

Executive Functioning in adult Attention Deficit Hyperactivity Disorder (ADHD)

From basic mechanisms to functional outcome

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Dissertation for the degree philosophiae doctor (PhD)
at the University of Bergen

2014

Dissertation date: 18.09.2014

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Year: 2014

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Print: AIT OSLO AS / University of Bergen

Scientific environment

The work with this thesis has been carried out at the Department of Biological and Medical Psychology at the University of Bergen, where also my main supervisor, professor Astri Lundervold, has been situated. My co-supervisor and leader of the project, professor Jan Haavik, has been at the Department of Biomedicine. However, the project is based on collaboration with several other departments, notably the Center of Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen. The project is part of the K.G. Jebsen centre for research on neuropsychiatric disorders and of the International Multicentre persistent ADHD CollaboraTion (IMpACT). I have also been enrolled in the International Graduate School in Integrated Neuroscience (IGSIN) at the University of Bergen.



Acknowledgements

The project that I have been a part of, “ADHD in Norway, from clinical characterization to molecular mechanisms”, was funded by the K.G. Jebsen Foundation, the Research Council of Norway and the Western Norway Regional Health Authorities. I have been enrolled in “The National Program for Integrated Clinical Specialist and PhD-training for Psychologists” in Norway. This program is a joint cooperation between the Universities of Bergen, Oslo, Tromsø, the Regional Health Authorities, and the Norwegian Psychological Association. The program is funded jointly by The Ministry of Education and Research and The Ministry of Health and Care Services. I am thankful that I got the opportunity to be enrolled in this program, and especially would like to thank the local coordinator professor Gerd Kvale, the program director professor Odd Havik and the administrative coordinator Arild Mellesdal.

I would like to deeply thank all the participants in the project who have contributed to increase our knowledge about this complex disorder.

I wish to thank my main supervisor, professor Astri Lundervold, for believing in me, supporting me and giving me the opportunity to work within this field of research. You are not only a great researcher and supervisor, but also a caring and warm person. I have been so lucky to have you as my supervisor! I would also thank my co-supervisor, professor Jan Haavik for letting me be a part of the project. You are a leader that listens to and sees everyone in the project, regardless if they are professors or students. I am thankful for you always taking time to discuss and showing interest in my work, and for sharing your knowledge and thoughts about this complex field of research.

I am thankful for the opportunity to work in a project group with an open and inspiring atmosphere. Thanks to all in the ADHD project group for contributing to this appreciable work-environment. Anne, I am so happy for the time we spent together in the first years of the project. Thank you also for being a co-author of one

of the articles. Stefan, thank you for the support and help with my first article. Lisa, I think we are so lucky to have you in our group, as you are one of the reasons why it is so nice to be in the project! I would like to thank Vivica Næss and Ragnhild Nordenborg for also doing a great job as project-coordinators. Liv is thanked for testing the participants in the project in an optimal way. Also, a special thank goes to Michael Lensing for the help in recruiting patients from the former Expert Committees of ADHD/Hyperkinetic disorders.

Mari, thank you so much for pleasant company and for sharing your knowledge during the first years I spent in research and in the clinic. Lin and Maj-Britt are thanked for being great colleagues and for valuable contributions as co-authors. Maj-Britt and Erlend are also thanked for giving valuable comments on this thesis. A special thank goes to Steinunn, Martin and Hilde, who have made my time as a doctoral student so enjoyable. Erlend, Eike, Hedda, Marit, Åsa, Randi, Benedicte, Anne, Siv, Berit and others in the 8th floor are also thanked for being nice colleagues during the years I have been at the University. Ragnhild Lossius is thanked for being a very knowledgeable supervisor and great colleague in the clinic. I would also like to thank Robert Murison, Holger Ursin and Jude Nicholas for introducing me to the world of research as a student.

I feel fortunate to have caring friends and family. Thank you for taking interest in my work, and for enriching other parts of my life. Especially, I would like to deeply thank you, mum and dad, for always believing in me and supporting me, for giving me a warm home with a lot of interesting discussions and for the many hours you have spent in our home babysitting!

Thanks to my dearest husband and best friend Andreas, for always supporting me, and to my sons Edvard and Erik, for putting things in perspective and for bringing so much happiness and joy into my life!

Preface

Attention Deficit Hyperactivity Disorder (ADHD) is a highly heritable, disabling condition that commonly persists into adulthood. Main features are symptoms of inattention, hyperactivity and impulsivity. The disorder is considered to be multifactorial and heterogeneous, and this complexity is reflected in this thesis by the inclusion of articles covering a range of issues concerning the nature of the disorder. The included studies all examine research questions that are relevant for our understanding of executive functioning in ADHD. The project “ADHD in Norwegian adults; from clinical characterization to molecular mechanisms” was established in 2004. At that time, relatively little was known about ADHD in adults, and there was an urgent need for more knowledge about this common psychiatric disorder. ADHD is characterized by severe functional impairments for those affected, with implications for the family and society. However, the disorder is clinically heterogeneous and probably has a multifactorial aetiology. This heterogeneity complicates doing research on ADHD, and what we call ADHD today might look different in the future as the field of psychiatric research is evolving. To take part in this process has been exciting. Although ADHD as a clinical entity has been recognized for a long time, the validity of the diagnosis is still frequently discussed in the media. This makes it even more difficult for patients and their relatives to cope with the impairments of the disorder. Although most people at some time may have some of the features of ADHD, it is required to be an impairing condition with early onset to fulfil the current diagnostic criteria. Most of the ADHD patients we meet in the clinic struggle with significant functional impairment, which is also well documented in the literature. To obtain more knowledge and to help this group of people is therefore a meaningful work, and I am grateful that I got the opportunity to take part in this.

Abstract

Background

Attention deficit hyperactivity disorder (ADHD) is characterized by age inappropriate levels of hyperactivity, inattention and impulsivity. A large proportion of children with ADHD have persisting symptoms into adulthood. However, the pathways from genetic susceptibility to symptoms and functional outcomes of ADHD are still not well understood. Some researchers argue that impairment of executive function (EF) is an essential part of the disorder. The present thesis was motivated by the need of more research to understand the genetics of EF, how to measure EF, the heterogeneity of EF and the functional outcomes of deficit of EF (EFD) in ADHD. In the first study included in this thesis, we used a dimensional approach to investigate *COMT* haplotypes and symptoms of ADHD, in addition to investigate genetic heterogeneity through the identification of potential subgroups within the disorder. The *COMT* gene has been shown to be important for the regulation of dopamine levels in prefrontal cortex, and has been associated with several aspects of EF, such as set shifting and inhibition. In the second study, we investigated these functions in ADHD, with the aim to obtain “pure” measures of EF. In the third study, these functions, in addition to other important EFs were included, and we investigated the heterogeneity of ADHD through characterizing functional impairment in the group with ADHD and psychometrically defined EFD.

Materials and methods

The thesis is based on three different papers. In the first paper, 435 participants with a clinical diagnosis of ADHD and 383 controls were included. The second paper included 60 participants with ADHD and 60 controls, while 79 participants with ADHD and 77 controls were included in the third paper. All participants filled in self-report questionnaires and supplied blood or saliva samples for genetic analysis. The questionnaires included items to assess demographical and clinical data, in addition to levels of ADHD-symptoms in adulthood and childhood. Participants included in the two last papers also went through a neuropsychological examination and a psychiatric

interview. The neuropsychological assessment included tests from the Delis-Kaplan Executive Function System (D-KEFS), Wechsler Abbreviated Scale of Intelligence (WASI) and Paced Auditory Serial Addition Task (PASAT).

Results

We found that *COMT* haplotypes were significantly associated with dimensional hyperactivity/impulsivity symptoms with a stepwise decreased score associated with the mid and low activity haplotypes. When stratifying for use of medication, the significance was only kept for hyperactivity in the subgroup of medicated ADHD patients. There was no significant association between *COMT* and measures of impulsivity. In the second paper, we found that participants with ADHD scored significantly lower than the control group on set shifting as measured with a subtest from the Colour-Word Interference Test (CWIT) from D-KEFS, also after control for basic functions, working memory and IQ. In the third paper, we found that the participants with ADHD and neuropsychologically defined EFD were characterized by a higher degree of functional impairment than those without EFD, including more reading and writing problems, lower IQ, more ADHD symptoms in childhood and lower work participation.

Conclusions

Our data show that examining *COMT* haplotypes may be useful to understand basic mechanisms in ADHD and the heterogeneity of the disorder. The second study indicates that set shifting as measured with the CWIT from D-KEFS may act as a potential endophenotype for ADHD. The third study, in line with the first one, supported that ADHD is a heterogeneous condition by showing that the group with ADHD and EFD combined may be a distinct subgroup characterized by a high level of functional impairment.

The results in the present thesis suggest that set shifting measures from D-KEFS should be included in the definition of EFD. Future studies should examine groups with and without psychometrically defined EFD, both at a genetic and psychosocial level, as the identification of such subgroups could lead to more targeted and

effective treatment.

List of publications and papers

- 1) Hallelund, H., Lundervold, A. J., Halmoy, A., Haavik, J., & Johansson, S. (2009). Association between catechol O-methyltransferase (COMT) haplotypes and severity of hyperactivity symptoms in adults. *Am J Med Genet B Neuropsychiatr Genet*, *150B*(3), 403-410.
- 2) Hallelund, H. B., Haavik, J., & Lundervold, A. J. (2012). Set-shifting in adults with ADHD. *Journal of the International Neuropsychological Society, JINS*, *18*(4), 728-737.
- 3) Hallelund, H. B., Sørensen, L., Posserud, M. B., Haavik, J., & Lundervold, A. J. (2014). Occupational status is compromised in adults with ADHD and psychometrically defined executive function deficits. Submitted

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Related publications not included in this thesis

- Lundervold, A.J., Halleland, H.B., Haavik, J., Sørensen, L. (2014). Verbal memory function in adults with ADHD - the impact of working memory and response inhibition. Submitted
- Halmøy A., Halleland H., Dramsdahl M., Bergsholm P, Fasmer, O.B., M.D. & Haavik, J. (2010). Prevalence and Correlates of Bipolar Spectrum Disorders in Adult Attention-Deficit/Hyperactivity Disorder (ADHD): A Cross-Sectional Study of 510 Clinically Diagnosed Adult ADHD Patients and 417 Population Based Controls. *Journal of clinical psychiatry*, 71 (1), 48-57.
- Johansson S, Halleland H, Halmoy A, Jacobsen, K.K., Landaas, E.T., Dramsdahl, M., Bergsholm, P., Lundervold, A.J., Gillberg, C., Hugdahl, K., Knappskog, P.M., Haavik, J. (2008). Genetic analyses of dopamine related genes in adult ADHD patients suggest an association with the DRD5-microsatellite repeat, but not with DRD4 or SLC6A3 VNTRs. *Am J Med Genet B Neuropsychiatr Genet*, 147B (8), 1470-1475.
- Franke B, Vasquez A.A, Johansson S, Hoogman M, Romanos J, Boreatti-Hümmer A, Heine M, Jacob C.P., Lesch K-P., Casas M, Ribasés M, Bosch R, Sánchez-Mora C, Gómez-Barros N, Fernández-Castillo N, Bayés M, Halmøy A, Halleland H, Landaas E.T., Fasmer O.B., Knappskog P.M., Angelien J.G., Heister A.M., Kiemeny, L., Kooij S., Boonstra A.M., Kan C.C., Asherson P., Faraone S, Buitelaar J.K., Haavik J., Cormand B., Josep Ramos-Quiroga J.A. and Reif A. (2010). Multicenter Analysis of the SLC6A3/DAT1 VNTR Haplotype in Persistent ADHD Suggests Differential Involvement of the Gene in Childhood and Persistent ADHD. *Neuropsychopharmacology*, 35, 656-664.
- Lundervold, A.J., Adolfsdottir, S., Halleland, H.B., Halmoy, A., Plessen, K., & Haavik, J. (2011). Attention Network Test in adults with ADHD - the impact of emotional problems. *Behavioral and Brain Functions*, 7, 27.

Abbreviations

ADHD: Attention Deficit Hyperactivity Disorder

ANCOVA: Analysis of Covariance

ANOVA: Analysis of Variance

ASRS: Adult ADHD Self-Report Scale

COMT: Catechol O-methyltransferase

CWIT: Colour-Word Interference Test

DA: Dopamine

D-KEFS: Delis-Kaplan Executive Function System

DSM: Diagnostic and Statistical Manual of Mental Disorders

EF: Executive Functioning

EFD: Executive Function Deficit

GWA: Genome Wide Association

IQ: Intelligence Quotient

MANCOVA: Multivariate Analysis of Covariance

NIMH: National Institute of Mental Health

PASAT: Paced Auditory Serial Addition Task

PLINK: PuTTY Link

RDOC: Research Domain Criteria

SNP: Single Nucleotide Polymorphism

SPSS: Statistical Package for the Social Sciences

WASI: Wechsler Abbreviated Scale of Intelligence

WURS: Wender Utah Rating Scale

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1. Introduction

1.1 Historical perspective

Symptoms and behaviour similar to what is currently recognized as part of ADHD have been described in fictional and scientific literature throughout history. As early as in 1775, the German physician Melchior Adam Weikard described a condition similar to the inattentive type of ADHD in the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013). He recommended cold baths, steel powder, mineral waters, gymnastic exercises and horseback riding as potential treatments (Barkley & Peters, 2012). In 1798, the Scottish physician Alexander Crichton described alterations of attention and “mental restlessness” that corresponds to some of the symptom descriptions of Attention Deficit Hyperactivity Disorder (ADHD) in the DSM-IV (Crichton, 2008; Lange, Reichl, Lange, Tucha, & Tucha, 2010). Several years later, the German physician Hoffmann created the history about the misbehaving boy “Fidgety Phil” which is still today used as a popular allegory for children with ADHD (Lange et al., 2010). Despite such early descriptions of ADHD-like symptoms, many authors consider the scientific starting point of the history of ADHD to be when the British paediatrician Sir George Frederic Still described children showing serious problems with sustained attention and linked this to difficulties with moral control (Lange et al., 2010; Still, 1902). In the beginning of the 20th century, the similarity between symptoms of ADHD and other neurological conditions lead to use of medical terms such as “Post-Encephalitic Behaviour Disorder” (S. Levy, 1959). The first effective treatment of hyperactivity in children was described by Charles Bradley in 1937 (Bradley, 1937), and was a result of the growing notion that hyperactive behaviour was related to brain damage. A hypothesis about minimal brain damage causing behaviour disorders was therefore established (Lange et al., 2010). The term “minimal brain disorder” was substituted with “minimal brain dysfunction” in the early 1960s as it was recognized that many children without indication of brain

damage displayed the syndrome (Barkley, 2006). Before 1970, ADHD was considered mainly a childhood disorder. However, in 1976, two reports described symptoms and impairments also in adults and proposed that ADHD could persist into adulthood (Hechtman, Weiss, Finklestein, Werner, & Benn, 1976; Wood, Reimherr, Wender, & Johnson, 1976). The inclusion of attention deficit disorder (ADD) in DSM-III in 1980 (American Psychiatric Association, 1980), represented a major change in that attention deficit also was seen as a significant component of the disorder. In DSM-III, a residual type of ADHD was also introduced for individuals who had a history of meeting full criteria, but presently displayed fewer symptoms that still caused significant impairment. In the revised DSM-III from 1987, the term “Attention Deficit Hyperactivity Disorder” was introduced (American Psychiatric Association, 1987) describing ADHD as an uni-dimensional disorder. The inattentive subtype and the residual type were removed and replaced by a new, more vague category; “undifferentiated ADHD”. However, several studies were published supporting the validity of an inattentive subtype and the residual type of ADHD, and both were again included in the DSM-IV (American Psychiatric Association, 1994).

1.2 What is ADHD? Diagnostic criteria and clinical features

Today, the diagnostic manual DSM-5 (American Psychiatric Association, 2013), like the DSM-IV, describes ADHD as a condition that involves either hyperactivity/impulsivity, or inattention, or both. The diagnostic criteria applied in the studies included herein are from the version of DSM-IV-TR (American Psychiatric Association, 2000), and these criteria are therefore described in this thesis. In Europe, most countries use the International Classification of Diseases (ICD-10; World Health Organization, 2003), where symptoms from both dimensions must be present for the diagnosis to be given. However, the DSM-criteria are commonly used also outside the USA, to comply with the international standard.

No single test can confirm the diagnosis of ADHD, and the diagnostic criteria are descriptive in nature. It has also been discussed if the criteria are suitable for adults as they differ from children in symptom presentation (Kessler et al., 2010).

The diagnosis is based on an interpretation where the clinician has to judge whether the symptoms are sufficiently strong and impairing to warrant a diagnosis.

To diagnose ADHD, the DSM-IV requires the presence of 6 of 9 symptoms from either dimension (hyperactivity/impulsivity or inattention). If fulfilling criteria for both dimensions, ADHD combined type is diagnosed. There is also ADHD Not Otherwise Specified (NOS) that comprises disorders where inattention or hyperactivity is prominent, but not so impairing that the formal diagnostic criteria are met.

1.2.1 Diagnostic criteria of Attention Deficit Hyperactivity Disorder according to DSM-IV

The following description is adapted from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision, American Psychiatric Association, 2000 (American Psychiatric Association, 2000).

A. Either (1) or (2):

(1) Six (or more) of the following **symptoms of inattention** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

- (a) Often fails to give close attention to details or makes careless mistakes in school-work, work, or other activities
- (b) Often has difficulty sustaining attention in tasks or play activities
- (c) Often does not seem to listen when spoken to directly
- (d) Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behaviour or failure to understand instructions)
- (e) Often has difficulty organizing tasks and activities
- (f) Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork and homework)
- (g) Often loses things necessary for task or activities (e.g., toys, school assignment, pencils, books, or tools)

(h) Is often easily distracted by extraneous stimuli

(i) Is often forgetful in daily activities

(2) Six (or more) of the following **symptoms of hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity

(a) Often fidgets with hands or feet or squirms in seat

(b) Often leaves seat in classroom or in other situation in which remaining seated is expected

(c) Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)

(d) Often has difficulty playing or engaging in leisure activities quietly

(e) Is often “on the go” or often acts as if “driven by a motor”

(f) Often talks excessively

Impulsivity

(g) Often blurts out answers before questions have been completed

(h) Often has difficulty awaiting turn

(i) Often interrupts or intrudes on others (e.g. butts into conversation or games)

B. Some hyperactive-impulsive or inattentive symptoms that cause impairment were present **before age 7 years**.

C. Some impairment from the symptoms is present **in two or more settings** (e.g., at school [or work] and at home).

D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder)

In the DSM-5, the definition of ADHD has been updated to more accurately describe the adult condition. The age criteria of 7 years has been changed to 12 due to research showing no clinical differences between children identified by 7 years versus those identified later, for example with regard to treatment response, course and severity or outcome (American Psychiatric Association, 2013). While children must present with

at least six symptoms from one or both subgroup dimensions, for older adolescents and adults (over age 17 years) it is enough with five symptoms.

1.3 Prevalence and persistence of adult ADHD

ADHD is one of the most common diagnoses in child psychiatry. However, prevalence rates have varied a lot between different studies. Use of different methods and criteria may be one reason for the different estimates. For example, using the ICD-10 criteria, where the inattentive subtype is not included in the manual, will give lower prevalence estimates than DSM-IV or DSM-5. In addition, gender, type of sample studied, different informants and age also may influence the prevalence rates in different studies, which have been found to vary between 1% and 20% (Faraone, Sergeant, Gillberg, & Biederman, 2003). When only applying DSM criteria, estimates have varied from 1 to 7.3% (Simon, Czobor, Balint, Meszaros, & Bitter, 2009). However, a pooled prevalence of 5.3% across studies worldwide has been found in a comprehensive review/meta-analysis (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007).

Some years ago, ADHD was seen as a disorder of childhood, but it is now recognized that a large proportion of children with ADHD have persisting symptoms into adulthood (Faraone & Biederman, 2005; Lara et al., 2009; Mick, Faraone, & Biederman, 2004; P. Rasmussen & Gillberg, 2000). The exact persistence rate is not known, but several studies have shown that adults with ADHD have a high load of symptoms, in addition to significant functional impairment (Adamou et al., 2013; Gjervan, Torgersen, Nordahl, & Rasmussen, 2012; Halmoy, Fasmer, Gillberg, & Haavik, 2009; Kupper et al., 2012). However, symptoms in adults may be expressed differently than childhood symptoms. For example, with increasing age, overt symptoms of hyperactivity and impulsivity are found to decline (Biederman, Mick, & Faraone, 2000). Interestingly, while basal ganglia regions associated with hyperactivity have been shown to be reduced in children with ADHD (Frodl & Skokauskas, 2012; Qiu et al., 2009), no significant volumetric differences were found

in the basal ganglia in adults with ADHD compared to age-matched controls (Frodl & Skokauskas, 2012; Qiu et al., 2009). In line with this, studies have shown that the overt symptoms of hyperactivity in ADHD decrease with age (Biederman et al., 2000). Several longitudinal studies have been conducted to investigate the persistence of ADHD from childhood to adulthood, and estimates of the proportions of children retaining the diagnosis in late adolescence/adulthood have varied between 8-72% (J. C. Hill & Schoener, 1996). However, the different versions of DSM may have influenced the results, as the earlier versions had most focus on hyperactivity. In longitudinal studies of children with ADHD, community surveys and epidemiological studies of population samples, the adult ADHD prevalence has been estimated to be 2.5% (Simon et al., 2009). However, because of the different problems associated with assessment of prevalence in adult ADHD, more research is needed to estimate the proportion of adults that is affected by this condition.

1.4 Neurobiology of ADHD

The aetiology of ADHD is not fully understood, but several studies show that ADHD has neurobiological underpinnings (De La Fuente, Xia, Branch, & Li, 2013). Studies have shown a reduction of 4-5% in cerebellar and cerebral volume in children and adolescents with ADHD compared to controls (Carmona et al., 2005; Castellanos et al., 2002). Several brain regions with volume reduction have been reported, e.g. the frontal lobe, anterior cingulate cortex, cerebellum, caudate nuclei, corpus callosum, amygdala, hippocampus and basal ganglia (Bush, 2011; Bush et al., 1999; Cubillo et al., 2010; Kieling, Goncalves, Tannock, & Castellanos, 2008; Krain & Castellanos, 2006; Plessen et al., 2006; Seidman, Valera, & Makris, 2005; Shaw et al., 2006). In children with ADHD, longitudinal studies have shown that maturation of the cortex is on average about 3 years delayed compared to controls (Shaw et al., 2007). In addition, studies have shown a reduced whole brain cortical thickness in children (Shaw et al., 2006) and in several regions in adults (Almeida Montes et al., 2013; Makris et al., 2007).

Recently, there has been a transition from models describing a single core deficit in ADHD to models positing multiple deficits (Sonuga-Barke, 2003), taking the heterogeneity in ADHD into account (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). For example, some models are described as “independent pathways” models and suggest that separate neuropsychological subtypes are caused by dysfunctions in different pathophysiological substrates (Nigg, Goldsmith, & Sachek, 2004; Sonuga-Barke, 2005). This was supported by a study (de Zeeuw, Schnack, et al., 2012) where differences in neuroanatomical profiles were found across the intelligence range: ADHD with lower IQ was more related to neuroanatomical developmental delay, whereas ADHD with higher IQ was more associated with more subtle, widespread volume reductions.

The importance of prefrontal cortex in explaining the symptomatology in ADHD is essential in most theories of the disorder (F. Levy, 2007). Cognitive control functions, or “executive functions”, are closely linked to this region of the brain, and many researchers view impairment of those functions as a core deficit of ADHD. For example, Barkley (1997) postulated that a core prefrontal cortex associated symptom of disinhibition influences several other cognitive functions. Studies using functional MRI indicate that EF is dependent on fronto-subcortical-cerebellar networks found to be involved in the pathology of ADHD, and research has shown that tasks requiring EF are associated with a decreased activation in those areas (Bush, Valera, & Seidman, 2005; Cherkasova & Hechtman, 2009).

There are probably several neurotransmitters involved in the pathology of ADHD. Monoamines, and particularly the catecholamines are of interest, especially since well-known medical treatments for ADHD (methylphenidate and amphetamine) act as agonists for dopamine and noradrenaline by blocking their reuptake in the synapses. Dopamine has been described as important for the activation in many brain regions, for example the prefrontal cortex (Goldman-Rakic, 1998). The activity of dopamine is crucial for motor and cognitive functioning, reward and motivation, and a dysfunction in a part of the dopaminergic system could lead to ADHD symptoms. For example, Coccaro and colleagues (2007) found that more severe symptoms of

ADHD were associated with less dopamine activity in the brain, while another study (Fan, Xu, & Hess, 2010) found that mice with deletions of specific dopamine receptors exhibited symptoms of ADHD. Symptoms were reduced with amphetamine treatment, which is a treatment of choice in ADHD. However, the relationship between ADHD symptoms and neurotransmitter systems is still rather poorly understood, and more studies are needed to understand the neurobiological underpinnings of ADHD.

1.5 Genetics of ADHD

There are different methods to study the genetic factors in ADHD. Quantitative genetics, such as family-, adoption- and twin-studies, are used to separate between heritable and environmental causes for a given disorder. The development of the field of molecular genetics, with linkage and association studies, has made it possible also to identify risk genes, and how these genes influence the phenotype.

Most psychiatric disorders are highly heritable. The estimated mean heritability of childhood ADHD has been reported by Faraone and colleagues to be around 76% (Faraone et al., 2005). This is much higher than for example some well studied somatic diseases such as Parkinson's disease and breast cancer (Burmeister, McInnis, & Zollner, 2008). For adults, the heritability estimates of ADHD have varied considerably, probably due to methodological differences between studies. However, when using multiple sources of information, the heritability in clinically diagnosed ADHD is quite similar in adults and children (Franke et al., 2012).

Identification of risk genes for this disabling condition may help to predict disease progression, improve treatment, and prevent the persistence of ADHD into adulthood (Franke et al., 2012). The genetic risk for ADHD is shown to be continuously distributed throughout the population, and quantitative genetic studies indicate that there are both unique and shared genetic influences on symptoms of hyperactivity-impulsivity and inattention. ADHD also shares genetic risk factors with traits and

clinical syndromes that are commonly co-occurring with ADHD (Asherson & Gurling, 2012), and as such, similar genotype may be associated with multiple phenotypes. Reversely, multiple genotypes could also be associated with similar phenotypes. In addition, genes interact with other genes and different environmental factors (Beaver et al., 2007; Li & Lee, 2013; Rosenberg, Pennington, Willcutt, & Olson, 2012), further complicating the relationship between phenotype and genes. Endophenotypes, that may be defined as “heritable quantitative traits that index an individual’s liability to develop or manifest a given disease” (Castellanos & Tannock, 2002, p. 617), may give a measure closer to the neurobiological underpinnings of the disorder than phenotypes, and are also quantifiable in contrast to the dichotomous diagnostic categories (Rommelse, 2008). In line with this, research also supports that the features characteristic for ADHD is dimensional (Marcus & Barry, 2011) and not qualitatively different in cases and controls.

In linkage studies, data in pedigrees are examined to look for genetic markers that run in the family. Association studies can be hypothesis driven (candidate-gene studies) or hypothesis free (Genome-Wide Association (GWA) studies). In candidate gene studies people with a specific trait or disorder are studied, and it is assessed if certain single-locus alleles or genotype frequencies are found more often in the cases than in the controls. It is also possible to look at combinations of single-nucleotide polymorphisms (SNPs) that are associated statistically- so called haplotypes. Such associations may identify other polymorphic sites in the region that could be important for disease. Haplotypes may capture the genetic complexity better than single SNPs (Nackley et al., 2006), and the studies of haplotypes are still relevant although it is now also possible to examine the whole genome with GWA studies. Because this is hypothesis free, the whole genome is examined. However, when performing such analyses, the risk of type I errors is very high, due to the large number of tests conducted. Thus, the criteria to reach statistical significance are very strict. A very large sample is therefore required to obtain adequate power to detect differences between groups. As such, examination of SNPs or haplotypes within candidate genes may be advantageous in studies based on existing hypotheses.

The genetic variants involved in adult ADHD may be similar to those involved in children, and both common and rare variants are probably implicated in the etiology of the disorder. However, some differences have been found in genetics between children and adults (Franke et al., 2010), although it is uncertain if this reflects different genetic effects across the life span or differences in assessment of ADHD in adults and children (Freitag, Rohde, Lempp, & Romanos, 2010).

Since ADHD symptoms may be related to low levels of dopamine in the prefrontal cortex (Sagvolden, Johansen, Aase, & Russell, 2005), many genes that code for proteins affecting the dopamine system have been proposed as candidates for ADHD, such as *COMT* (coding for the enzyme Catechol-O-methyl transferase), *DRD4* (coding for Dopamine receptor D4) and *SLC6A3* (coding for Sodium-dependent dopamine transporter) (Franke et al., 2012). The regulation of dopamine in the prefrontal cortex has been shown to be important for EF (Diamond, Ciaramitaro, Donner, Djali, & Robinson, 1994), often considered to be the essential function that is compromised in ADHD (Barkley, 2012; Brown, 2006). The *COMT* gene may be especially relevant in studies of ADHD, as it encodes a key enzyme in the catabolism of dopamine in the prefrontal cortex. This is in contrast to subcortical brain regions where the dopamine transporter primarily is responsible for the metabolism of dopamine (Floresco, West, Ash, Moore, & Grace, 2003) (Figure 1).

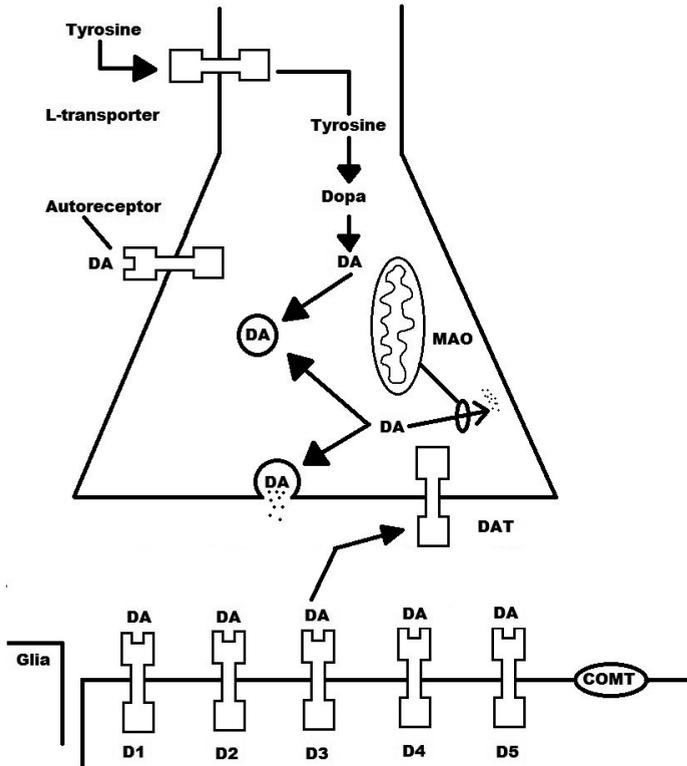


Figure 1. Synthesis and degradation of dopamine. The L-transporter transports the amino acid tyrosine across the cell membrane, and via dopa, tyrosine is converted to dopamine (DA). Before it is released to the synaptic cleft, it is stored in synaptic vesicles. DA can bind to presynaptic autoreceptors, or five different postsynaptic receptors (D1-5). D2 and D3 are also found presynaptically. In the synaptic cleft, dopamine is degraded by COMT or by the reuptake by a dopamine transporter (DAT) in the presynapse. There, it is recycled or degraded by monoamine oxidase (MAO). COMT is mainly found postsynaptically, but has also been detected intracellularly and in glia cells.

In a study of rats, it was estimated that the COMT enzyme accounted for more than 60% of the degradation of dopamine in the prefrontal cortex, in contrast to less than 15% in the striatum (Karoum, Chrapusta, & Egan, 1994). In line with this, studies have shown a relationship between the *COMT* gene and EF (Favaro et al., 2013), such as impulsivity (Soeiro-De-Souza, Stanford, Bio, Machado-Vieira, & Moreno, 2013) and set shifting (Tunbridge, Bannerman, Sharp, & Harrison, 2004). Most

studies on the *COMT* gene and ADHD have examined the *COMT* Val158Met polymorphism, where the Val allele has been suggested to lead to faster degradation of prefrontal dopamine than the Met variant (Lachman et al., 1996). The research concerning this polymorphism has been inconclusive, probably due to problems such as small samples or methodological differences. The inconclusive results could also be related to the fact that linkage disequilibrium in different populations varies between Val158Met and other nearby SNPs, which may lead to different results in different populations. Nackley and colleagues (Nackley et al., 2006) suggested that *COMT* haplotypes modulate the expression of the protein by altering the secondary structure of mRNA and that the Val158Met and other SNPs interact to determine the functional expression of the gene. The study of *COMT* haplotypes therefore may give more information about the functional properties of this gene than the Val158Met polymorphism alone.

However, so far, genetic studies of ADHD have been inconclusive, and the effects have generally been small. In large-scale attempts with Genome-Wide Association (GWA) studies, no genes have reached the criteria for significance. This may be due to the polygenic and heterogeneous nature of the disorder, methodological differences and random variations. However, GWA studies have yielded significant results in other psychiatric disorders, and this may also happen in the field of ADHD when even larger samples are examined. Despite this, other, more theory based methods, such as the study of haplotypes in relation to different clinical measures, are still relevant in the field of neuropsychiatric genetics.

1.6 Executive functioning (EF) in ADHD

1.6.1 Executive functioning

The word “executive” is derived from latin “executio”, meaning to perform or fulfill. In line with this, the concept of EF has been defined as “general-purpose control mechanisms that modulate the operation of various cognitive sub processes and

thereby regulate the dynamics of human cognition” (Miyake et al., 2000 p. 50). However, many different definitions and theories have been presented aiming to describe the nature of this complex concept. Barkley (2012) claimed that 40 to 50 different definitions of EF have been published. There are also different opinions with regard to how broadly this concept should be defined. This has implications for the understanding of EF in neuropsychiatric disorders. Several questions and challenges exist concerning our understanding of EF in ADHD, some of which are described below.

1.6.2 Is ADHD a disorder of executive dysfunction?

Impairment of EF has been described as a core deficit in ADHD (Barkley, 2010; Castellanos, Sonuga-Barke, Milham, & Tannock, 2006). EF is often assessed by neuropsychological tests. Such tests are widely used in studies and assessment of neuropsychiatric disorders. However, there is often considerable overlap between controls and patients in performance on neuropsychological tests designed to measure EF. In ADHD groups, the variance in performance is generally higher than in controls (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005), and far from all individuals with ADHD show impairment on tests intended to measure EF (Willcutt et al., 2005). It is possible that this reflects the heterogeneity of ADHD, where several factors may constitute pathways to ADHD (Nigg et al., 2005; Wahlstedt, Thorell, & Bohlin, 2009). As such, those displaying EF deficit on neuropsychological tests may represent a distinct subgroup separate from subgroups, possibly with a different pathophysiology. This was supported by a study indicating that neurocognitive subtyping is possible based on information about cognitive control, temporal processing or reward sensitivity (de Zeeuw, Weusten, van Dijk, van Belle, & Durston, 2012). In line with this, Nigg and colleagues (2005) have proposed that the assumption of etiologic homogeneity has had a negative impact on ADHD research and suggested to separate between ADHD with and without EFD. They argued that this would stimulate research validating subtypes of ADHD, lead to the development

of more sophisticated causal models, and that this in longer term could provide clinicians with better ways to tailor and target treatments.

However, it has also been argued that neuropsychological tests do not capture all EF problems experienced by patients with ADHD because the test-situation in itself is very structured and far from the daily life where the patients often experience and describe such problems (Barkley & Fischer, 2011). It has been shown that a patient may pass lab-based EF tests despite having severe problems with EF in daily life (Saver & Damasio, 1991). Toplak, West & Stanovich (2013) suggested that although intended to index the same underlying mental construct of EF, rating scales and performance based measures actually measure different underlying mental constructs. They also cited empirical work that only has demonstrated small to modest correlations between such measures. This supports the notion that the subgroup with test-defined EFD is a qualitatively different group with specific features.

1.6.3 The unity and diversity of executive functioning

Today, it is widely acknowledged that the structure of EF in adulthood is characterized by both unity and diversity. Originally, this was proposed by Teuber (1972). An important contribution to this knowledge is the research by Miyake et al. (2000), who attempted to examine the underlying structure of EF by examining three basic, important parts of EF (inhibition, updating and set shifting) proposed to be involved in more complex functions, such as planning. They used latent variable analyses, where the latent variables represented purer measures of the target ability free from measurement error, and concluded that both “unity and diversity” characterize EF. The latent variable is defined as an ability that is influencing performance on a set of tests. The selected tests should therefore measure a common underlying construct, in addition to measuring different nonexecutive variance. Statistical extraction is used to tap the target construct that is implicated in all tests. In the study by Miyake et al. (2000), the “unity” was confirmed in that different aspects of EF correlated with one another and as such probably tapped some common underlying ability. However, separability was also shown, supporting the notion that

EF in addition is characterized by diversity. Miyake & Friedman (2012) referred to several studies (Friedman et al., 2006; Friedman, Miyake, Robinson, & Hewitt, 2011; Rose, Feldman, & Jankowski, 2011; Vaughan & Giovanello, 2010) that support this view of EF. In addition, it is supported by studies showing that both common and unique brain areas are involved in the three functions studied by Miyake et al. (Collette et al., 2005). At a clinical level, specific EFs are probably more closely related to certain disorders or symptoms than others. For example, Friedman et al. (2008) have shown that inhibition is more closely related to externalizing behavior and attention problems in the classroom than updating and shifting (Friedman et al., 2007; Young et al., 2009). Their study also suggested that individual differences in EF, measured as latent variables, are nearly entirely genetic, and probably more heritable than IQ (Friedman et al., 2008). The results indicated that the unity of EF is due to impact of a common factor of EF with 99% heritability. The genetic influence was also high for specific functions with unique genetic influence to shifting (42%) and updating (56%), but not for inhibition. This highlights that genes are influencing EF at multiple levels, and that latent variables may be useful to distinguish these influences.

1.6.4 The task impurity problem

The assessment of EF is challenging because the tests are complex and also involve other, more basic functions in addition to the EFs. For example, Willcutt, Doyle, Nigg, Faraone & Pennington (2005) argued that it may be difficult to know whether a weak result on a test is really due to a weakness in the construct for which the task is intended to measure, and that future studies should try to isolate specific parameters of interest. They suggested that this may be done with careful analyses of the task and by developing suitable within-task and between-task controls. This so called “task impurity problem” (Miyake et al., 2000) complicates the interpretation of studies based on single tasks, as nonexecutive variance may be involved and this makes it unclear to what extent positive and null results reflect EF (Friedman et al., 2008). Miyake & Friedman (2012) proposed that any score on an EF task includes

systematic variance attributable to non-EF processes like color processing and articulation speed. They described this measurement error of systematic non-EF variance as substantial, and stated that this makes it difficult to measure the clean EF variance of interest. As a solution to the problem, they used the before mentioned latent-variable approach where they “extracted” what is common between the tasks, producing a more “pure” latent variable as measure of EF. Correlations between the common EF factor (latent variable) and perceptual speed/IQ were far from 1.0, suggesting that the EF factor not only reflects those functions, but goes beyond perceptual speed and IQ (Friedman et al., 2008). In addition to latent variable analyses, it is possible to control for the basic functions, using measures of more basic functioning as covariates. Then, there is no need to include several tests measuring the same construct. Some tests, such as tests included in the D-KEFS, comprise conditions that assess basic functioning, which makes it possible to subtract the lower level functions from the higher-level functions. The inclusion of such “pure” scores in the test manual makes D-KEFS applicable and useful also in a clinical setting. Since D-KEFS is standardized and validated on a relatively large sample, and is widely used also in a clinical setting, the contrast scores from D-KEFS may be suitable in studies of “pure measures” of EF.

Several of the D-KEFS tests are measuring set shifting, defined as the ability to move back and forth between multiple tasks, operations and mental sets (Miyake et al., 2000). This function has been described as a potential endophenotype for ADHD (Boonstra et al., 2008), i.e. a measure that lies between the geno- and phenotype. However, although set shifting has been widely studied in ADHD (Barkley, Murphy, & Fischer, 2008; Piek, Dyck, Francis, & Conwell, 2007), the results have been inconclusive. This may be due to ceiling effects, different tests and methodologies used and not controlling for basic functions. One of the tests measuring this function in D-KEFS is the Color-Word Interference Test (CWIT), which is a further development of the traditional Stroop-test. The Stroop-test is widely used in ADHD research, as it measures inhibition, which is suggested to be a core function implicated in ADHD (Barkley, 2012). However, the newer version of this test

including set shifting may also be relevant in ADHD since it probably reduces some of the earlier problems related to the assessment of this function in ADHD.

Although the influence of basic functioning may be the greatest challenge when assessing EF, other EFs than the target function could be involved in the task as well. For example, working memory may be implicated in several EF tasks, even if this is not the targeted function. In line with this, Ravizza & Ciranni (2002) pointed to the relationship between set shifting and working memory. To control for other EFs could be important to obtain a “pure” measure of the targeted function, but may be problematic. For example, in ADHD, working memory may be a part of the disorder itself, and controlling for this could therefore lead to removing variance that is due to ADHD instead of the targeted function.

The same challenge concerns the relationship between EF, ADHD and IQ. The influence of IQ on EF tests and ADHD symptoms has been found in several studies (e.g. Adolfsdottir, Sorensen, & Lundervold, 2008; Tillman, Bohlin, Sorensen, & Lundervold, 2009). Dennis et al. (2009) argued that even though IQ accounts for all the variance in a measure of cognitive performance, it does not explain the relationship between IQ and EF, as there may be a common latent variable that accounts for both results, such as ADHD. This is supported by Rommelse et al. (2008), who found independent familial segregation of EF and intelligence measures in families with ADHD.

1.6.5 Functional outcomes of adult ADHD and executive function deficit (EFD)

Adults with ADHD are often impaired in a wide range of functions (Biederman, Faraone, et al., 2006; Gjervan et al., 2012; Halmoy et al., 2009). In addition, they may have a history of school failure, struggle with comorbid disorders, such as antisocial, depressive and anxiety disorders, and are often involved in traffic accidents. In a study from our group, 24% of the patients were in work, compared to 79% in the population-based control group (Halmoy et al., 2009). In USA, the work loss cost of

adults with ADHD and adult family members in the year 2000 was estimated to be \$3.7 billion (Birnbaum et al., 2005). Even among workers, ADHD on average leads to around 4-5% reduction in work performance (Kessler, Lane, Stang, & Van Brunt, 2009). Halmøy et al. (2009) found that substance abuse, combined subtype of ADHD and a history of depression/anxiety were correlated with being out of work, while medical treatment in childhood was the strongest predictor for being employed in adulthood. Current medical treatment for ADHD was also positively correlated with employment. Despite this, only a small minority of workers in a recent survey undertaken by the World Health Organization was treated for ADHD (de Graaf et al., 2008). To identify possible risk factors for negative functional outcome within the heterogeneous group of individuals with ADHD may be of importance for treatment and interventions. One such risk factor may be EFD. As discussed earlier, some researchers argue that ADHD is a disorder of EF dysfunction, while others suggest that only a subgroup within ADHD have such problems. Regardless what perspective is taken concerning this issue, the group with test defined EFD may be a distinct subgroup characterized by different functional outcomes than the group without EFD. For example, research indicates that deficits in a test-defined EFD-group are important for a range of daily-life activities (Miller, Nevado-Montenegro, & Hinshaw, 2012; Nigg et al., 2005), and research is therefore needed to characterize the deficits and functional outcomes in this subgroup.

1.7 Heterogeneity in ADHD

As already mentioned, studies suggest that ADHD is a complex, heterogeneous condition, probably consisting of different subgroups. The multifactorial nature of the disorder points to a high degree of aetiological heterogeneity, probably with a different degree of environmental and genetic contributing factors in different individuals. As Nigg (2005) argued, the search for homogeneous explanations in ADHD research may be misleading. At a basic neurobiological level, separate mechanisms may be implicated in different subgroups of patients, while this may be reflected in separate neuropsychological profiles at another level. At a clinical level,

the heterogeneity could be reflected in different presentations of the disorder, which may be associated with certain functional outcomes. The name of the main study: "ADHD in Norwegian adults: From clinical characterization to molecular mechanisms" reflects a translational perspective and highlights the importance of investigating ADHD at different levels, from more basic mechanisms, to long term functional outcome. The studies included in this thesis also reflect this perspective through focusing on a range of issues concerning EF in ADHD, spanning from basic mechanisms to occupational outcome.

1.8 The present study

1.8.1 Aims

The aims of this thesis were to apply translational research and involve information at multiple levels to improve our understanding of ADHD. Specifically, we aimed to: 1) investigate if *COMT* haplotypes, suggested to lead to different dopamine levels in the prefrontal cortex, are related to symptom dimensions of ADHD, 2) investigate a "pure" measure of set shifting in ADHD patients using the CWIT from the D-KEFS, 3) examine functional outcomes of psychometrically defined EFD in patients with ADHD.

2. Materials and method

2.1 Participants

All participants in the three studies were enrolled in the main project: “ADHD in Norwegian Adults: From clinical characterization to molecular mechanisms”. When the third study was conducted, 800 adults with ADHD diagnosed according to the DSM-IV criteria and 909 control persons had been included in the project. The recruitment of patients and controls is illustrated in figure 2.

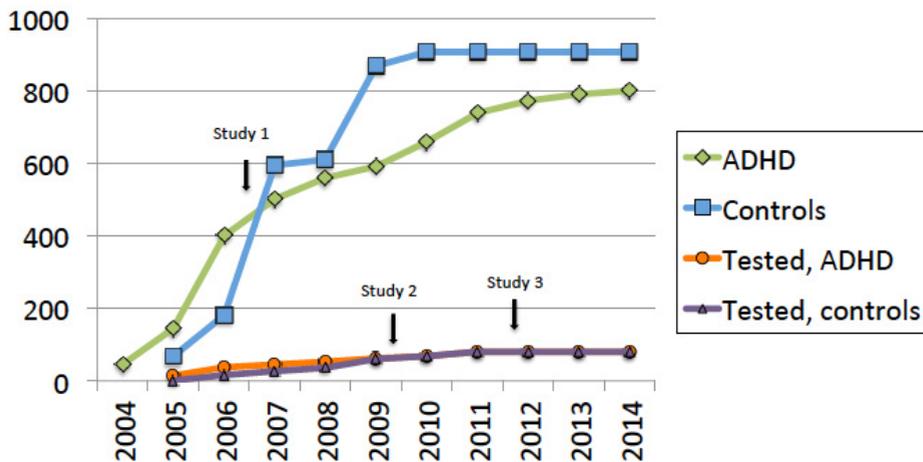


Figure 2: The cumulative recruitment in the period from 2004-2014 is illustrated for patients and controls in the main project, and for the neuropsychological tested patients and controls. The arrows indicate end of inclusion for the different studies.

Patients (>18 years old) were recruited through clinicians (mainly psychiatrists) nationwide or from a national registry of adults diagnosed in Norway from 1997 to May 2005.

This national registry was based on a diagnostic assessment conducted by three to five clinicians with specialized experience in diagnosing ADHD in children and adults (mainly psychiatrists and neuropsychologists) in three national expert committees of ADHD/hyperkinetic disorder. The background for establishing the teams was that prescription of central stimulants was legally restricted for adults in Norway until 1997. However, it was possible to receive this treatment from October 1997 to May 2005 if the committees approved the diagnostic evaluation. Thus, the teams ensured that the diagnostic practice was standardised across the country. Although ICD-10 is the official diagnostic system in Norway, allowance was made for the diagnosis of the inattentive subtype in DSM-IV. In addition, presence of comorbid disorders was also allowed if the criteria for ADHD were fulfilled and present before the comorbid disorders appearance. Psychiatrists, hospital doctors or general practitioners referred the patients to the committees. The referral procedure required patient records, describing current symptoms and functioning, collateral information about childhood behaviour and functioning and results from psychiatric and physical examinations. Through reviewing the patients' records, a confirmation or disapproval of the diagnosis of ADHD was made, and use of treatment with central stimulants was recommended or not based on the diagnosis and contra-indications for such treatment.

Although the data from the committees were not designed as a patient registry, it represents a national cohort of adult ADHD patients. More than 5000 patients were handled, of which nearly 70% (N=3397) were recommended for treatment. Between 2005 and 2007, 1700 invitation letters were sent to adults with ADHD included in the lists from the teams, mainly targeting individuals referred after the year 2000.

National Guidelines for Diagnosing Lifespan ADHD were effectuated in May 2005 by the Norwegian Health Authorities, and from that point of time, diagnostics of

ADHD was done by specialists in psychiatry without the mandatory evaluation by the expert committees. Psychologists and psychiatrists nation-wide were therefore also invited to recruit adults with ADHD who were formally diagnosed according to the national guidelines based on the criteria used by the expert teams, but without the evaluation of the teams.

Criteria for inclusion in the project were age 18 years or older at time of inclusion in addition to a diagnosis of ADHD or Hyperkinetic Disorder (according to the DSM-IV or ICD-10 criteria) received in adulthood or childhood prior to the inclusion in the project.

The Medical Birth Registry of Norway (MBRN) was used to recruit the control group. This registry includes individuals born in Norway after January 1st 1967. Invitation letters were sent to a randomly selected nation-wide sample of 2963 individuals between 18-40 years. In addition, a subsample was recruited by means of local advertisements (N=189).

All participants were asked to complete a set of questionnaires and donate a sample of blood or saliva for DNA-extraction. Persons from the main study living in or around Bergen were also randomly selected and invited to take part in a psychiatric interview (performed by psychiatrist) and a neuropsychological examination (performed by a trained test technician).

In the first paper, 435 diagnosed ADHD-patients and 383 controls with self-report data and saliva/blood samples were included. In the second paper, 60 patients and 60 controls were included, while 79 patients and 77 controls were included in the third paper. In the two last studies, the participants went through neuropsychological testing and a psychiatric interview.

The recruitment procedure is illustrated in figure 3.

Self-report questionnaires

The Wender Utah Rating Scale (WURS: Ward, Wender, & Reimherr, 1993) was used to measure ADHD symptoms in childhood. This questionnaire has been validated and contains 25 questions that should be answered on a 5-point Likert scale. The Adult ADHD Self Report Scale (ASRS: Kessler et al., 2005) was used to assess current ADHD symptoms. This is the World Health Organization's rating scale for adult ADHD, and measures ADHD symptoms on a 5-point Likert scale. The questionnaire is split in two, where the first 9 questions assess inattention symptoms, and the last 9 cover symptoms of hyperactivity and impulsivity. Although those questionnaires were not officially validated in Norway, they have been extensively used both in the clinic and in research (K. Rasmussen, Almvik, & Levander, 2001). The version of ASRS included in this project was also used by the Expert Committees of Hyperkinetic Disorder/ADHD, and was originally translated and retranslated by an English-native employee of the Norwegian Department of Health and Social Welfare. It was later evaluated by 4 experienced psychiatrists in our project group. (See Appendix for the questionnaires used in the present studies).

2.2.2 Genotyping

DNA was either extracted from saliva using the Oragene DNA Self-Collection Kit from DNA Genotek (DNA Genotek, Inc., Ontario, Canada) at the HUNT biobank (Levanger, Norway), or from whole blood. DNA from both cases and controls were mixed on 96-well plates with two blank samples and at least two internal controls on each plate. Genotyping of SNPs (rs4680, rs4818) was done using the MassARRAY iPLEX System (SEQUENOM, Inc., San Diego, CA) and the TaqMan allelic discrimination assay (rs6269, rs4633). The concordance rate for total genotyping was 100%, and no SNP deviated from Hardy-Weinberg equilibrium.

2.2.3 Neuropsychological tests

Wechsler Abbreviated Scale of Intelligence

Two subtests (Matrix Reasoning and Vocabulary) from the Wechsler Abbreviated Scale of Intelligence (WASI) were used to get an estimate of IQ according to the norms presented in the test manual (Wechsler, 1999)

Tests from D-KEFS

D-KEFS is the first battery of tests designed to exclusively measure EF which is co-normed on a representative and large sample (Homack, Lee, & Riccio, 2005). It includes tests assessing several functions, such as flexibility of thinking, impulse control, planning and inhibition. D-KEFS also includes contrast measures, where the influence of basic functions is subtracted from the targeted measure. The battery comprises nine tests that may be administered together or separately, and provides a standardized examination of adults and children from 8 to 89 years.

Four tests from the D-KEFS measuring functions that have been reported affected in ADHD (Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Hallelund, Haavik, & Lundervold, 2012; Wodka et al., 2008) were used in the third paper, while the Colour Word Interference Test (CWIT) was used in the second paper. The chosen tests are all traditional tests that have been further developed and modified in D-KEFS.

Trail Making Test

The fourth condition was used as a measure of working memory function and visual set shifting and requires the participant to draw a line between letter and number sequences, measuring number of seconds completing the test.

Word Fluency Test

The first condition, where the participants are asked to search for words beginning on a specific letter, was selected as a measure of the ability of word-generation. The fourth and fifth conditions measure different aspects of verbal category switching

(number of correct responses and switching accuracy). The number of correct responses, correct switches and switching accuracy are measured.

Colour Word Interference Test (CWIT)

The third condition of CWIT was used as a measure of inhibition. The task in this condition is to inhibit reading words denoting colours while naming the incongruent colour of the word. In the fourth condition, the test person is asked to alternate between inhibiting an automatic response of reading (as in the third condition) and reading the colour word if the word is framed. This condition therefore requires both inhibition and set shifting abilities. The outcome measure is time to complete each condition.

Tower Test

In this test, the participant is instructed to build a tower while following certain rules. The primary score is the “achievement score”, which is based on if the tower is correct or not, number of moves and time. This score measures working memory function and the ability to plan ahead.

Paced Auditory Serial Addition Task

Paced Auditory Serial Addition Task (PASAT: Gronwall, 1977) was used to measure working memory. Participants were presented (auditory) a number between 1 and 9 every 3 seconds, and should always add the two last numbers. Working memory was defined as number of correct responses given on this task.

2.2.4 Psychiatric interview

In the subgroup undergoing neuropsychological assessment, the semi-structured diagnostic interview MINI Plus version 5.0.0 (Sheehan et al., 1998) was used by the psychiatrists to assess psychiatric comorbidity (current substance abuse/dependence and current depressive/manic episode in study 2).

2.3 Statistics

Different versions of SPSS were used to perform statistical analyses in the three studies. A p-value of 0.05 was used when the basic assumptions (equality of covariance, equality of error variance etc.) were fulfilled. Analysis of variance (ANOVA), and χ^2 tests were used to compare clinical and demographical data among the groups in all the articles. In the first article, single marker tests and allele frequencies were calculated with use of the PuTTY link (PLINK) software. PLINK and the Statistical Package for the Social Sciences (SPSS) software were used to perform linear regression analyses, while WHAP and PLINK was used to perform haplotype analyses. In the second study, factorial multivariate analysis of covariance (MANCOVA), ANOVA and analysis of covariance (ANCOVA) were used to investigate differences between groups on the neuropsychological measures. Working memory and IQ were added as covariates for significant results. For residual scores, hierarchical and standard regression analyses were used. In the third study, ANOVA and χ^2 (Pearson) analyses were used to investigate differences between groups in functional impairment. ANCOVAs and logistic regression analyses were performed for significant results.

2.4 Ethics

All participants filled in a written informed consent. The project was approved by the Regional Committee for Medical Research Ethics of Western Norway IRB # 3 (FWA 00009490, IRB 00001872) and the Norwegian Data Inspectorate. The participants received NOK 250 for returning blood or saliva samples and questionnaires, and additional NOK 500 if interviewed and tested.

3. Results

3.1 Paper 1

In this study, we investigated the association between *COMT* haplotypes and ADHD symptoms. We found that all markers (rs6269, rs4633, rs4818, rs4680) showed a trend for association with the hyperactivity/impulsivity scale, peaking at marker rs6269 ($p=0.007$). The risk allele of rs6269 was through haplotype analysis found to tag the proposed high *COMT*-activity haplotype ($P=0.01$) that in our sample was associated with the highest hyperactivity/impulsivity score. In addition, for the proposed mid and low activity haplotypes, an associated stepwise decreased hyperactivity/impulsivity score was found. No association was found for the questions addressing impulsivity when investigated separately. Analysis stratified for use of medication showed that the haplotype association primarily was caused by the subgroup on medication.

3.2 Paper 2

This study examined if adult ADHD patients showed difficulties of set shifting and inhibition using the CWIT from the D-KEFS. A group of adults with ADHD obtained significantly lower scores than population derived controls on both primary summary ($P<0.001$) and contrast measures ($P=0.004$) of set shifting. In addition, similar results were found when using an alternative way to calculate the contrast scores based on raw scores, with use of residuals. Differences between the groups were statistically significant after controlling for intellectual function and working memory ($P=0.003$). No significant differences were observed on any measure of inhibition.

3.3 Paper 3

In this paper, we examined if the group with EFD displayed distinct features. In the ADHD group, 24.3% showed EFD, while this was found in 10.8% of the control group. When controlling for age, this difference was not statistically significant ($p=0.098$). The ADHD-group with EFD was characterized by a significantly higher frequency of unemployment, more reading and writing problems, lower IQ and higher self-reported score of ADHD-symptoms in childhood as measured with the Wender Utah Rating Scale (WURS) than the ADHD-group without such impairment. In the ADHD-group with EFD, only 6.7% were employed, while 52.1% were employed in the ADHD group without EFD. This difference was statistically significant also after controlling for age and reading and writing problems. In contrast, none of the participants in the control group with EFD were unemployed. In addition, there was a significant difference between the groups on the CWIT in frequency of impairment. This difference was only found for the inhibition/set shifting condition. In the ADHD-group, 28.4 % showed impairment on this condition, while this was true for only 6.8% in the control group ($p<0.001$).

4. Discussion

4.1 Main findings

The thesis includes themes ranging from basic mechanisms in ADHD to functional difficulties and occupational outcome. Despite the wide range of topics, many questions concerning the nature of ADHD are relevant to the findings in all three papers. In the following, some topics related to the understanding of ADHD are discussed in light of the results from the studies included in this thesis.

4.1.1 A dimensional approach to ADHD

In the study of *COMT* haplotypes, ADHD symptoms were defined along a continuum from no symptoms in some of the controls to severe symptoms in some of the adults with ADHD. According to this perspective, the symptoms of ADHD are not limited to patients, but are present, albeit to a lesser degree, also in the general population. Instead of using distinct categories, we examined quantitative symptoms as measured by the ASRS, controlling for group status. The continuum approach may be closer to the nature of many psychiatric disorders than a categorical classification (Levy, Hay, McStephen, Wood, & Waldman, 1997) and also increases statistical power by retaining the variance. This was supported by our study, where a tendency for association was found between the tested SNPs and the hyperactivity/impulsivity dimension of the ASRS in the whole sample, but to a lesser extent when using ADHD as a categorical variable. Twin studies, indicating that similar set of genes are involved in the clinical syndrome of ADHD and the subclinical form of the disorder are in line with this finding (F. Levy, Hay, McStephen, Wood, & Waldman, 1997). Faraone (2000) argued that many of these genes are associated with the development of ADHD. Those with only a few of these genetic variants will be asymptomatic, while those in between will have some symptoms, but not enough to meet the threshold for the disorder. The relationship between genes and symptoms will also be

mediated by epigenetics and the interaction between genes and environment.

Somewhat counterintuitive to the dimensional perspective, we found a symptom specific effect of *COMT*; the association between the ASRS and the *COMT* haplotypes was only statistically significant for the hyperactivity/impulsivity scale. This is in line with results from studies indicating that although similar genes are associated with both the hyperactivity/impulsivity dimension and the inattentive dimension, there are some symptom specific effects (McLoughlin, Ronald, Kuntsi, Asherson, & Plomin, 2007). In addition, it has been suggested that EF problems may be related only to the combined or hyperactive/impulsive subtypes (Barkley, 1997). This supports that *COMT* variants may be related to the hyperactivity dimension of ADHD through influencing EF, and is in line with studies showing that *COMT* are related to EF. The different results for the groups with and without medications also suggest that there are subgroups within the diagnostic group. Nevertheless, a dimensional approach may still be the best way to investigate heterogeneity in ADHD, as subgroups do not necessarily follow conventional diagnostic borders.

4.1.2 Heterogeneity in ADHD and regulation of dopamine in prefrontal cortex

The finding that *COMT* haplotypes were related to symptoms of hyperactivity support the hypothesis that low levels of dopamine in the prefrontal cortex are implicated in ADHD (Sagvolden et al., 2005; Solanto, 2002). This hypothesis has also been supported by studies showing that methylphenidate reduces symptoms of hyperactivity (Gorman, Klorman, Thatcher, & Borgstedt, 2006). It is also in accordance with the finding of an association between the high activity Val allele of the Val158Met polymorphism and ADHD (Kereszturi et al., 2008), and associated problems, such as conduct disorder, aggression (Caspi et al., 2008) and impaired performance on cognitive tasks (Egan et al., 2001). However, results from different studies are conflicting, with some studies also showing association between ADHD symptoms and the low activity Met allele (DeYoung et al., 2010; Nikolac Perkovic et al., 2013; Palmason et al., 2010). Faraone (2000) has argued that if ADHD is not a

unitary disorder, but consists of several disorders with different non-genetic and genetic aetiologies, one should expect small genetic effects, and inconsistent patterns of replication. This was supported by our study, as the association between *COMT* haplotypes and symptoms of hyperactivity was only found in the ADHD group on medication. The participants in the non-medicated group may be non-responders who represent a qualitatively different group with another aetiology than the group on medication. Such differences may be due to several factors, such as a different genetic background, gender effects, gene-gene interactions and gene-environment interactions influencing the regulation of dopamine in the prefrontal cortex (Nobile et al., 2010). We have recently found that the non-responders have significantly different *DATI* genotypes than the responders, supporting this hypothesis (Hegvik et al., personal communication). As such, it is possible that different *COMT* variants may be beneficial for different individuals due to unknown factors influencing the total level of dopamine in prefrontal cortex. The theory of the inverted u-curve, where either too little or too much dopamine is leading to impaired performance, is in accordance with this finding. This was supported by a study where participants with ADHD and the low activity met/met *COMT* genotype showed an increased risk for adverse response to amphetamine compared to the val/val homozygotes (Mattay et al., 2003). Another study also found that those with the high activity val/val genotype showed a better response to treatment with methylphenidate than the val/met or the met/met genotype (Cheon, Jun, & Cho, 2008). Interestingly, using functional imaging, Cheon and colleagues (2008) found that genotype by drug interaction was restricted to the prefrontal cortex, which supports the involvement of *COMT* in prefrontal functioning. However, although impulsivity is shown to decrease with increasing level of dopamine in prefrontal cortex (Kayser, Allen, Navarro-Cebrian, Mitchell, & Fields, 2012), we found no specific association between items on the ASRS aimed to measure impulsivity and the *COMT* haplotypes. Further studies are needed to gain knowledge about the complex relationship between *COMT* genotypes, regulation of dopamine and symptoms of ADHD. In addition to factors influencing the level of dopamine in prefrontal cortex, several other factors are expected to contribute to the development of this complex disorder. Sun and colleagues (Sun,

Yuan, Shen, Xiong, & Wu, 2014) argued that information about gene-gene and gene-environment interactions should be included in future studies of the COMT gene. To gain more knowledge about the relationship between geno- and phenotype, biologically based phenotypes lying between genes and behaviour (endophenotypes), such as neuropsychological measures of EF, may also be useful (Doyle et al., 2005; Gau & Shang, 2010; Goos, Crosbie, Payne, & Schachar, 2009). Doyle et al. (Doyle et al., 2005) suggested that endophenotypes might be especially important for the understanding of the aetiology in complex disorders where different environmental factors and several genes influence the phenotype. Because the endophenotype is expected to be less genetically complex than the underlying disorder, it may lead to stronger statistical power that makes it possible to detect the effects of different genes.

4.1.3 Is it possible to obtain “pure” measures of EF?

In the second study, we found a difference in set shifting between the ADHD- and control group, also after controlling for covariates, which indicates that set shifting difficulties may signal a potential endophenotype in ADHD. However, it is an ongoing discussion whether it makes sense to split EF into subfunctions, a procedure that is commonly used by clinicians and neuropsychological researchers. Rabbitt (1997) has argued that trying to measure specific processes through isolating one variable violates the central assumption of the nature of EF, as this involves the ability to simultaneously manage several different functional processes. Despite this, it could also be that EF includes specific functions partly unrelated to other functions. The research by Miyake and colleagues (2000), showing both unity and diversity in EF, indicates that it makes sense to study EF at a more general level, with summary scores from several tests, but also at a more specific level to obtain “pure” measures.

When using standard clinical tests, it may be difficult to obtain such “pure measures”. In the second study, we therefore included tests from D-KEFS, which makes it possible to control for basic functions. We also controlled for IQ and working memory. However, we cannot conclude that we have controlled for all relevant

functions. In addition, there may be better methods to control for basic functioning than using the D-KEFS contrast measures. Since Crawford et al. (2008) argued that most of the variance in the contrast scores is measurement error variance, and therefore recommended not to use these measures, we also included an alternative method of calculation of “pure measures” based on raw scores. We obtained similar results, which supports the validity of the D-KEFS contrast measures, at least for the set shifting condition from the CWIT that was used in the present study.

In addition to the challenge of controlling for basic measures, IQ is often controlled for in studies of ADHD and EF. However, it may be impossible to separate IQ from the effects of the studied function, because when controlling for IQ, we probably also control for a part of the disorder itself (Dennis et al., 2009). This was supported by a study showing genetic overlap between IQ levels and ADHD (Kuntsi et al., 2004). Dennis et al. (2009) further argued that IQ often does not meet the criteria for being a covariate and that the practice of controlling for IQ has led to overcorrected, anomalous and counterintuitive findings. We therefore chose to present results both with and without controlling for IQ in the second paper. The similar results for set shifting with and without control for IQ are in line with previous studies, showing a minimal influence of IQ on set shifting (Friedman et al., 2006).

The problem of what to control for, and when, is an on-going debate in neuropsychological research. To reduce this problem, the method of latent variable analyses used by Miyake et al. has been used to extract more pure measures from several tests, and should be considered when designing future studies of set shifting and other EFs in ADHD. This is probably also relevant when relating EF to genetic information, as this gives an opportunity to separate the different levels (general versus specific) of genetic influence on EF, which is impossible when using only one, complex EF test (Friedman et al., 2008). However, if not choosing proper tests, for example if similar basic conditions are affecting the tests used to extract the pure measure, it will still be a problem to obtain a pure measure of EF.

In addition, Miyake et al. (2000) argued that a test could measure different functions depending on the experience the person has with a test or similar tasks. If a person is familiar with the present task, the test would no longer tap EF. One possible hypothesis is thus that the ADHD-group in our study has lower scores on the set shifting condition because they get less effect of training from the previous condition than the control group.

It is also possible that the differences between the ADHD and the control group reflect the complexity of the task, and that this complexity is more than just an additive effect of inhibition and set shifting. As such, it may be impossible to separate the functions, which is a view supported by Rabbitt (1997). However, it is also possible that the ADHD group have real problems with set shifting, and that this measure should be investigated further to determine if it could be used as an endophenotype for ADHD. Doyle et al. (2005) cited researchers who have linked components of executive functions to frontal systems (Willcutt et al., 2005) and argued that these components may constitute a core deficit that lies in the pathway that leads to behavioural symptoms in ADHD (Barkley, 2000; Castellanos & Tannock, 2002). However, several criteria have to be fulfilled for a measure to be considered an endophenotype. First, it should co-occur with the studied disorder, but it is not required to be universal for the disorder as it may be important for the understanding of heterogeneity in the condition. It should also be measured by instruments with good psychometric properties, be heritable and show familial-genetic overlap with the studied disorder (Doyle et al., 2005). The second study included in this thesis suggested that set shifting as measured with the CWIT from the D-KEFS co-occurs with ADHD. It could also be argued that it has been measured with an instrument showing good psychometric properties. However, more research is required, especially to determine heritability and familial-genetic overlap with ADHD. Several problems are also related to genetic research and the use of neuropsychological endophenotypes in ADHD, and the reported findings have been difficult to replicate (Kebir & Joober, 2011). Recent studies also question the validity of EF endophenotypes (Thissen et al., 2013) in adults, showing that after childhood, most influence on ADHD seems to be genetically independent from the influence on

EF (Thissen et al., 2013). This suggests that EF may not be a pathway from genes to symptoms of adult ADHD. However, the authors pointed to the possibility that EF and ADHD may be aetiologically related in a subgroup of patients with ADHD. They also argued that the endophenotype construct of EF in ADHD is probably dependent on the stage of development. This is in line with the massive developmental changes that occurs in the brain through adolescence (Blakemore & Choudhury, 2006).

4.1.4 Psychometrically defined EFD in ADHD- a subgroup characterized by functional impairment?

In the first study, we chose to investigate dimensional symptoms by combining results in the ADHD and control groups, as well as examining subgroups within and across the groups. Such an approach may be useful as it could be questioned if examining group-differences between the ADHD and control-group is appropriate, considering the heterogeneous nature of the disorder. In accordance with this, we identified a subgroup with ADHD and psychometrically defined EFD in the third study. This group showed more functional impairment than the ADHD group without EFD. The group with ADHD and EFD was characterized by higher frequency of unemployment, lower IQ, more self-reported ADHD-symptoms in childhood and more reading and writing problems. Interestingly, only 6.7% of the group with ADHD and EFD was employed, while this was true for 52.1% of the group with ADHD without EFD. In contrast, all participants were employed in the control group with EFD. This confirms studies showing that ADHD alone has a negative impact on work status (Halmoy et al., 2009), but that the combination of ADHD and EFD makes this even more severe (Biederman, Petty, et al., 2006), and that this combined group may represent a distinct subgroup.

However, if ADHD is a disorder of EF, as Brown (2006) and Barkley et al. (2008) have suggested, it may not make sense to identify a subgroup with EFD. In this perspective, neuropsychological tests are not sufficient to discover the EF difficulties in ADHD. This is supported by Barkley & Fischer (2011), who found that rating scales were better to predict occupational functioning than neuropsychological EF

tests in ADHD. However, they did not create a summary score for EF or defined "EFD" from the tests, but rather assessed the contribution of each test on the outcome variable. In our study, we used a cut-off for deficit including several tests from the same test battery, because previous studies have shown that a combination of tests is necessary to discriminate between ADHD groups and controls (Doyle, Biederman, Seidman, Weber, & Faraone, 2000). Still, more than 70% of the participants with ADHD in our study did not show EFD according to the definition, and the frequency of impairment in the ADHD and control group was not significantly different. However, results from our study indicate that this relatively small group of adults with ADHD is a vulnerable group with poor outcome. This highlights the importance of identifying this group, and supports previous research suggesting that ADHD is a highly heterogeneous condition.

Nigg et al. (2005) have shown that there may be multiple pathways to ADHD, and suggested inclusion of a new subtype with EF deficits in DSM-5. They proposed that the strongest argument for such a new subtype would be if it could be possible to demonstrate that for some, the disorder is caused by EF problems, and as such is different from ADHD that is associated with other processes that are nonexecutive. They argued that this subgroup should represent a qualitatively different condition, or should change the risk for a certain negative outcome, not only increase the complexity of the disorder. The results from our third study indicate that the group with ADHD and EFD is at higher risk for certain negative outcomes than the group with ADHD alone, something that supports that the group with ADHD and EFD may be a distinct subgroup. However, we only found an association, and cannot assume that the functional impairments are caused by EFD. It could also be the other way around; that people without work develop EFD as a result of being out of work, or that lack of diagnosis and treatment in childhood leads to EFD. The latter was supported by the fact that none in the ADHD group with EFD had been diagnosed in childhood, compared to 12.7% in the ADHD group without EFD. Studies showing that treatment in childhood is a strong predictor for being employed in adulthood also agree with this hypothesis (Halmoy et al., 2009). Another possibility is that the group with EFD and ADHD rather has more difficulties with compensating for the EF

problems than the ADHD group without EFD. Mahone (2002) suggested that individuals with ADHD and high IQ are better able to compensate for EF deficits than those with ADHD and low IQ, which may be the case in the group with EFD and ADHD in our study. This is in accordance with studies showing that IQ scores that lie below the average range may be correlated with several neuropsychological deficits, while this is not true for higher IQ scores (Dodrill, 1997, 1999). However, although we found a lower IQ in the group with EFD and ADHD, the IQ was still relatively high, suggesting that this explanation is unlikely. We also did not find a correlation between IQ and D-KEFS subtests in the ADHD group with EFD, which indicates that although IQ in the ADHD group with EFD is lower than in the group without EFD, IQ is not directly associated with the deficit.

Regardless if ADHD is a disorder of EF impairment or not, studies have shown that the subgroup displaying deficit on neuropsychological tests designed to measure EF are characterized by more functional impairment than the group without such difficulties. It is therefore of interest to examine those with ADHD and EFD combined, also at a genetic level, as this may lead us closer to identifying risk-factors for functional impairment in ADHD, with implications for clinical practice in terms of more targeted treatment.

4.2 Methodological considerations

In addition to the limitations already mentioned in the discussion, the studies included in this thesis have some methodological limitations that are important to take into consideration when interpreting the results. The study of complex neuropsychiatric disorders includes practical as well as theoretical challenges, some of which are described here.

4.2.1 Sample

The participants in the main project were already diagnosed at different clinical sites when they were enrolled in the project. This may have given a more heterogeneous, but also a more ecologically representative and valid sample than in many other studies recruiting from one or a few specialized centres. The participants with ADHD in the present study were recruited according to two different procedures, resulting in samples that may have somewhat different characteristics. The participants recruited by the expert teams using common guidelines may reduce the diagnostic heterogeneity. In addition, this group may represent a chronically impaired subsample, as they were the first group of adults in Norway with ADHD considered for medication. On the other hand, the most affected individuals have probably not been able to follow the extensive inclusion procedure, where they should fill in the questionnaires, take a blood- or saliva test and send this through posted mail. This requires a certain degree of organization and planning, and could explain a response rate of approximately 20%, which may have led to an underestimation of difficulties related to ADHD in our study.

The other part of the ADHD sample was directly recruited from clinicians. The vast majority were receiving treatment and may therefore represent patients that are more affected than if they were recruited from a community sample. The sample of patients is therefore consisting of two groups that are recruited slightly differently, and it may be that the effects level each other out. However, it is difficult to estimate exactly how these possible biases have influenced our sample, but the patients studied probably represent a population-based, naturalistic clinical setting, something that is crucial for the external validity of the findings.

In the control group, the response-rate was about the same as in the ADHD group (20%). This also points to a bias towards the most well functioning individuals. However, it is also possible that the motivation for participating was low in this group because many do not have personal interest in the studied disorder. As such, there may be a bias towards a higher response-rate among persons with symptoms of

ADHD, or with family or friends with the disorder. This may have led to an underestimation of the true effects in the studies.

4.2.2 Reported measures

Questionnaires

Self-report data were included in the present studies, and the participants may have been influenced by a wide range of factors modulating their symptom presentation on these questionnaires. Despite this, we believe that the information to the participants about anonymous treatment of data reduces this problem. A large part of the patients were on medication when filling in the questionnaires, which may have lowered the symptom-scores on the ASRS. The WURS assesses retrospective symptoms in childhood, and it could be difficult to remember childhood symptoms in adulthood. Awareness about the diagnosis of ADHD in adulthood may also lead to reporting more symptoms in childhood than were actually present. In some studies, high WURS scores have been related to a large number of false positives, and this indicates that it may partly reflect present personality instead of symptoms specific to ADHD (B. D. Hill, Pella, Singh, Jones, & Gouvier, 2009; Suhr, Zimak, Buelow, & Fox, 2009). However, although not officially validated in Norway, several studies have supported the validity of the questionnaires in Norway and comparable countries (Halmoy et al., 2009; Kessler et al., 2005; Luty et al., 2009), and they are widely used in both clinical- and research settings.

Neuropsychological tests

We used tests from the D-KEFS to examine EF in study 2 and 3. Because of the criticism from Crawford, Sutherland & Garthwaite (2008) concerning the validity and reliability of the D-KEFS contrast scores, we did not only include contrast measures in the second study, but also used an alternative statistical method to calculate “pure measures”. Despite the criticism of the D-KEFS contrast measures, there are several reasons for using subtests from D-KEFS in the present project. This battery of tests represents the first standardized method for assessment of EF, and provides a

“cognitive-process” approach to testing, which also makes it possible to examine the process of task-solving, not only the outcome measure. D-KEFS is used extensively in clinical settings, something that makes studies including the tests more clinically relevant (Homack et al., 2005).

5. Conclusions

The results from the first study support that *COMT* haplotypes should be studied in ADHD rather than only the val158met polymorphism. However, the fact that a significant association between symptoms and *COMT* haplotypes was found only in the medicated subgroup indicates that ADHD patients potentially can be divided into more subgroups than the subtypes described in the diagnostic manual (DSM-IV). The heterogeneity in ADHD was also supported by the third study, where we found that the group with psychometrically defined EFD and ADHD was significantly more functionally impaired than the group with ADHD without EFD. Several EF subtests from the D-KEFS were used to define the EFD, including the set shifting condition from the CWIT. This condition was shown to be the only test documenting significant differences between the ADHD and control group. These results are in accordance with the results from our second study, showing a significant difference for set shifting between the ADHD and control group also when controlling for basic functioning, IQ and working memory. Together, the present studies provide new knowledge that increases our understanding of the heterogeneity in ADHD.

6. Future perspectives

The present thesis includes topics ranging from fundamental biological mechanisms to functional outcomes of ADHD and EFD. The first study was published in 2009, and reflects the state of molecular genetic research at that time. During the past five years, GWA studies have become very common, while candidate gene studies dominated the field in 2009. It has also become clear that the genetics of ADHD is highly complex, and that many different genes with small effects are involved in the disorder (Cross-Disorder Group of the Psychiatric Genomics et al., 2013; Franke et al., 2012; Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2014; Neale et al., 2010; Yang et al., 2013). However, investigation of *COMT* haplotypes in ADHD had never been done when our study was published, and the interest in including haplotypes in future studies of ADHD and other neuropsychiatric disorders is illustrated by the many citations referring to this paper.

The second study indicates that the set shifting condition from CWIT should be investigated in further studies, as the ADHD group showed impaired performance even after control for more basic functions. Although this finding was promising with regard to the validity of D-KEFS contrast measures, and indicated that this measure may be a potential endophenotype of ADHD, we cannot exclude other, alternative explanations of the finding. The measurement of EF is challenging. More complex designs that examine multiple EFs with the use of multiple exemplar tasks to define latent variables for the different EFs may be needed, as the use of a single, complex EF test makes it difficult to distinguish the multiple levels of genetic influence on EF (Friedman et al., 2008).

In the third study, we also used the set shifting condition from the CWIT in addition to other EF tests from D-KEFS, to identify a subgroup with ADHD and EFD. Building on the experiences from the first study, it would be of interest to characterize this group genetically as this may give more insight into the genetic heterogeneity of ADHD. As genes highly expressed in specific regions in the brain

may also reflect functional specialisation, such studies may benefit from linking brain regions related to different EFs to sets of genes expressed in these brain regions (Ersland et al., 2012). However, since many genes with small effects probably are involved in ADHD, large samples are needed, which could be challenging in studies where neuropsychological testing is required. Multicentre studies with close collaboration concerning test procedures to secure high reliability between centres would improve the chance to obtain large samples with adequate power. In the future, functional outcome studies using national registry data with millions of records may also provide more insight into the nature of ADHD, especially if this could be linked to genetic information or other biomarkers.

In addition, to deal with the heterogeneity and complexity in ADHD, a more "personalized" psychiatric research approach, examining what characterizes individuals displaying certain features (or lack of such features), may be important to get more knowledge about the individuals within and across the present diagnostic categories. As a diagnosis is basically made by counting descriptive symptoms, there are arguments for establishing new classifications systems for psychiatric disorders. The Research Domain Criteria project (RDoC) has been launched by National Institute of Mental Health (NIMH) to define basic dimensions of functioning, including genes, neural circuits, as well as basic behavioural and neurobiological research. This could lead to a more integrative understanding of psychopathology in addition to better treatment. The background for this project was the lack of clearly defined subtypes of mental disease, without specific biological findings. This led to the question if this specificity may exist, but not necessarily for the clinical categories that are recognized today. The RDOC project takes a dimensional approach that spans from normal to abnormal function, and aims to generate classifications based on neurobiological underpinnings (Insel et al., 2010). This represents a relatively new perspective on psychiatric disorders, and may also generate more knowledge about the heterogeneity of ADHD in the future.

Source of data

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