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Neurocognitive mechanisms and vulnerability to autism and ADHD symptoms in the 22q11.2 deletion syndrome

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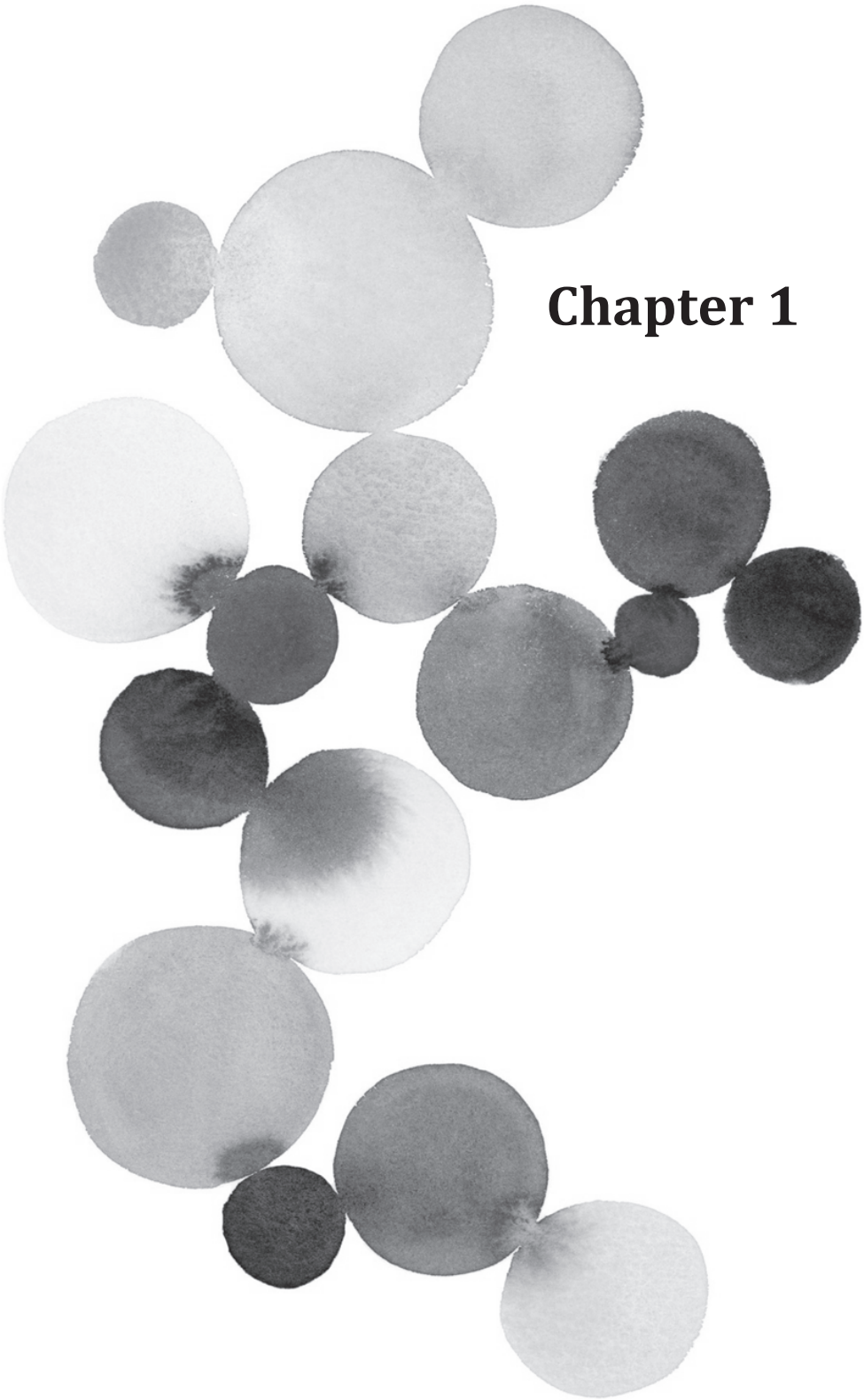


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Chapter 1

General Introduction

Neurodevelopmental disorders

Neurodevelopmental disorders have an onset in early childhood. The origin, expression and developmental trajectories of these disorders is determined by genetic factors, often in interaction with the environment. For some of these disorders it is suggested that they share at least part of their genetic etiology (Rommelse *et al.* 2010; American Psychiatric Association. 2013; Posthuma & Polderman, 2013; McCarthy *et al.* 2014). Children diagnosed with these disorders experience the impact of associated developmental difficulties in their personal, social, academic, and occupational functioning during lifetime. These deficits include specific problems with learning, executive functioning, or more global impairments of social skills or intelligence (American Psychiatric Association. 2013). Discovering the mechanisms involved in the outcomes of these disorders is important to improve the developmental perspectives of these children. It is recognized that the number of symptoms accompanying these disorders and its severity can differ across individuals. This, so called, variable expressivity of symptoms might be an important starting point in studying the mechanisms that determine severity of symptomatology and developmental outcomes of these disorders (Reynolds & Mayfield, 2011).

Two neurodevelopmental disorders of which it is widely known that genetic factors are involved and for which the high frequency of comorbid occurrence suggests an overlap in genetic etiology are autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) (Ronald *et al.* 2008; Rommelse *et al.* 2010; Vorstman & Ophoff, 2013). Variable expressivity plays a role in both disorders and is also recognized by the Diagnostic Statistical Manual, 5th edition (DSM 5) through the inclusion of specifying severity of present symptoms. Diagnostic criteria of ASD include persistent deficits in social communication and social interaction as well as restricted, repetitive patterns of behavior, interest and activity. ADHD is characterized by severe symptoms of inattention, hyperactivity and impulsivity associated with cognitive and behavioral problems that interfere with daily functioning and development (American Psychiatric Association. 2013). Because of the suggested overlap in genetic etiology of ADHD and ASD, investigating a genetic syndrome that is associated with symptoms of both disorders is a unique opportunity to improve our knowledge about these disorders (Rutter 1997; Scourfield *et al.* 1999).

The 22q11.2 deletion syndrome is an example of a genetic disorder that is known to be associated with ASD and ADHD. Investigating neurocognitive dysfunctions as possible underlying mechanisms of the behavioral and emotional problems of these disorders in 22q11DS may provide insights in the etiology of ASD and ADHD and enlarge our knowledge about gene-brain-behavior relationships.

The 22q11.2 deletion syndrome

The 22q11.2 deletion syndrome (22q11DS), also known as the velo-cardio-facial or DiGeorge syndrome is one of the most commonly known recurrent copy number variants (CNVs) associated with a high vulnerability to psychopathology. The prevalence of 22q11DS is estimated around 1: 2,000-4,000 live births, with boys and girls equally affected. Each year around 50 children are born in the Netherlands with this syndrome (Devriendt *et al* 1998; Oskarsdottir *et al.* 2004; Shprintzen 2008). This autosomal dominant genetic disorder is caused by a microdeletion on the long arm of chromosome 22. The inheritance rate of the syndrome is 50%, however in 90% of the cases the deletion is a 'de novo' mutation where none of the parents carry the genetic defect. The phenotypic expression of the syndrome is characterized by a diverse variability of physical, metabolic, endocrine and behavioral features (Bassett *et al.* 2011). Physical manifestations include conotruncal cardiac anomalies, palatal anomalies, nasal regurgitation, and/or hypernasal speech, immunodeficiency, hypocalcemia and typical facial features (Swillen *et al.* 2000; Green *et al.* 2009; Bassett *et al.* 2011; Cancrini *et al.* 2014). The neurocognitive phenotype is characterized by delays in motor development and speech, and language difficulties. Learning difficulties are common and most individuals with 22q11DS function at an intellectual level of borderline or mild to moderate intellectual disability (De Smedt *et al.* 2007; Niklasson & Gillberg 2010; Philip & Bassett 2011; Duijff *et al.* 2012). The behavioral phenotype of the syndrome is highly variable, including ADHD, ASD, anxiety disorders, oppositional deficit disorder, and mood disorders (Jolin *et al.* 2009; Baker & Vorstman 2012; Jonas *et al.* 2014; Schneider *et al.* 2014). Around 25% of the patients with the syndrome develop schizophrenia in adolescence or adulthood (Murphy *et al.* 1999; Schneider *et al.* 2014).

Over the last years a large amount of studies investigated the cognitive and the behavioral phenotype of 22q11DS providing insights in the high variability of these phenotypes (Philip & Bassett 2011). Knowledge about the association between the cognitive and behavioral phenotype may lead to a better understanding of the developmental pathways of the syndrome and improve interventions and treatment strategies. However, only a limited number of studies investigated the association between cognitive functioning and the development of emotional and behavioral problems. The findings thus far are inconsistent, with some studies failing to find an association between degree of cognitive impairment and psychopathology (Janssen *et al.* 2007; Hooper *et al.* 2013; Niarchou *et al.* 2014), while in other studies differences in neurocognitive profiles have been reported between individuals with and without psychopathology (Chow *et al.* 2006; Hooper *et al.* 2013). Differences in neurocognitive functioning were found between adults with 22q11DS with and without schizophrenia, despite the finding that mean estimated IQ levels did not differ (Van Amelsvoort *et al.* 2004; Chow *et al.* 2006). In adolescents, lower full scale IQ in childhood was found predictive for the severity of schizophrenia symptoms (Hooper *et al.* 2013). Most of these studies focused on the mechanisms involved in the emergence and severity of (prodromal) symptoms of schizophrenia in patients with 22q11DS. To understand the association between the genotype and phenotype

of the syndrome, it is important to find out if and how cognitive dysfunctions of children with 22q11DS are involved in the emergence and severity of associated social and behavioral outcomes (Shprintzen 2000).

Neurocognitive functions and autism and ADHD symptomatology

There are different ways to investigate how genetic factors, in interaction with the environment, influence brain development and function as well as the behavioral outcomes that are ultimately associated with it. One approach is to look at associations between disabilities at the behavioral level and disturbances in functioning of the developing brain; the neuropsychological perspective (Goldstein & Reynolds 2011; Swaab *et al.* 2011). Neurocognitive functions are used to process information and direct behavior as an intention to influence, or a response to the outside world. These functions can therefore be seen as an expression of the complex mechanisms in the brain and are associated to specific areas or networks in the brain (Swaab *et al.* 2011). Neurocognitive functions as reflection of brain functioning are useful for entangling the associations between genetic factors and social and behavioral problems associated with ASD and ADHD. Studying the association between behavior and neurocognitive processes in children and adolescents with 22q11DS may help to clarify the association between a genetic factor (22q11DS) and the development of social and behavioral problems through the mediating role of these neurocognitive dysfunctions. The high prevalence of autism and ADHD symptomatology in children and adolescents with 22q11DS makes this syndrome highly relevant in investigating the mechanisms on a neurocognitive level that possibly underlie the behavioral and emotional problems that are characteristic for autism and ADHD. Additionally, knowledge about the specificity of impairments in cognitive functioning and its relations to vulnerability to autism and ADHD symptoms may help develop interventions or adjust treatments to the needs of these children. This knowledge may bring us further in understanding developmental trajectories of ASD and ADHD, especially in individuals with 22q11DS.

Objective of the current thesis

The objective of this thesis is to understand the mechanisms that result in vulnerability to autism and ADHD symptomatology in individuals with 22q11DS. To this purpose we focused on the associations between neurocognitive functioning and symptomatology of the neurodevelopmental disorders ASD and ADHD.

Participants and instruments

The studies reported in this thesis are part of a nationwide study and include 102 children and adolescents with 22q11DS aged 9 – 18.5 years at time of assessment. Intellectual functioning was assessed using the Wechsler Intelligence Scales (Wechsler 1974; 2002; 2005a; 2005b). Various executive functions were evaluated using the Amsterdam Neuropsychological Tasks (ANT) program (De Sonneville 1999; 2005), the Wisconsin Card Sorting Test (WCST, Heaton et al. 1993) and the Rey-Osterrieth Complex Figure (RCFT, Rey 1964). Visual (social) information processing was assessed with the use of the ANT program (De Sonneville 1999; 2005). Detailed descriptions of tasks and procedures are provided in the respective chapters.

The described variability in expression of ASD and ADHD and the clinical reality of co-occurrence of ASD and ADHD symptomatology in 22q11DS encouraged us to investigate the severity of the associated social and behavioral problems. To this end, we investigated the three major domains of ADHD symptomatology: inattention, hyperactivity, impulsivity. Symptoms were rated with a semi-structured interview based on the criteria of the DSM-IV as a measure of severity of ADHD symptoms. The interview consisted of items comparable to those of the CRS-R (Conners 1997) and the Dutch version of the ADHD DSM-IV rating scale (Kooij *et al.* 2008). To investigate severity of symptoms on the three major domains of autism symptomatology: reciprocal social interaction, communication impairment, and repetitive and stereotyped behaviors, the algorithmic scores of the Autism Diagnostic Interview-Revised were used (Rutter *et al.* 2003).

Outline

For a thorough investigation of how neurocognitive processes are associated with the severity of autism and ADHD symptomatology in patients with 22q11DS the following topics were addressed:

- 1) In idiopathic ASD and ADHD populations specific impairments in subdomains of intelligence have been found, but in 22q11DS only few studies focused on factor and subtest levels of intelligence and no consistent associations have been reported yet. The study presented in chapter 2 aimed to add to literature thus far by expanding the knowledge about the association between profiles of intelligence and the neurodevelopmental disorders ASD and ADHD. Therefore, we assessed intellectual functioning on global and subdomain levels in the total sample ($N=102$) and explored the associations between strengths and weaknesses in intelligence profiles and the severity of symptomatology of both disorders (Chapter 2).
- 2) To explore whether a specific profile of (dys)executive functions can be found in individuals with 22q11DS, which is possibly associated with the social and behavioral problems that are part of ASD and ADHD, a wide range of executive functions was evaluated in a subsample of 58 individuals with 22q11DS. Associations between the quality of executive functioning and the severity of autism and ADHD symptoms were investigated (Chapter 3). For both ADHD and ASD it is known that deficits in executive functions underlie

behavior and adaptation problems that are part of these disorders. Investigating if, and how these deficits in executive functions are associated with the severity of these problems in individuals with 22q11DS may enlarge our knowledge about the underlying mechanisms of the neurodevelopmental disorders ASD and ADHD and provide opportunities to develop cognitive interventions.

- 3) Social problems are part of the core problems in both ADHD and ASD and social cognitive skills contribute to the development of adequate social behavior. Therefore in a subsample of 45 individuals it was investigated how quality of social cognitive functioning is associated with the severity of social behavioral problems in 22q11DS (Chapter 4). Based on previous findings of deficits in the processing of visuospatial information, we included two tasks that examine quality of face recognition and facial emotion recognition, respectively, and a pattern recognition task measuring quality of abstract visuospatial information processing as a contrast.
- 4) Because it is known that social deficits are part of the phenotypic expression of 22q11DS and associations have been found between COMT and plasma proline and social cognition, in the final study we focused on the association between the genotype of the remaining allele of COMT, and plasma levels of the amino acid proline, and the high vulnerability to social cognitive and behavioral deficits in the same subsample of 45 individuals with 22q11DS (Chapter 5).

A summary and integrated discussion of the presented finding will be provided in the final chapter (Chapter 6).

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