms, Non-verbal cognitive functioning and co-morbid problems**

**Autism Diagnostic Observation Schedule (ADOS).** The ADOS (Lord et al., 2001) is a semi-structured, standardized, observational assessment covering the three major domains of dysfunction in autism: communication, reciprocal social interaction, and restricted, repetitive behaviours and interests (RRB). In the current study, at T1 children were administered to either Module 1 (non-verbal module; \( n = 233 \)) or Module 2 (module for young children that speak in short sentences but have no fluent language; \( n = 6 \)). At T2, modules were applied as follows: Module 1 \((n= 45)\), Module 2 \((n=110)\), Module 3 \((n=15)\). In order to compare groups over time we applied the revised algorithm scores (Gotham, Risi, Pickles, and Lord, 2007), which allow for inter-module comparisons of domain scores [Social Affect (SA), Restricted and Repetitive Behaviors (RRB) and the sum of these two domains (SARRB)].
**Autism Diagnostic Interview-Revised (ADI-R).** The ADI-R (Rutter et al., 2003) is a semi-structured, standardized, parent interview covering the three major domains of dysfunction in autism: communication, reciprocal social interaction, and restricted, repetitive behaviors and interests (RRB). Individuals are classified as autistic or not autistic, based on standard algorithm scores. In this study we used sum scores for the reciprocal social interaction domain and on the RRB domain. In order to compare groups over time, for communicative functioning, we could only use sum scores on the *non-verbal* domain and, as an indication of verbal abilities, the item score on ‘Overall level of expressive language’ (item 30) with scores ranging from 0 (indicating functional use of speech that involves utterances of three words or more on a daily basis) to 2 (fewer than 5 words total or no speech on a daily basis).

**Cognitive measures.** Because of the big differences in developmental level of the participants a non-verbal IQ was computed using different instruments. At T1, if feasible, the *Mullen Scales of Early Learning* (MSEL; Mullen, 1995) was used. The MSEL is a developmental test with a high reliability and validity intended for use in children aged 0 to 68 months and yields an Early Learning Composite score (mean = 100, SD = 15). This test could be administered to 62% of the toddlers. Non-verbal IQ was calculated as mean score on the visual reception and fine motor subscales. In toddlers who were hard to test with the MSEL, e.g. because of non-compliance or difficulties to remain focused, the *Psycho Educational Profile-Revised (PEP-R)* (Schopler, Reichler, Bashford, Lansing, & Marcus, 1990) was administered (38% of the cases). The PEP-R offers a developmental approach to the assessment of children aged 6 months to 7 years. An indication of non-verbal IQ based on the PEP-R were calculated as: (mean developmental age in months on the non-verbal subscales /
chronological age in months) * 100. At T2, in most cases (72%) the Snijders-
Oomen nonverbal (Dutch) intelligence test (SON-R; Tellegen, Winkel, Wijnberg-
Williams, & Laros, 1998) was used. Otherwise the PEP-R (13%) or one of the
Wechsler tests (WISC, 12%; WPPSI 3%) was applied (Wechsler, 1997; 2002).

Child Behavior Checklist (CBCL – preschool version). The CBCL for ages 1.5
through 5 years is a 99-item checklist, filled in by caregivers, which describes
specific kinds of behavioral, emotional, and social problems. Items are scored
on eight syndrome scales: Emotionally reactive, Anxious/Depressed, Somatic
complaints, Withdrawn, Sleep problems, Attention, Rule breaking behavior and
Aggression. The manual for the CBCL reports adequate reliability and validity
for scale and composite scores (Achenbach & Rescorla 2000; Ivanova et al.
2010).

Analyses

With regard to the first research question, to study gender differences in the
screening results and phenotypical presentation of ASD (ASD core symptoms,
cognition, and co-morbid problems) in very young children at initial diagnosis,
we used, chi-square analyses and independent sample T-tests. OLS regression
models with two tailed tests of significance were used to study underlying
influence of developmental age (non-verbal IQ) on effects of gender. Alpha was
set at 0.05.

Regarding our second research question, to study how eventual observed
gender differences at T1 evolve as early ASD diagnosed children grow into
childhood as well as the difference in differences on core symptoms in this
stable ASD group, we also applied independent sample T-tests with alpha set at
0.05.
Results

Participants

The flowchart (see Figure 1) shows that a total of 252 children were included in the study. After our first assessment (T1) 163 (34 girls /129 boys) of them were diagnosed with ASD. At follow up (T2) 70 children (43 of them with an ASD diagnosis) did not participate (drop-out = 28%). A total of 112 children (21 girls/91 boys) showed a stable ASD positive (ASD) diagnosis and there were 36 children (11 girls / 25 boys) with a stable ASD negative (non ASD) diagnosis. Only 8 children (3 girls / 5 boys) moved from the ASD group at T1 to non ASD group at T2, and remarkably 26 (3 girls / 23 boys) moved from the non ASD group at T1 into the ASD group at T2. Because of the small number of cases in the subgroups that moved from one diagnostic group to another no further analyses could be made for them. So in order to study gender differences in
ASD as toddlers grow into childhood, we could only study those 112 children with a stable ASD diagnosis at both time points.

In addition, before starting to apply analyses on the follow up data and in order to prevent systematic faults, it was verified whether the group that did not participate at follow-up (drop-outs) differed in any significant way from individuals in the stable ASD group in terms of gender, demographics, non verbal IQ or (core) symptoms. No significant differences were found. Therefore, we consider it valid to report only on those children with stable ASD diagnosis and of whom we have data available for both T1 and T2.

Gender differences at initial diagnosis (T1)

Gender differences were studied at two levels, namely: 1) Screening results and age of first worries, and 2) Phenotypic expression with regard to ASD-core symptoms, cognition, and co-morbid problems.
**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Girls</th>
<th></th>
<th></th>
<th>Boys</th>
<th></th>
<th></th>
<th>Δ</th>
<th>Sig-2 tailed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>M</td>
<td>SD</td>
<td>N</td>
<td>M</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESAT sum score</td>
<td>33</td>
<td>6.07 (2.63)</td>
<td>128</td>
<td>5.98 (2.89)</td>
<td>+0.08</td>
<td>0.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age first worries (in months)</td>
<td>33</td>
<td>14.34 (8.72)</td>
<td>120</td>
<td>17.95 (9.25)</td>
<td>-3.56</td>
<td>0.045*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADOS SA</td>
<td>31</td>
<td>14.74 (5.28)</td>
<td>124</td>
<td>12.21 (5.62)</td>
<td>+2.53</td>
<td>0.03*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADOS RRB</td>
<td>31</td>
<td>2.97 (1.85)</td>
<td>124</td>
<td>2.15 (1.77)</td>
<td>+0.81</td>
<td>0.02*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADOS SARRB</td>
<td>31</td>
<td>17.71 (6.37)</td>
<td>124</td>
<td>14.36 (6.83)</td>
<td>+3.35</td>
<td>0.02*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADI-R Comm NV</td>
<td>27</td>
<td>9.33 (3.44)</td>
<td>121</td>
<td>8.27 (3.48)</td>
<td>+1.06</td>
<td>0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADI-R Overall level of language - item 30</td>
<td>28</td>
<td>1.39 (0.69)</td>
<td>121</td>
<td>1.03 (1.03)</td>
<td>+0.36</td>
<td>0.03*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADI-R RSI</td>
<td>28</td>
<td>14.57 (4.75)</td>
<td>121</td>
<td>12.73 (5.39)</td>
<td>+1.84</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADI-R RRSPB</td>
<td>28</td>
<td>3.43 (1.73)</td>
<td>121</td>
<td>3.17 (2.08)</td>
<td>+0.26</td>
<td>0.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NV IQ</td>
<td>30</td>
<td>53.74 (22.32)</td>
<td>117</td>
<td>72.32 (23.21)</td>
<td>-18.58</td>
<td>0.00*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Note: ESAT sum = ESAT total score; ADOS RRB = ADOS Restricted, Repetitive Behavior total (revised algorithm); ADOS SARRB = ADOS Social Affect and Restricted Repetitive Behaviors total (revised algorithm); ADI-R RSI = ADI-R Reciprocal Social Interaction total; ADI-R Comm NV = ADI-R Communication non-Verbal total; ADI-R RRSPB = ADI-R Restricted, Repetitive, and Stereotyped Patterns of Behavior total; ADOS SA = ADOS Social Affect total (revised algorithm); NV IQ = Nonverbal IQ

**screening results and age of first worries**

As shown in Table 1, no gender differences in screening results on the ESAT were found, though parental first worries started significantly at an earlier age in girls (M = 14.34 months, SD = 8.72) as compared to boys (M 17.95 months, SD = 9.25).
**Phenotypic expression: ASD-core symptoms, cognition, and co-morbid problem**

With regard to the ASD core symptomatology there is a slight difference between the clinical symptoms as observed by professionals (ADOS) and the symptoms as reported by parents (ADI-R). On the ADOS, the total mean scores on social affect and restricted and repetitive behavior (SARRB) is significantly higher in girls (M = 17.71, SD 6.37) than in boys (M = 14.36, SD = 6.83), meaning that girls are more impaired than boys with regard to ASD core symptoms. The same picture is true for the Social Affect (SA) and Restricted and Repetitive Behavior (RRB) separately (see Table 1).

On the ADI-R, we observe a trend going in the same direction as scores on the ADOS with girls showing higher scores than boys on verbal ability (item 30, overall level of language) as well as on the three ADI-R domain scores (non-verbal communication, reciprocal social interaction, and repetitive, restricted and stereotyped patterns of behavior; see Table 1). However, as opposed to the ADOS, gender differences on ASD core symptoms are not significant as measured with the ADI-R, except for the mean item scores for verbal ability. Girls show more verbal delay than boys.

At the cognitive level, girls with ASD show more pronounced developmental delay than the boys. I.e.: non-verbal IQ is significantly lower in girls (M = 53.74, SD = 22.32) compared to boys (M = 72.32, SD = 23.21). Moreover, girls are strongly overrepresented in the group with a developmental quotient below 50. Almost fifty-seven percent (56.7%) fell in this category compared to 19.7% of the boys (chi-square=16.5; p. 0001). Interestingly, all significant gender differences on the ADOS as well as on the ADI-R disappeared, when IQ was used as a control variable in an OLS regression model (results available on request).
Table 2 shows the syndrome scale scores on the CBCL at T1. With regard to the coexisting psychopathology girls scored significantly higher on Withdrawn (girls $M=76.44$ (SD 10.93) vs boys $M=71.71$ (SD 10.41) p.02). In contrast boys scored significantly higher on attention problems (girls $M=58.65$ (SD 8.95) vs boys $M=62.51$ (SD 9.82).04) and rule breaking behavior (girls $M=56.74$ (SD 7.17) vs M=63.26 (11.79) p.00). There was not a significant difference between girls and boys on the factors Emotionally reactive, Anxious / Depressed, Somatic complaints, Sleeping-problems or Aggressive behavior.

Gender differences at follow up (T2)

In order to study how gender differences in toddlers with ASD evolve when children grow into childhood, we analyzed the group with a stable diagnosis of ASD (See Figure 1; n = 112). The mean time between initial diagnosis (T1) and the follow up assessment (T2) was 35 months (SD = 7.7 months).
Looking at gender differences as observed by a professional (ADOS), the significant higher score of girls as compared to boys on the Social Affect factor remained (see Table 3). However, the gender effect on the RRB scales (as found at T1) has disappeared. Hence, it can be subtracted that the difference on the SA factor is responsible for the significant difference between girls and boys on the total SARRB factor (M=16.79 (6.32) in girls / M=13.25 (6.91) in boys).

In this group, at the level of ASD core symptoms we observe the same slight difference between the clinical observation of symptoms (ADOS) and the symptoms as reported by the parents (ADI-R) on social interaction problems (M=14.05 (SD 5.21) in girls and M=10.88 (SD 5.49) in boys) on the ADOS and no significant difference but the same trend on the ADI-R. There was no longer a significant gender difference in stereotyped behavior on the ADOS as well as on
the ADI-R (Table 3). Again, the difference in social communicative functioning disappeared after controlling for IQ.

At the cognitive level we found that the mean non-verbal IQ was higher at T2 for both genders. As at T1 girls had lower mean non-verbal IQ as compared to boys, (M= 65.47 (32.54) in girls and M=78.67 (29.75) in boys, p .079), but this was no longer significant, which could be due to the slightly lower sample size (Table 3).

Table 4
CBCL scores in girls and boys at T2

<table>
<thead>
<tr>
<th></th>
<th>Girls N18</th>
<th></th>
<th></th>
<th>Δ</th>
<th>Sig. 2 tailed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Emotionally reactive</td>
<td>62.67</td>
<td>(10.11)</td>
<td>65.05</td>
<td>(9.74)</td>
<td>-2.38</td>
</tr>
<tr>
<td>Anxious/depressed</td>
<td>56.78</td>
<td>(7.04)</td>
<td>56.35</td>
<td>(7.50)</td>
<td>0.43</td>
</tr>
<tr>
<td>Somatic complains</td>
<td>58.28</td>
<td>(9.18)</td>
<td>59.14</td>
<td>(8.20)</td>
<td>-0.86</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>68.89</td>
<td>(10.12)</td>
<td>70.20</td>
<td>(9.60)</td>
<td>-1.31</td>
</tr>
<tr>
<td>Sleep problems</td>
<td>53.61</td>
<td>(5.25)</td>
<td>54.68</td>
<td>(5.99)</td>
<td>-1.07</td>
</tr>
<tr>
<td>Attention problems</td>
<td>60.44</td>
<td>(9.76)</td>
<td>64.27</td>
<td>(8.81)</td>
<td>-3.83</td>
</tr>
<tr>
<td>Rule breaking behavior</td>
<td>58.06</td>
<td>(9.74)</td>
<td>63.61</td>
<td>(11.24)</td>
<td>-5.55</td>
</tr>
<tr>
<td>Aggressive behavior</td>
<td>62.56</td>
<td>(9.66)</td>
<td>64.39</td>
<td>(8.79)</td>
<td>-1.84</td>
</tr>
</tbody>
</table>

P-value ≤ .05

Table 4 shows the factor scale scores on the CBCL at T2 in the stable ASD group. In contrast with the scores at T1 it shows that at T2 no significant differences were found between girls and boys on any of the eight syndrome scales tested, though trends are discernable with boys showing higher scores on the factors “attention problems” and “rule breaking behavior” than girls.
We also calculated the “difference in differences” (DiD) on core symptoms and on non-verbal IQ between girls and boys with a stable diagnosis of ASD at T1 and T2. Overall, for girls as well as for boys, scores on the ADOS and ADI-R decreased (meaning – small - improvement) from T1 to T2, whereas their non-verbal IQ’s improved. However, no significant results were found for the DiD, meaning that improvement of girls on domains on the ADOS or ADI-R and on non-verbal IQ are no different from improvements of boys on these domains (see Table 5).

### Discussion

Within a longitudinal design, the current study aimed at focusing on similarities and differences between boys and girls with ASD as diagnosed in toddlerhood. These children had been referred for clinical assessment after being identified
as at risk for ASD based on a systematic screening at “well baby” clinics. Two research questions were addressed: First: what are gender differences in screening results and in phenotypic expression (ASD core symptoms, cognition and comorbid problems) in very young children diagnosed with ASD?, and second: how do eventual gender differences in infancy and toddlerhood evolve when these children grow into early childhood?

In summary, the results show that, at first screening, no gender differences were found on the ESAT between girls and boys with a confirmed diagnosis. On the other hand, it must be noted that the age at which parents first started to worry about the development of their child was significantly earlier in the diagnosed girls as compared to the diagnosed boys.

At first clinical assessment (T1) girls showed significantly higher scores on core ASD symptoms in the domains of social communicative functioning (SA) and restricted and repetitive patterns of behavior (RRB) as compared to boys and as based on the direct observation with the ADOS. The same trends were observed by information based on parental judgments, as measured with the ADI-R, but did not reach significances. In addition, on average, girls in the current sample showed significantly more overall developmental delay; a large part (57%) of the girls had a co-occurring intellectual disability as compared to only 20% of the boys. Remarkably, the significant differences in phenotypic expression of ASD between boys and girls disappeared after controlling for IQ. With regard to the coexisting psychopathology girls showed significantly higher scores in the CBCL internalizing domain “Withdrawn”, referring to shyness – aloofness and anxiety, whereas boys scored higher on the externalizing domains of “Attention problems” and “Rule breaking behavior”.

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At follow-up (T2), three years later, at symptom level, based on clinical observation, girls still had significantly higher scores on social communicative functioning which disappeared after controlling for IQ. There were no longer significant differences in the scores for restricted and repetitive patterns of behavior. The average non-verbal IQ’s in girls were still lower than in boys, but the differences were no longer significant.

The results at screening presented here confirm earlier findings by Ozonoff et al. (2010) and Rivet et al. (2011) who also identified a distinct group of girls with severe ASD and learning disorder diagnosed at a very young age. Also in line with several studies (Holtmann et al. 2007; McLennan et al. 1993; Tsai and Beisler 1983), our findings at initial diagnosis, confirm that girls, as compared to boys, with a very early diagnosis of ASD show more social communicative problems in toddlerhood. However, this is contradictive to results of other studies that did not find differences between boys and girls with regard to levels of dysfunctional social-communicative behavior (Bolte et al. 2011; Banach et al. 2009; Carter et al. 2007; Holtmann et al. 2007; van Wijngaarden-Cremers et al 2014a). In addition, our study shows significantly more stereotyped behaviors and restricted patterns of behavior (RRB) in girls with very early diagnosis as compared to boys. This is in contrast with other studies that report significantly more rigid and repetitive features in boys than in girls (Bolte et al. 2011; Banach et al. 2009; Carter et al. 2007; Holtmann et al. 2007; van Wijngaarden-Cremers et al 2014a ). These ambiguous findings might be explained by a recruitment bias. Whereas in our study participants were recruited from a systematic screening in an at risk sample other studies mainly recruited participants from clinical referred children. In these clinically referred children, girls with ASD in combination with serious developmental delay could
have been missed by their pediatricians. For example, repetitive behaviors in these low functioning girls could have been attributed to their intellectual disability instead of co-morbid ASD (Matson et al. 1997; Matson et al. 2010; Wilkins and Matson 2009). Therefore a group of girls with ASD might be underrepresented in some of the studies referred to here, and this could be an explanation for the fact that more girls with ASD and severe “repetitive and stereotype” behaviors were detected in our study as compared to other studies.

All together our results contribute to support the assumption that there is some evidence for a specific female phenotype in autism representing severe cases of autism with co-occurring marked intellectual disability that subsequently are diagnosed early in life. The question remains whether this group is also similar at other levels (van Wijngaarden-Cremers et al. 2014b) as their clinical homogeneity does not imply that they would be genetically similar nor at endophenotypical level alike.

In general, studies on “female phenotype of severe autism with a marked developmental delay” all attributed the gender differences in very young children to the striking developmental delay in girls (Carter et al. 2007, Hartley & Sikora 2009; Holtmann et al. 2007; McLennan et al. 1993; Pilowskey et al. 1998). In our study, the girls, show a marked progression on IQ measurements between the initial assessment and the follow-up into early childhood. Moreover in second instance the girls in our study do not differ significantly anymore from the boys in developmental age. This could be attributed to the benefits of early detection and intervention. But it also questions the relation between intellectual disability and ASD. Are they just merely co-occurring, or do autism and general development impact on each
other? It is possible that the severity of the autism hampers general development. In other words the severe autism could have a negative impact on the overall development of these children. Our data tend to confirm this hypothesis. Girls in our study seem to catch up once they have been diagnosed and possibly have been stimulated in an different way according to their communicative and social impairment, and then partially compensate for the earlier delays in development.

In our sample the average developmental IQ’s are under 70 with a marked lower IQ in the girls. In other words high-functioning girls with ASD are hardly identified at a very young age. This finding is in line with recent studies that show that “milder autism” is diagnosed far later in high functioning girls and women than in boys and men (Begeer et al. 2013; Shattuck et al 2009). It also supports the hypothesis that along with the phenotype that we describe of severely impaired girls with ASD and intellectual disability, there could be a second phenotype of ASD in females of high-functioning girls with autism that are less well acknowledged. The question is why these girls are diagnosed so late. On one hand some suppose that this second female phenotype in intellectually high functioning girls with ASD, has factors ‘protecting them for ASD’ (Lai et al. 2014). This supposes that these girls have competencies e.g. less problematic social-communication, less bizarre preoccupations and less stereotypies that make them go clinically unnoticed (Dworzynski et al 2012; Kopp and Gillberg 2011; Lunegård et al 2011). On the other hand, it could also be the case that high function girls and women do not present with the “male criteria for autism as currently used for the nosological identification of ASD cases” (Lai et al. 2014). Several studies draw attention to the fact the girls and women with late ASD diagnoses have often been previously “misdiagnosed”
with having affective disorders or personality disorders, mainly borderline type (Begeer et al. 2013; Kopp and Gillberg 1992; Nilsson et al. 1999). Moreover their parents, relatives, and health professionals tend to attribute their deviances as being female qualities as shyness or anxiety. In fact, several studies draw attention to the phenomenon. So the late diagnosis of high functioning girls with ASD could be explained by gender-differences in symptom presentation as well as symptom misinterpretation (Holtmann et al. 2007).

**Strengths and limitations of this study**

The undoubtable strength of this study is that it is based on a population wide, systematic two-step screening in two provinces in the Netherlands. After detection in the community paediatric well-being centres the positive cases were thoroughly assessed at our university medical centre. Though it must be said that this early detection accounts only for an identification of an odd 20 pro mille cases so far below the estimated 1% of clinical cases of ASD in the general population. In other words, screening in very young children only yields the most severe cases within the autism spectrum.

The current study has also several limitations. A major limitation is that we have no information about the children that screened negative on the ESAT and did not enter our study. So we could not compose a contrast group to monitor for developmental variation in very young children. Though the attrition rate was low we could not account for all the cases at follow-up. Moreover, the number of cases in the subgroups with children at follow up that moved in or out of the ASD diagnosis was too small that no further analyses
could be made. On the other hand it could also mean that ASD is a stable diagnosis.

**Future directions**

It seems clear that the early screening instruments (such as ESAT) are not appropriate screening instruments for detecting ASD in female toddlers with a normal or higher IQ. Therefore more research is needed to understand and describe the different symptom presentation in girls and women. And subsequently based on those criteria it will be important to develop (screening) instruments, that are better adapted at detecting the female phenotype of ASD. Some have already been elaborated like the ASSQ-REV (Kopp and Gillberg, 2011) for school aged children in which more female sensitive items have been added. Longitudinal studies

This study sheds some light on gender differences in very young children with autism: in this group a sample of severely affected girls draws without any doubt our attention. It remains on the other hand intriguing why in adolescence and adulthood so many girls and women are clinically diagnosed with autism that apparently had gone unnoticed before. Intriguing to know what kind of toddlers they were. Hopefully some population based prospective studies, like Trails and generation R in Rotterdam in the Netherlands, and ABC in Norway, will be able to help us solve that puzzle.
References


Chapter 7

General Discussion
General Discussion

In this Chapter, we first summarize the main findings on gender and developmental psychopathology that we address in this thesis. After a critical reflection on the strengths and limitations of our study, we will outline possible future directions for research. Finally, we will discuss the implications of our findings for clinical practice and education of professionals. We will also make recommendations for the services involved in diagnosing and treating girls and women with (potential) developmental disorders, in particular for those with autism spectrum disorders.

Introduction

The original starting point of our study was the intriguing finding of large comorbidity of developmental disorders in patients with substance use disorders (research question 1). Remarkably, in our cohort autism-spectrum-disorder (ASD) was only identified in men. Thereafter, the main aim of this study was to get a greater insight in differences in underlying causal mechanisms in the development of the phenotypic presentation of psychiatric disorders, and especially with regards to the role of gender (research question 2).

The question was raised how gender has a developmental impact on the genes, brain functioning, the neuropsychological profile and the behavioural coping
mechanisms that help individuals adapt in varying circumstances (research question 3).

In third instance we were wondering if these insights would contribute to our understanding of gender differences in the clinical presentation of developmental disorders in particular Autism Spectrum Disorder (ASD) (research question 4).

As ASD is often diagnosed late in life in girls and women with a average to above average intelligence, we aimed to investigate why these women were not identified at a very young age (research question 5).

**Main findings**

Our starting question was which are the comorbidities between Substance use Disorder and Developmental Disorders and how could they be explained.

**Research question 1**

1) The results of our first study show that attention deficit hyperactivity disorder (ADHD) is highly comorbid with Substance Use Disorder (SUD). But is also raised awareness for the often underestimated comorbidity between SUD and autism spectrum disorder (ASD). Moreover it occurred to us that like ADHD and ASD, addiction (SUD) can be perceived as a developmental disorder in which genetic predisposition and exposure to environmental vulnerability play a role. SUD can be induced by very early stress and exacerbated by current stress, thus affecting the functioning of the cortico-striatal dopamine regulation systems and the HPA axis. In this respect there is an overlap at this level of brain functioning between ADHD, ASD and SUD (Lange et al. 2011).
This last finding poses fundamental questions with regard to how psychopathology is currently conceived. Is there still validity for the current “distinct” categories in classification systems like DSM 5 and ICD 10?

We wanted to look into what is known about the different mechanisms in development at different levels (genes – brain – neurocognition – behaviour) that eventually can lead to psychopathology as a result of interaction with the environment. In this process we became interested in the role of the environment, as well as in the role of gender on the expression of psychopathology.

The second, subsequent, research question was whether the current classification systems with diagnostic categories and comorbidities are still viable both from a conceptual as from a clinical point of view.

**Research question 2**

Our study into the mechanisms in development of psychopathology, as published in our scientific essay, shows that a conceptual stratification in five levels - (1) genetics (2) epigenetics (3) brain-structure and functioning, (4) neurocognitive capacities (5) behavioural expression - is actually the most favoured model. At all levels the permanent interactions with the biological psychological and social environment influences development. In return the individual has a strong impact on his/her direct environment. The outcomes of these processes express themselves in cognitions, emotions and behaviour or deviances in these. In other words: genetic and epigenetic deviances in interaction with (external) risk- or protective-factors lead to “different” brains, which through “different cognitive and emotional pathways can result in
“different” behaviours. Clinical categories are no longer valid as we could show that they often are merely different behavioural (phenotypical) expressions of the similar underlying causal mechanisms and factors. Our subsequent third research question was on the influence of gender on development and psychopathology.

**Research question 3**

In this study we conclude that gender plays an important role in not only the vulnerability to develop certain physical and/or mental diseases, but also in the different ways women and men (learn to) cope with them. Gene-environment interactions are highly gender sensitive and lead to neurobiological differences between females and males in the development of stress regulation. Women are biologically more vulnerable to stress because of a different level of HPA axis activity and are more likely to develop psychopathology (affective disorders) when facing the same stressful events as men. Stress seems to have a greater negative impact on the psychological health of (pre-menopausal) women, and conversely, men appear less at risk for developing psychopathology. Typically men will be far more prone to respond with metabolic disease in relation to acute and chronic stress. Gender differences influence the social environment that in return plays a role in both the development of (psycho)pathology and the interactive social learning processes of how to cope with stress and its consequences. The social rules are culture and gender-related. The way parents respond to their children’s emotions is influenced by both child gender and type of emotion. There is growing evidence that links parental emotion-socialization practices with various
aspects of child adaptation and maladaptation. Moreover, the impact on and influence from the social environment are different: women are far more sensitive to rejection, absence of social support and social structure, whereas defeat has a greater impact on stress regulation in men. In other words gender influences physical, mental as well as social health.

The question is how does this relate to psychopathology. Our fourth research question focussed on what do we currently know about gender differences in autism spectrum disorder (ASD).

**Research question 4**

This meta-analysis of 20 studies investigated gender differences in ASD at symptom levels. Overall, it appears that there are few differences in symptom severity between males and females. Males and females with ASD show similar symptom severity in the domain of communication and social behaviour, but girls have less restricted interests and behaviours and stereotypes than boys from 6 years onwards but not in the younger children.

Our final research question addressed the issue of gender in the early detection and evolution of symptoms in ASD.
Research question 5

In this study we looked into gender differences in toddlers at first detection and at our follow up. This cohort was composed of very young children diagnosed with ASD after a population based screening (the Diagnosing Autism in the Netherlands – DIANE - project). In follow-up they were re-assessed at a follow-up two to three years later. This study confirmed earlier findings that there definitively is a distinct group of girls with severe autism and a low developmental quotient that can be diagnosed early in life. These girls have significant more social interaction and communication problems as well as more stereotyped behaviours and interest as compared to the larger group of boys equally diagnosed early. Parents started to worry about their child at a significantly earlier age in these girls, and the non-verbal IQ was significantly lower in these girls as compared to boys. Their diagnosis remained stable over time, though their intellectual development progressed. But remarkably it appears that the “high functioning” group of girls with ASD typically clinically diagnosed with autism in late childhood, adolescents and even often in adulthood, cannot be detected with the current diagnostic tools in early childhood.

Discussion
The results of our studies shed some light on the influence of gender and the social environment on the complex multilevel interactive cascade of development. The issue of gender is important. It remains unclear why psychopathology as severe as ASD can be masked for such a long time in a particularly vulnerable group of girls and women, who are severely handicapped in adulthood by their autistic features and limitations, while at
the same time they are not acknowledged for the severity of their developmental disorder. How is this possible?

Our meta-analyses (4) as well as our study of ASD in very young children (5) show underrepresentation of females with ASD who have an average to high intelligence. This is in line with recent studies which show that ASD is more often diagnosed in females presenting with classic symptoms and intellectual disability, and report under diagnosis in females with a higher IQ or with less extreme stereotypies (Kopp and Gilberg 2011; Dworzynski et al 2012; Lunegård et al 2011). Females could present another autistic phenotype than males. The risks for developing ASD are likely to be multifactorial, with many different genetic variants and environmental factors contributing to the likelihood. Sex chromosomal gene dosage and levels of sex hormone may be involved (Baron-Cohen et al, 2011). Biological theories that explain the sex difference in ASD prevalence propose that females have a higher threshold for reaching the affected status than males. Genetic studies hypothesize that females with ASD are likely to be carrying a higher heritable load than affected males (Werling and Geschwind 2013). But so far, the male-skewed bias towards restricted interests and behaviors and stereotypes has not been precisely elucidated by biological theories. The underlying mechanisms are yet to be identified.

Another hypothesis is that the diagnostic criteria of ASD could have been unjustly biased towards males. It has recently indeed been recognized that the behavioral phenotype of ASD is different in girls and women to that in boys and men, whereas the formulation of diagnostic criteria are based on the symptoms as seen in boys (Kirkovski et al. 2013). Dworzynski and her colleagues (2012) recognized this difference and hypothesized that an
unknown mechanism helps girls with ASD to cope in such a way that their symptoms do not reach the diagnostic threshold.

When we look at the findings of our study of the development of psychopathology (2) and the influence of gender on this (3) it could be so that gender exerts influence at all or most of the 5 levels (genetic, epigenetic, brain, neurocognitive, behavioural) of the interaction with the biological psychological and social environment. Gender thus contributes to the development and the female phenotype of ASD. It could also be the fact that gender affects the way girls and women handle their social and communicative shortcomings and display a different type of restricted pattern of behaviours and interests that is far less odd that those in boys. As we pointed out in our gender study, parental emotion socialization practices influence various aspects of child adaptation and maladaptation. The impact of gender on the social environment is different. Sensitivity to rejection, absence of social support or social structure are typically feminine characteristics. It could therefore be that all these factors play a role when it comes to the different phenotypical presentation of ASD in girls and woman. The specific features that distinguish girls with ASD are increasingly recognized. Girls with ASD have better imaginative play than affected boys (Knickmeyer, et al. 2008). Girls with ASD show more interest in social relations (Attwood 2007) and have more socially accepted special interests (horses, dolls, pop stars). Unfortunately, these characteristics contribute at masking their ASD (Kopp and Gillberg 1992) and its severity.

As ASD is now defined according to the male phenotype this could also imply that there is an ascertainment bias. Several studies have shown that girls with milder symptoms and a normal IQ tend to be diagnosed at a later age than
boys (Kopp and Gillberg 1992; Goin-Kochel et al. 2006; Siklos and Kerns 2007; Begeer et al. 2013; Russell et al. 2011; Giarelli et al. 2010) or have been misdiagnosed (Kopp and Gillberg 1992; Nilsson et al. 1999; Begeer et al. 2013). It has been argued that girls with ASD show different and less severe social and communicative impairments than boys do, and parents, relatives, and health professionals may consider these impairments as being due to “normal” female shyness or anxiety. This misinterpretation of symptoms leads to mis-referrals and ultimately to misdiagnosis (Holtmann et al. 2007). Autistic girls may be diagnosed as having anxiety disorder, avoidant personality disorder, etc. This implies that ASD is potentially under-diagnosed in girls and women (Mandy et al. 2011). Moreover, girls with “internalizing” problems are referred to professionals less often than boys with similar problems, probably because these behaviors are considered to be “normal” in females (Rucklidge 2010) and cause little disruption. However, once the diagnosis ASD has been established, studies show that there are no differences in the type or severity of the core symptoms and the same type of comorbid conditions accompanying ASD in girls as in boys (Lugnegård et al. 2011). This indicates that the ascertainment bias is a real problem in the identification of females with ASD as a group of girls with milder symptoms in whom the disorder is not or only later diagnosed.

It must be said that we may have created a paradox by stipulating that on one hand the categorical approach to psychopathology is obsolete and that a multilevel “a-theoretical” approach should be favored, whilst on the other hand, we have focused on Autism Spectrum Disorders as a distinct condition that in its actual classification is not suited for diagnosing girls and women – without questioning ASD’s clinical validity. On one hand this holds true and may
seem strange. On the other hand the category “Autism Spectrum Disorder” is one of the few examples in which DSM 5 has really taken into account the scientific progress of the past three decades. The choice was made to bring all individuals with “autistic features” under an umbrella category. There are indications that this is a well-established clinical reality. Lord et al. (2010) clearly showed that clinicians and researchers, all together, are good at distinguishing ASD conditions from non-ASD conditions. But within ASD there are no solid and distinct sub-groups. This calls for heuristic efforts to tease out in research which underlying different mechanisms can be identified, both in a causal way, eventually leading to well defined subcategories. Cluster analyses could be performed at all levels involved. But the distinctiveness of ASD has been seriously challenged at a genetic level. Recent findings show that different psychiatric (developmental) disorders such as autism, ADHD, affective disorders and schizophrenia, in fact have a common genetic predisposition and appear to be merely different clinical expressions of common underlying vulnerabilities (Cross-Disorder Group 2013). So this again questions the genetic specificity of the diagnostic category such as defined in the current classification systems. And what to think of characteristics at brain level (different forms of deviant connectivity patterns – functional dysfunctions in perception – different neurotransmitter deviances), neuropsychological (executive functioning – central coherence and Theory of Mind) and finally not to forget co-occurring features like anxiety, obsessively, aggression regulation and mood) which could be even more gender sensitive and again not exclusive and thus not specific for the category ASD. This is certainly going to impact profoundly on the way mental conditions and disorders will be diagnosed. Instead of a single minded categorical approach, the multilevel diagnostic profiles will open windows of opportunity for a more individualized treatment
This will be based on features that are not specific to one of the current categories of psychopathology, but could be highly important when it comes to targeting treatment at individual characteristics that are in play. One of the dimensions that will have to be strongly acknowledged by health professionals is that of gender. This implies that interventions will need to be gender responsive in order to be successful. Therefore “gender sensitive” actions will be necessary at various levels aiming at cross-sector policies, in families and communities, and the way services are provided in health care. Thus, in order to improve health for all, we need to raise awareness for gender issues and improve gender sensitivity into healthcare practice, society and policy makers.

**Strengths and Limitations of our studies**

**Strengths**

We have taken another point of view to approach (developmental) psychopathology. This opens windows of opportunities for future directions in research and a different clinical approach of psychopathology. Another strength is that we have taken gender seriously into account and explicitly raised the question of the role of gender in the interplay of risk- and protective factors in development.

We believe that gender should be considered as important as environmental factors when it comes to considering causal pathways of development typical as well as atypical.

From a methodological point of view, in order to answer our questions we have used several solid methods to tease out the hypotheses stemming from an
exploratory search and two clinical essays with a thorough systematic review and meta-analysis and a prospective follow-up of a vulnerable group of children with ASD recruited in a population based sample.

**Limitations**

Yet, it is obvious that we generated hypotheses that need far more empirical proof than the two small experimental studies reported here. Our first clinical search was methodologically weak as it was a retrospective chart-review based on files that had not been set up in order to be subject to a systematic comparative analysis. The scientific essays we conducted on the state of psychopathology and the influence of gender are very useful in generating hypotheses. When they are not seriously tested by empirical research, however, they could be more biased by pre-hypotheses that one would wish for.

Another limitation is the paradox we created by ruling out categorization on clinical features as a meaningful approach to psychopathology, whilst retaining on namely autism spectrum disorder that in turn does not appear to be as distinct as clinicians like to think.

Finally we have speculated quite often about the clinical characteristics that could be helpful in promoting an earlier detection of ASD in girls and women, but the studies that could yield these criteria have yet to be conducted.
Future directions and implications

For research

Research should take a different approach towards targeting genes and endophenotypes by taking development and gender into account as crucial features for studying developmental (psycho) pathology. This means that research should focus more on groups defined by common genotypes and endophenotypes instead of sticking to the current clinical syndromes. Also, more research should take (social) environmental risk factors seriously into account at all five levels (genetic, epigenetic, brain, neurocognitive, behavioural). One should also take gender into account as it is clear that gender influences developmental pathways at all levels. Finally one should tease out the difference between direct influence of gender as compared to its indirect influence gender itself is in interaction with the environment.

It is also important to trace antecedents of women diagnosed with autism to look for patterns that may help to understand why their diagnosis was missed for such a long time. The question is 1) which symptoms should raise awareness in clinicians to potential autism in girls, and 2) which underlying neuropsychological patterns (for instance executive functioning, central coherence, or theory of mind) or others features that could be identified as risk factors for ASD in girls and women. More research is needed to develop (screenings) instruments, which are better-adapted or fit to help defining and identifying a female phenotype of ASD.
Consequences for clinical practice, training and education and health policy

Clinical practice

In our opinion, clinicians should favour individual multilevel diagnoses and take gender into account. It is important that they assess the environment in order to trace and identify gender-linked risks- (from rearing style to trauma) and protective-factors. Finally clinicians should be aware of overlapping clinical categories and of developmental (and gender) aspects. This means that clinicians could enrich their diagnostic assessment by an ongoing process of evaluating strengths and weaknesses in each individual patient at the level of 1) symptoms, behavioral and emotional responses, 2) the psychological and social environment characteristics and 3) the neuropsychological profile of the patient and in the future 4) aspects of brain physiology and 5) the genetic constitution of the individual.

In terms of ASD in girls and women, clinicians should be well aware of the fact that the phenotypical presentation in females can be very different and is often masked by conditions like anxiety disorders, PTSD, and SUD, or an inaccurate interpretation of symptoms like social anxiety and OCD.

Finally, although it was not a main focus in our study, we think that clinicians should realize and be aware of the high risk girls with ASD (like our patient Mary) have to get sexually abused because of the lack of adequate interpretation of the intentions of others and thinking that this is what is normal and expected from them.
For medical professionals education and training

Education and training of medical and other healthcare professionals will need to change the focus from a segmented approach to (psycho) pathology with a “one-fits-all” guideline treatment approach, to a far more integrated approach. Disease should be perceived in its interactive context between genetic assets and risks, expressed at different physiological and psychological levels and subject to influences of gender over different periods in life and the impact of the close, rearing and supportive environment and the broader socio-economic context.

It is interesting to note that awareness will have to be raised on the relative complexity of gender and environmental influences as they are bidirectional and often indirect.

For general health policies

The changing view on defining (psycho) pathology and the broader approach of diagnosis and treatment asks for changes in the way we organize our healthcare. It implies that the health care system should reflect on the necessity for personalized medicine in which individual aspects, gender and the social context should be valued more than in the actual tendency to diagnose and treat patients according to guidelines and protocols that are based on diagnoses. Where this can be useful in strictly defined diseases such as strictly genotyped cases in oncology, even there the treatment options should take far more into consideration the persons age, abilities to cope, gender and social context.
It also asks for a broader societal reflection on the consequences of the new definition of health (Huber 2011). Health perceived not as the absence of disease but as the ability to adapt to varying circumstances. This is in line with the new interactive approach to diagnosing and treatment as put forward in this thesis.

The question will be how to organize it, in a context where patients should be more aware of their own role and responsibility and the imperative for them to develop better coping competencies in order to live a worthwhile healthy life.
References


Chapter 8

Summary

Samenvatting

Dankwoord

Curriculum Vitae

Publications
Summary

The research described in this dissertation arose from clinical curiosity. As an addiction-psychiatrist I ran into patients with Substance use disorders that seemed to be different. Behind their addiction, undiagnosed developmental disorders appeared when one looked closely into their social functioning and behaviours and took a serious look into their developmental history. I got deeply puzzled by the so loosely used notion of comorbidity. Patients received a broad array of diagnostic labels, whereas most of them were subsequently diagnosed with autism. This comprehensive diagnosis explained many of their complications, better than just coining them as “separate” comorbid conditions. At that time I became acutely aware of the fact that developmental trajectories leading to ill understood clinical features, are of importance in the field of adult psychiatry.

Yet it was striking that in our first clinical study on potential comorbidities between SUD and developmental disorders, autism-spectrum-disorder (ASD) was only identified in men. This intrigued me greatly, until I came across an impressing patient. She had been given many different diagnoses like borderline personality disorder, post-traumatic-stress-disorder (PTSD), ADHD, until she was finally diagnosed with Autism. With this diagnosis things fell into place. But the question that kept puzzling me is why it takes clinicians in adult psychiatry such long time before making the correct diagnosis and acknowledge the fact that in her case the autistic features were in fact responsible for a misleading variety of morbid expressions such as addiction, anxiety, social fear and a rigid compulsivity. This is the starting point for of the present studies.
After a general introduction (chapter 1), we presented the first study on the comorbidity between substance use disorders and ASD (chapter 2). From that point on, the main aim of this study was to get more insight in differences in underlying causal mechanisms and especially the role of gender in the development of the phenotypic presentation of psychiatric disorders (Chapters 3 and 4). The question being how gender impacts on the disclosure of genes and their epigenetic spin-off; how gender impacts on the development of brain functioning, the emergence of the neuropsychological profile and finally on the behavioural coping mechanisms that help individuals react to varying circumstances (Chapter 4).

In third instance we were wondering if these insights would contribute to our understanding of gender differences in the clinical presentation of developmental disorders particular in Autism Spectrum Disorder, that is so often diagnosed so late in high functioning women (Chapter 5) and why these women were missed out at a very young age (Chapter 6). The findings are discussed in a final chapter 7 the general discussion.

**What are the main findings?**

Our starting question was which are the comorbidities between Substance use Disorder and Developmental Disorder and how they can be explained.

(1) The results of our first study showed that Substance Use Disorder (SUD) has, as is well known, a strong comorbidity with attention deficit hyperactivity disorders (ADHD), but that there might be also a less common but greatly underestimated comorbidity with autism spectrum disorder (ASD). Surprisingly in our mixed sample of patients with SUD this comorbidity was exclusively
identified in men. In other studies the gender distribution was either not taken into consideration or quite extreme with only 1 in 6 women with concurrent ASD in an addicted population. It also occurred to us that ASD and addiction both could be perceived as developmental disorders in which the interaction of a genetic predisposition and environmental vulnerability play a role. They can be induced by very early stress and exacerbated by current stress thus affecting the proper functioning of the cortico-striatal dopamine regulation systems (and also the HPA axis). At that level there is a remarkable overlap between addiction and ASD/ADHD, which questions the validity of the distinction between these at first glance so different clinical categories.

This raised fundamental questions with regard to how psychopathology is currently conceived and what the validity of current distinct classificatory categories still is. We wanted to look into what is known about the different developmental mechanisms at different levels that lead to psychopathology. In this process we became interested in the role of the environment as well as the role of gender on the expression of psychopathology.

The second, subsequent, research question was if the current classification systems with diagnostic categories and comorbidities are still viable both from a conceptual as from a clinical point of view.

(2) Our study into the mechanisms in development of psychopathology showed that a conceptual stratification in five levels (genetic, epigenetic, brain, neurocognitive, behavioural) is actually the most favoured model. At all levels the interaction with the biological- psychological- and social environment influences development. In return the individual has a strong impact on his/her
direct environment. The outcome of these processes expresses itself in cognitions, emotions and behaviour or deviances in these. The causal chains are complex and by no means unequivocal.

In conclusion we strongly advocate for a reconsideration of the actual classification systems in psychiatry. These are equally ill fit for clinical practice as for research. In the latter case research into underlying factors should be favoured above sticking to clinical categories that are no longer valid, as they could be merely different expressions of the same underlying causal factors/mechanisms. For clinical purposes we plea for a more individualized approach to diagnosis taking the different levels, as we described, into account.

Our third research question was on the influence of gender on development and (psycho)pathology.

In this essay we conclude that gender plays an important role in not only the vulnerability to develop certain physical and/or mental diseases but also in the way individuals learn how to cope with them. Gene-environment interactions are highly gender sensitive and lead to neurobiological differences between females and males in the development of stress-regulation. Gender plays a role in child rearing and gender differences are present in the cultural and social context in which individuals live. All these environmental/social factors in turn also play a role in both the development of psychopathology as well as in the way to cope with it. In other words gender influences physical-, mental- as well as social health.
Our fourth research question focussed on what is the current knowledge of gender differences in autism spectrum disorder (ASD).

Our meta-analysis of 20 studies investigated gender differences in ASD at symptom levels. Overall, it appears that there are very little differences in symptom-severity between males and females. Males and females with ASD showed similar symptom severity on communication and social behaviour, but girls showed less restricted interests and behaviours and stereotypes than boys from 6 years onwards but not in the younger children. But this could also be due to the fact that only girls and women that meet “male defined” criteria for ASD are diagnosed, leaving many girls and women out of consideration.

Our final research question addressed the issue of early detection and evolution of symptoms in ASD.

In our follow up study we looked into gender differences in toddlers. This cohort was first assessed after a population based screening (the Diagnosing Autism in the Netherlands {DIANE} project) and eventually diagnosed with ASD. In a second tear they were re-assessed at a follow-up two to three years later. This study confirmed earlier findings that there definitively is a separate group of girls with severe autism and a low developmental quotient that can be diagnosed early in life. These girls have significant more social interaction and communication problems as well as more stereotyped behaviours and interest as compared to the larger group of boys equally diagnosed early in life. Parents started to worry about their child significantly at an earlier age in these girls. Moreover the non-verbal IQ was significantly lower in this group of girls as compared to the boys. Their diagnosis appeared to remain stable over time, although their development progressed. Remarkably the “high functioning”
group of girls with ASD typically clinically diagnosed with autism in late childhood, adolescents and even often in adulthood, cannot be detected with the current diagnostic tools and defining criteria in early childhood.

In the general discussion we addressed the question why psychopathology as severe as ASD can be masked for such a long time in a particularly vulnerable group of girls and women. These women are, severely handicapped in adulthood by their autistic features and limitations, but were not acknowledged for the severity of their developmental disorder. We hypothesised that females could present with other or different autistic phenotypes as compared to males. The risks for developing ASD risk are likely to be multifactorial, with many different genetic variants and environmental factors contributing to the liability. Sex chromosomal gene dosage and levels of sex hormone may be involved. Biological theories that explain the sex difference in ASD prevalence, propose that females have a higher threshold for reaching the affected status than males. Genetic studies hypothesize that affected females are likely to be carrying a higher heritable load than affected men. So far, the male-skewed bias towards restricted interests and behaviors and stereotypes has not been precisely elucidated by biological theories. The underlying mechanisms are yet to be identified.

Another hypothesis is the diagnostic criteria of ASD could be unjustly biased towards males. It has recently indeed been recognized that the behavioural phenotype of ASD is different in girls and women than in boys and men, whereas diagnostic criteria are mainly based on the symptoms seen in boys. Some researchers suggest that an unknown mechanism helps girls with ASD to cope in such a way that their symptoms do not reach the diagnostic threshold.
When we look at the findings of our study of the development of psychopathology (2) and the influence of gender on this (3) it could be so that gender exerts influence at all (or most) of the five levels (genetic, epigenetic, brain, neurocognitive, behavioural) of the interaction with the biological-psychological- and social environment which can contribute to the development and the female phenotype of ASD. It could also be the case that it affects the way girls and women handle their social- and communicative shortcomings. And explain why they display a different type of restricted pattern of behaviours and interests that is far less odd that those seen in boys. As we pointed out in our gender study, parental emotion-socialization practices are linked to various aspects of child adaptation and maladaptation. Moreover the impact of the social environment is different. So it could be that all these factors play a role leading to a different phenotypical presentation of ASD in girls and woman.

As ASD is now defined according to the male phenotype this could also imply that there is an ascertainment bias. It has been argued that High Functioning girls with ASD show different and less severe social and communicative impairments than boys do, and parents, relatives, and health professionals may consider these impairments as being due to “normal” female features like shyness or anxiety. This misinterpretation of symptoms could lead to miss-referrals and ultimately to misdiagnoses. Autistic girls might therefore be diagnosed as having anxiety disorder, avoidant personality disorder, etc., which means that ASD is potentially underdiagnosed in girls and women. However, once the diagnosis ASD has been given, studies show that there are no differences in the type or severity of the core symptoms and the same type of comorbid conditions accompanying ASD in girls as in boys.
Future directions and implications

For research

We argue that research should take a different approach namely at targeting genes and endophenotypes (at a different level) and take development and gender into account as crucial features when studying (developmental (psycho) pathology. It will also be important to trace antecedents of women diagnosed with autism to look for patterns that may help to understand why their diagnosis was missed for such a long time and which symptoms should raise awareness in clinicians. More research is needed to develop (screenings) instruments, that are better adapted or fit to help defining and identifying a female phenotype of ASD.

For clinical practice / training / education and health policy

Clinicians should favour individual multilevel diagnoses and take gender into account. It is important that they assess the individual’s environment in order to trace gender-linked risk- and protective factors. Clinical awareness of broader underlying categories and developmental (and gender) aspects will be of great importance. In terms of ASD in girls and women clinicians should be aware of the facts that the phenotypical presentation in females can be different and often is masked by “comorbidity”.

Education and training of medical and other healthcare professionals is needed in order to help foster the change of focus from a segmented approach to (psycho) pathology with a “one-fits-all” guideline treatment approach, to a far more integrated approach. In this broader approach disease is defined in the context of permanent interaction between individual and environment and
subject to influences of gender. All the external influences can be either protective or risk enhancing.

The health care system should seriously reflect on the necessity for personalized medicine in which individual aspects, gender and the social context are valued more than in the actual situation instead of the current tendency to diagnose (or even merely classify) patients and subsequently treat them according to guidelines and protocols that are based on loose diagnostic categories.
Samenvatting

De in dit proefschrift beschreven studie is voortgekomen uit klinische nieuwsgierigheid. Als psychiater werkzaam in de verslavingspsychiatrie kwam ik in aanraking met patiënten die naast hun verslaving psychiatrische aandoeningen hadden die “anders” leken te zijn. Ze vielen op door hun inadequate sociale gedrag. Door zorgvuldig te diagnosticeren en door goed naar hun ontwikkelingsgeschiedenis te kijken, bleek er vaak sprake van een ontwikkelingsstoornis te zijn. Wat mij tevens verbaasde was de aanwezigheid van de hoeveelheid comorbide diagnoses die waren gesteld. Tegelijkertijd kwam het besef dat verstoorde ontwikkelingstrajecten kunnen leiden tot niet altijd even goed begrepen klinische kenmerken met een reeks uiteenlopende classificaties van verschillende psychische aandoeningen tot gevolg.

Daarnaast was het opvallend dat in onze eerste klinische studie naar een mogelijke co-morbiditeit tussen verslaving en ontwikkelingsstoornissen, autisme-spectrum-stoornis (ASS) alleen geïdentificeerd werd bij mannen. Dit intrigerende mij zeer en ik kon het voor mijzelf niet goed verklaren totdat ik in aanraking kwam met een indrukwekkende patiënte. Ze had reeds veel verschillende diagnoses, zoals borderline persoonlijkheidsstoornis, post-traumatische stress-stoornis (PTSS) en ADHD opgeplakt gekregen totdat ze eindelijk door ons werd gediagnosticeerd met autisme. Met deze diagnose vielen zaken op zijn plaats. Maar de vraag die mij bleef puzzelen was waarom het zo lang duurde voordat de juiste diagnose werd gesteld. In feite waren haar autistische kenmerken verantwoordelijk voor de misleidende verscheidenheid
aan morbide gedrag (verslaving, angst, sociale angst en dwang). Dit vormde het uitgangspunt voor deze studie.

Na een algemene inleiding (hoofdstuk 1), presenteren we de eerste studie over de co-morbiditeit tussen verslaving en ASS (hoofdstuk 2). Vanaf dat moment ontstond de behoefte om meer inzicht te krijgen in de verschillen in de onderliggende causale mechanismen en met name ook de rol van gender, in de ontwikkeling tot de fenotypische (waarneembare uiterlijke kenmerken) presentatie van psychiatrische stoornissen (hoofdstuk 3), het belangrijkste doel van dit onderzoek. Hierdoor komen wij tot de vraag welke impact gender heeft op de genetische en epi-genetische expressie, op het functioneren van de hersenen, het neuropsychologische profiel en tot slot op de gedragsmatige coping-mechanismen die individuen helpen omgaan met wisselende omstandigheden (hoofdstuk 4).

In derde instantie zijn we benieuwd of deze inzichten kunnen bijdragen aan ons begrip van genderverschillen in de klinische presentatie van ontwikkelingsstoornissen, met name een autisme spectrum stoornis, die bij hoog functionerende vrouwen vaak pas laat wordt gediagnosticeerd (hoofdstuk 5) en hoe het komt dat de diagnose bij deze vrouwen op zeer jonge leeftijd wordt gemist (hoofdstuk 6).

Alle bevindingen worden besproken in het laatste hoofdstuk (7) de algemene discussie.
Wat zijn de belangrijkste bevindingen?

Onze eerste vraag was of de co-morbiditeit van verslaving en ontwikkelingsstoornissen bestaat en zo ja, hoe deze verklaard kan worden.

(1) De resultaten van onze eerste studie toonde aan dat verslaving, zoals bekend, vaak samen met aandachttekortstoornis met hyperactiviteit (ADHD) voor komt, maar ook met autisme spectrum stoornis (ASS). Dit laatste lijkt een sterk onderschat probleem te zijn. Verrassend werd in onze gemengde steekproef van patiënten met verslaving deze co-morbiditeit uitsluitend bij mannen gezien. In andere studies is de geslacht verdeling ofwel niet mee genomen of wordt die slechts in 1 vrouw op de 6 mannen gezien. Verder concludeerden wij dat beide aandoeningen als een ontwikkelingsstoornis kunnen worden opgevat waarin de interactie tussen de genetische aanleg en de invloed van de omgeving een rol spelen. Ze kunnen door zeer vroege- en huidige stress worden uitgelokt. Hierdoor kan de werking van het centrale stressregulatiesysteem (de cortico-striatale dopaminerge regelmechanismes en ook de brein bijniers ofwel HPA-as), soms blijvend worden beïnvloed. Op dat niveau is er een opmerkelijke overlap tussen verslaving en ASS / ADHD, waardoor het stellige onderscheid tussen deze zo verschillende klinische categorieën vraagtekens oproept.

Dit leidde tot fundamentele vragen met betrekking tot hoe psychopathologie momenteel wordt opgevat en wat de waarde van de huidige afzonderlijke classificatie categorieën eigenlijk nog is. Vervolgens gingen we kijken naar wat er bekend is over de verschillende stoornissen in ontwikkelingsmechanismen die zich uiten op verschillende niveaus en die vervolgens kunnen leiden tot
psychopathologie. In dit proces zijn we geïnteresseerd geraakt in zowel de rol van de omgeving, als die van gender op de expressie van (psycho)pathologie.

De tweede vraagstelling was of het huidige classificatiesysteem in diagnostische categorieën en co-morbiditeit (zowel vanuit conceptueel als klinisch oogpunt) nog wel houdbaar is. Ons onderzoek naar de mechanismen in de ontwikkeling van psychopathologie, toont aan dat een conceptuele gelaagdheid in vijf niveaus (genetisch, epi-genetisch, hersenen, neurocognitief, gedrags) eigenlijk het meest plausibele model is. Op alle niveaus vindt er interactie plaats tussen de eigenschappen van het individu met de bio- psychosociale omgeving welke de ontwikkeling beïnvloedt. Het individu beïnvloedt echter zelf ook in sterke mate zijn / haar directe omgeving. Al deze processen uiten zich in vervolgens in cognities, emoties en gedrag of afwijkingen in deze.

De oorzaakelijke verbanden zijn complex en geenszins eenduidig.

Tot slot pleiten we sterk voor een fundamentele heroverweging van de classificatiesystematiek in de psychiatrie. Deze is, volgens ons, nog maar erg matig geschikt voor de klinische praktijk of onderzoek. Wetenschappelijk onderzoek zou zich dus meer kunnen gaan focussen op groepen gedefinieerd door gezamenlijke onderliggende genotypes/endofenotypes in plaats van vast te houden aan de huidige klinische syndromen. Clinici zouden zich bewuster moeten worden dat zij kennis van de individuele ontwikkelingsaspecten en de interactieve aspecten van psychiatrische stoornissen kunnen kunnen betrekken bij het onderzoek van hun patiënten.
Onze derde onderzoeksvraag richt zich op de invloed van het geslacht op de ontwikkeling en (psycho) pathologie.

In dit essay concludeerden wij dat gender een belangrijke rol speelt niet alleen in de gevoeligheid voor het ontwikkelen van bepaalde fysieke en / of psychische aandoeningen, maar ook op de manier hoe men hier mee om gaat. Gen-omgeving interacties leiden tot neurobiologische verschillen tussen vrouwen en mannen in de ontwikkeling van stress- regulatie. Geslacht speelt ook een rol bij de opvoeding van kinderen evenals de culturele man-vrouw verschillen die de sociale context bepalen waarin individuen leven. Al deze milieu / sociale factoren spelen op hun beurt een rol bij de ontwikkeling van (psycho)pathologie en in de manier waarop ze hiermee omgaan. Met andere woorden: het geslacht is van invloed op zowel de fysieke-, als de mentale- en de sociale gezondheid.

Onze vierde onderzoeksvraag richt zich op de huidige kennis van de genderverschillen in een autismespectrumstoornis (ASS).

In onze meta-analyse van 20 studies werden genderverschillen in ASS op het niveau van klinische kenmerken/symptoom niveau onderzocht. Kort gezegd blijkt dat er maar heel weinig verschillen in ernst van symptomen tussen mannen en vrouwen bestaan. Manlijke en vrouwelijke individuen met ASS toonden vergelijkbare ernstscores op de symptomen reeks van communicatie en sociaal gedrag, maar meisjes vertonen minder beperkte interesses en gedrag en stereotypieën dan jongens vanaf 6 jaar, maar dat verschil wordt niet gezien bij hele jonge kinderen.
Onze laatste onderzoeksvraag richt zich op de vroegtijdige opsporing en de evolutie van de symptomen bij ASS.

In onze follow-up studie hebben we gekeken naar genderverschillen bij peuters tot in de basisschool leeftijd. Dit cohort werd samengesteld vanuit een bevolkingsonderzoek op ASS (in het Diagnostiek en Interventie voor Autisme in Nederland: het DIANE project). De kinderen bij wie er n.a.v. deze screening een verdenking op ASS bestond, werden vervolgens aan een geprotocolleerd diagnostisch onderzoek onderworpen. Bij follow up (twee tot drie jaar later) werden deze kinderen opnieuw onderzocht.

Deze studie bevestigt eerdere veronderstellingen dat er een aparte groep meisjes bestaat met ernstig autisme en een laag ontwikkelingsniveau die al heel vroeg kan worden gediagnosticeerd. Deze meisjes vertonen aanzienlijk meer sociale interactie- en communicatie-problemen en meer stereotiep gedrag, dan jongens met autisme op die zelfde jonge leeftijd. De ouders van deze meisjes begonnen zich al veel eerder aanzienlijk meer zorgen te maken over hun kind dan de ouders van jongens met autisme. Daarnaast lag het non-verbale IQ significant lager bij deze meisjes dan bij de jongens. Na drie jaar, bleek hun diagnose stabiel te zijn gebleven, terwijl ze cognitief behoorlijk gevorderd waren.

Opmerkelijk bij dit onderzoek is ook het feit dat de groep "hoog functionerende" meisjes met ASS, die klinisch meestal pas laat in de kindertijd, of zelfs pas op volwassen leeftijd met autisme gediagnostiseerd worden, met de huidige diagnostische hulpmiddelen niet reeds in hun kindertijd kunnen worden gedetecteerd.
In de algemene discussie staan we stil bij de vraag waarom ernstige psychopathologie zoals ASS, zo verborgen kan blijven, in het bijzonder bij een kwetsbare groep van meisjes en vrouwen, die gehandicappt zijn door hun autistische kenmerken en beperkingen, maar waarbij de ernst van hun ontwikkelingsstoornis niet wordt onderkend. Waarschijnlijk hebben vrouwen een ander (autistische) fenotype dan mannens. De risico's voor het ontwikkelen van ASS zijn waarschijnlijk multifactorieel, met veel verschillende genetische varianten en omgevings factoren die bijdragen aan de expressie. De mate van impact van het sekse-chromosoom en de hoeveelheid geslachtshormonen kunnen hierbij een rol spelen. Biologische theorieën stellen dat het sekseverschil in prevalentie van ASS zouden kunnen komen doordat de drempel voor klinische expressie bij vrouwen veel hoger ligt dan bij mannen. Genetische studies veronderstellen dat vrouwen met ASS waarschijnlijk een hogere erfelijke belasting hebben. Tot nu toe, is de nogal scheve verdeling rondom de aanwezigheid van “beperkte interesses en gedrag en stereotypieën” bij mannen niet goed opgehelderd. De onderliggende mechanismen zijn nog niet geïdentificeerd.

Een andere hypothese is de diagnostische criteria van ASS ten onrechte te veel vanuit mannen beschreven zijn waarmee verondersteld wordt dat deze dan voor allen gelden. Er wordt inmiddels wel erkend dat het gedragsfenotype van ASS anders is bij meisjes en vrouwen dan bij jongens en mannen, maar de diagnostische criteria zijn nog steeds gebaseerd op de wijze waarop symptomen bij jongens worden gezien. Sommige onderzoekers suggereren dat een nog onbekend mechanisme meisjes helpt met hun ASS om te gaan op een zodanig wijze dat hun symptomen niet de diagnostische drempel bereikt oftewel niet opvallen.
Wanneer we kijken naar de resultaten van onze studie over de ontwikkeling van psychopathologie (2) en de invloed van het geslacht hierop (3) is het erg waarschijnlijk dat de geslachtsenmerken invloed uitoefenen op alle of een deel van de 5 niveaus (genetische, epigenetische, hersenen, neurocognitieve, gedrag). Dit kan bijdragen aan de ontwikkeling van vrouwelijke fenotypes, o.a. bij ASS. Het kan ook zo zijn dat het vrouw-zijn, voor sociale- en communicatieve tekortkomingen compenseert en dat meisjes en vrouwen een soort “beperkt patroon van gedragingen en stereotypieën” vertoont dat veel minder vreemd en bizar over komt dan dat van jongens. Zoals we reeds concludeerden in onze gender studie, speelt de wijze waarop ouders omgaan met de emotie-regulatie en socialisatie van hun kind een belangrijke rol bij het al dan niet ontwikkelen van een adequaat adaptatie vermogen. Ook de invloed van de sociale omgeving verschilt per geslacht. Dus het zou zo kunnen zijn dat al deze factoren een rol spelen in de *andere* fenotypische presentatie van ASS bij meisjes en vrouw.

Zoals ASS nu wordt gedefinieerd op basis van het mannelijk fenotype kan dit ook betekenen dat er sprake is van vooringenomenheid. Hoog functionerende meisjes met ASS kunnen zich anders uiten zich en hebben minder ernstige sociale en communicatieve beperkingen dan jongens met ASS, waardoor de ouders, familieleden en zorgverleners deze “eigenaardigheden” beschouwen als passend bij “gewone” vrouwelijke verlegenheid of angst. Deze verkeerde interpretatie van de symptomen kan leiden tot foutieve verwijzingen en uiteindelijk tot een verkeerde diagnoses. Autistische meisjes krijgen dan bijvoorbeeld allerlei diagnoses zoals angststoornis of een vermijdende persoonlijkheidsstoornis, etc, waardoor het daadwerkelijke probleem de autisme spectrum stoornis ASS over het hoofd wordt gezien. Kort samengevat
is er sprake van aanzienlijke onderdiagnostiek van ASS bij meisjes en vrouwen. Vreemd genoeg blijkt evenwel dat als de diagnose ASS eenmaal is vastgesteld, de verschillen tussen meisjes en jongens wegvallen zowel voor wat betreft de aard of de ernst van de kernsymptomen als ook in het type co-morbiditeit.

**Consequenties**

**Voor onderzoek**

Onderzoek zou, volgens ons, vanuit een andere invalshoek benaderd moeten worden. Men zou zich meer moeten richten op onderliggende factoren als genen en endofenotypes en de rol van gender bij het onderzoeken van de ontwikkeling van (psycho)pathologie.

Daarnaast is het van belang om prospectief te kijken naar gedragspatronen bij meisjes en vrouwen, die later met ASS gediagnostiseerd worden, maar die in eerste instantie niet als zodanig herkend worden. Dit zal helpen verklaren waarom de diagnose zo lang gemist is, maar vooral ook helpen om criteria te ontwikkelen voor vrouwelijke symptomen bij autisme. Kennis van deze kenmerken zal artsen en andere werkers in de gezondheidszorg alerter en bewuster kunnen maken van de diagnose ASS als mogelijkheid bij meisjes en vrouwen. Op grond van die kenmerken kunnen vervolgens geschiktere (screenings) instrumenten, voor het identificeren van een vrouwelijke fenotype van ASS, ontwikkeld worden.
Voor de klinische praktijk / training / opleiding en gezondheidsbeleid

Artsen zouden de voorkeur moeten geven aan individuele multi-level diagnostiek waarbij ze de rol van genderinvloeden meenemen. Tevens is het belangrijk dat ze vanuit gender oogpunt de luxerende, onderhoudende en beschermende omgevingsfactoren op sporen. Zij zullen zich meer bewust moeten worden van het feit dat achter klinische verschijnsels ruimere onderliggende categorieën en ontwikkelingsaspecten liggen. Voor de diagnostiek van ASS bij meisjes en vrouwen zouden artsen zich meer moeten realiseren dat de fenotypische presentatie bij vrouwen anders kan zijn en vaak gemaskeerd wordt door "co-morbiditeit".

In het onderwijs en in de opleiding van medische professionals en andere zorgverleners is het belangrijk om het focus te verleggen van een gesegmenteerde aanpak van (psycho)pathologie met een "one-fits-all" benadering van behandeling, naar een veel meer geïntegreerde benadering. In deze bredere benaderingswijze wordt ziekte gezien als uitkomst van voortdurende wisselwerking tussen het individu en zijn omgeving. Geslacht speelt hierbij een belangrijke rol. Net zoals andere omgevingsfactoren kan deze invloed beschermend of risico verhogend zijn.

Tot slot zou in het zorgstelsel nagedacht moeten worden over de wenselijkheid en noodzaak van een meer persoonsgerichte geneeskunde, waarin de individuele aspecten, het geslacht en de maatschappelijke context meer dan nu gebruikelijk is worden gewaardeerd in plaats van vast houden (met name in de psychiatrie) aan de huidige trend om patiënten te diagnosticeren (eigenlijk te classificeren) en te behandelen op basis van richtlijnen en protocollen die gebaseerd zijn op “twijfelachtige” diagnoses.
Dankwoord

Het was een lang en niet altijd even makkelijk traject. Ik ben blij dat dit nu is afgerond en dit wat nooit gelukt zonder de hulp, steun en inspiratie van anderen.

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Curriculum Vitae

Patricia Cremers was born as the second of five children, on June 6th 1960 in Amsterdam. She grew up in different parts of the Netherlands. After completing secondary school in Sneek (Friesland) in 1979 she studied medicine in Groningen, where she graduated in 1988. After a short residency in psychiatry in Zuidlaren, during which she trained in psychotherapy, she specialised in Psychiatry at the University Medical Centre in Groningen 1992-1996. After her certification as a psychiatrist, she worked as an addiction psychiatrist in the northern provinces at the Dr. Kuno van Dijk foundation for two years. During this period she was involved in research on early traumatization in patients with addiction.

In 1998 she moved with her family to the Salland region where her husband settled as cardiologist in the Deventer hospital and she joined the Zwolse Poort (currently Dimence Mental Health) for mental health care in Zwolle. She set up a comprehensive department for addiction psychiatry. There she was struck by the substantial amount of patients with dual diagnoses addiction and developmental disorders. In her clinical practice she was became more and more aware of the under diagnosis of ADHD and Autism Spectrum Disorders (ASD) in women. She joined from the start the Dutch Network for ADHD in Adults and is involved in the network for Autism Spectrum Disorders in Adults at the National Autistic Society (UK).

Her interest in the co morbidity between addiction and developmental disorders lead to a close cooperation with the Amsterdam Institute for Addiction Research (Prof Wim van den Brink & Dr Marten Koeter) and the department of psychiatry of the Radboud university medical centre and Karakter Child & Adolescent psychiatry (Prof Rutger Jan van der Gaag). This lead to two dissertations: 2009 Chrisje Couwenbergh "Substance abuse and it's cold-occurrence with other mental health problems in adolescents and 2010 Mr. Bram Sizoo: Developmental disorders and substance use disorder: a phenotypical, endophenotypical and genetic exploration.

Meanwhile she lectured nationally and worldwide to raise awareness both in
the research communities on addiction and developmental disorders for the important comorbid overlap especially in woman. This dissertation combines research in the different clinically areas that intrigue her.

In 2012 she joined the Centre for Developmental Disorders to help and develop a centre of clinical excellence (Top GGz) for adults with autism.

The author combines her clinical work in Deventer and Zwolle, with countrywide consultation (CCE: Centrum voor consultatie en expertise), training of residents in psychiatry as adjunct director of training and teaching in the Northern Consortium, Windesheim University of applied sciences (addictionpsychiatry), the Radboud University (psychiatry and gender studies) and many lectures and courses in developmental psychopathology.

Patricia is married to Jan van Wijngaarden, they have three young-adult children Marielle, Caroline and Jeroen.
Publications


