Attention-Deficit/Hyperactivity Disorder in adults

Clinical characteristics and pre- and perinatal risk factors

Anne Halmøy

Dissertation for the degree philosophiae doctor (PhD)

at the University of Bergen

2011

Dissertation date: January 28th 2011

Scientific environment

The work of this thesis has been carried out at the Department of Biomedicine at the University of Bergen, where I was a research fellow during the years 2006-2010. Professor Jan Haavik, who also was my main supervisor, directed the multidisciplinary research group on ADHD.

The research is based on collaborations with several other departments; the Section for Psychiatry, Department of Clinical Medicine, University of Bergen (Ole Bernt Fasmer); the Center of Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen (Stefan Johansson, Per Knappskog); the Medical Birth Registry of Norway, the Norwegian Institute of Public Health, Bergen and the Department of Public Health and Primary Health Care, University of Bergen (Kari Klungsøyr, Rolv Skjærven), the Department of Medical and Biological Psychology (Helene Halleland, Astri Lundervold). Professor Ole Bernt Fasmer and Associate Professor Kari Klungsøyr were my co-supervisors.

Acknowledgements

The multidisciplinary research project “ADHD in Norway; from clinical characterization to molecular mechanisms” was funded by the Research Council of Norway, and the Western Norway Regional Health Authorities. My research fellowship was financed by the Faculty of Medicine and Dentistry, the University of Bergen. The Institute of Biomedicine has provided me with modern work-place facilities and a friendly atmosphere at the BB-building.

During the four years I have been working with this thesis, I have had the pleasure to work with many competent people from different fields. Without their contributions, this thesis would not have been accomplished.

First of all, I want to express my sincere gratitude to my supervisors.
Jan - your continuous support and interest in my work, always being encouraging and available, have been invaluable to me. Your vast knowledge and intellectual curiosity, your team-builder qualities and academic coaching skills have been a great source of inspiration. Thank you for having invited me into the world of research, and for letting me participate so actively in this project. I have learnt so much from our discussions. Ole Bernt - thank you for your interest in my work, and in particular for generously sharing your clinical knowledge and experience on ADHD and bipolar disorders. Kari - thank you for your enthusiastic support and for introducing me to the Medical Birth Registry and the world of epidemiology.

I am thankful to Stefan Johansson for his efforts and comprehensible way of communicating his knowledge about molecular genetics, and to Helene Halleland for the appreciable collaboration we had during our first years as research fellows in the project.

My other co-authors, Christopher Gillberg, Per Bergsholm, Margaretha Dramsdahl, Ingeborg Winge, Jeffrey McKinney, Per Knappskog, and Rolv Skjærven are thanked for their important and valuable contributions to the papers.

The whole ADHD group deserves a special thank; the multidisciplinary, collaborative and open-minded spirit of our Thursday lunches, with fruitful discussions and sharing of knowledge, have been a great source of inspiration and learning during these years. I hope to continue them in the future.

A special thank goes to Michael Lensing at Ullevål University Hospital in Oslo. His collaboration and help in recruiting patients from the former Expert Committees of ADHD/Hyperkinetic disorders have been invaluable to the project. His initiative and organizing of the National Research Network Meetings on ADHD is also highly appreciated. Geir Egil Eide at the Centre for Clinical Research at Haukeland University Hospital is thanked for statistical advices.

The ADHD project's coordinators - Vivica Næss, Ragnhild Nordenborg and Lisa Vårdal- who have also been my successive room-mates during these years- are thanked for their efficient work, practical help and pleasant company.

I am indebted to all the patients, their family members, the controls, and clinicians who participated in this study. Without their volunteering time and effort, this project would never have been possible.

Last, but not least, I feel fortunate to have a caring family and friends who take interest in my work - but most of all enrich other parts of my life.

My dearest Geir, Ulrik, Aksel and Emil: you're the best that ever happened to me!

Bergen, September 2010

Anne Halmøy

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Preface

Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent disorders encountered in child psychiatry and is increasingly being recognized also in adults. Still, controversies exist about the diagnosis both among health care practitioners and lay people.

Current diagnostic criteria for psychiatric disorders are purely descriptive in nature, classified on the basis of empirical observations of clustering and course of symptoms and behaviour into clinically recognizable entities. Due to insufficient knowledge about their etiology, there are no objective tests that can verify a diagnosis. Assessment of psychiatric disorders is therefore to a large extent dependent on clinical knowledge and experience.

As diagnostic criteria, research and clinical experience on ADHD are historically mainly based on children; clinical knowledge of ADHD in adults has so far been limited. Recent years' awareness of ADHD as a lifespan disorder, with increasing proportions of people being referred for assessment for ADHD also in adult psychiatry, has led to an urgent need of more knowledge about ADHD in adulthood. The question about what causes a disease is not restricted to researchers' curiosity, but is of practical importance also for clinicians as well as society and people affected by the disease.

Together, these aspects have been my main motivation for performing the work presented in this thesis.

Abstract

Attention-deficit/hyperactivity disorder (ADHD) is currently a prevalent diagnosis in child psychiatry, typically affecting 2-5 % of school-aged children world-wide. The recent and increasing awareness that ADHD may persist to adulthood for a considerable proportion of the affected children has created a need for more knowledge about ADHD as a lifespan disorder.

Aims: The aims of the thesis were to: 1) assess occupational functioning among adults with ADHD; 2) explore the relationship between ADHD and mood disorders; 3) investigate the role of pregnancy- and birth related complications as possible risk factors for persistent ADHD; 4) study the effect of an impaired serotonin production *in utero* on the development of ADHD symptoms and related behaviour.

Material and methods: The thesis is based on four separate articles (Paper I-IV). The first two papers are clinical studies based on questionnaires obtained from 414 and 510 adults with a clinical diagnosis of ADHD, respectively, and controls (n=359/417) from the general population. The third paper is an epidemiologic population-based study using data from the Medical Birth Registry of Norway (MBRN), in which we compared pre- and perinatal risk factors of a national cohort of 2123 adults with ADHD and the rest of the Norwegian adult population born in the same time period (n=1.17 million). The fourth study explores the possible causative role of reduced serotonin production in ADHD related symptoms and behaviour by studying the presence and effects of mutations in the tryptophan hydroxylase 1 gene (*TPH1*) in adult ADHD patients, their family members and controls.

Results: In paper I we showed that only 24 % of adult ADHD patients (mean age 34.5 years) were currently in work, compared to 79 % of controls (mean age 29.9 years). Having been diagnosed and treated for ADHD in childhood was the strongest predictor for being in work as an adult, independently of symptom severity, psychiatric comorbidity, and current treatment (OR 3.2, p=0.014). In the second paper, 51 % of

ADHD patients screened positive for a bipolar spectrum disorder (BSD) according to the Mood Disorder Questionnaire (MDQ), compared to 8.3 % of the controls. Patients screening positive for a BSD had lower occupational functioning and significantly more drug problems than patients with low levels of affective symptoms.

In the epidemiological population-based study from the MBRN, we found that low birth weight, preterm birth, and low Apgar scores were associated with ADHD in adulthood, with the highest risk for the lowest measures. We also found that maternal epilepsy and infant oral cleft were associated with ADHD in the adult offspring.

In the last study, sequencing of *TPH1* in 646 adults (patients and controls) resulted in the identification of 7 different missense mutations, of which 6 resulted in reduced enzyme function *in vitro* compared to wild type *TPH1*. Family based analyses showed that offspring of mothers with *TPH1* mutations had higher levels of ADHD related symptoms and behaviour, compared to offspring of fathers with such mutations or controls, independently of the individuals' own *TPH1* status.

Conclusions: Adults with a clinical diagnosis of ADHD had an impaired occupational functioning and a high prevalence of comorbid psychiatric problems. Symptoms of affective disorders were frequent among adults with ADHD, and were associated with lower occupational functioning and more substance abuse. Patients who were diagnosed and treated for ADHD in childhood had a more favourable outcome in adult life compared to patients who were first diagnosed in adulthood.

Factors indicating a suboptimal foetal development, such as being born extremely preterm or with very low birth weight, were associated with development of ADHD. Impaired maternal serotonin production in early embryonic life may be a causative pathway in the putative altered brain development, resulting in subsequent ADHD related symptoms and behaviours.

List of publications

The thesis is based on the following four original papers:

I. Halmøy, A., Fasmer, O.B., Gillberg, C., Haavik, J.: **Occupational outcome in adult ADHD: Impact of symptom profile, comorbid psychiatric problems and treatment. A cross-sectional study of 414 clinically diagnosed adult ADHD patients.** *Journal of Attention Disorders* 2009; 13 (2):175-87

II. Halmøy, A., Halleland, H., Dramsdahl, M., Bergsholm, P., Fasmer, O.B., Haavik, J.: **Bipolar symptoms 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* 2010; 71 (1):48-57

III. Halmøy, A., Melve, K.K., Skjærven, R., Haavik, J.: **Pre- and perinatal risk factors in adult ADHD: A population-based nested case-control study.** *(submitted)*

IV. Halmøy, A., Johansson, S[*]., Winge, I., McKinney, J., Knappskog, P., Haavik, J.: **ADHD symptoms in offspring of mothers with impaired serotonin production.** *Archives of General Psychiatry* 2010; 67 (10):1033-1043

[*] *Halmøy and Johansson contributed equally and share the first authorship of this paper.*

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Abbreviations

ADHD attention-deficit/hyperactivity disorder

ASRS adult ADHD self report scale

BD bipolar disorder

BSD bipolar spectrum disorder

CS central stimulants

DA dopamine

DSM Diagnostic and Statistical Manual of Mental Disorders

FDA Food and Drug administration

5HT 5-hydroxytryptamine (serotonin)

HD hyperkinetic disorder

ICD International Classification of Diseases

LBW low birth weight

MBRN Medical Birth Registry of Norway

MDQ mood disorder questionnaire

N number(s)

NA noradrenaline

OR odds ratio

RR relative risk

SSRI selective serotonin reuptake inhibitor

TPH tryptophan hydroxylase

WURS Wender Utah rating scale

Introduction

Attention-Deficit/Hyperactivity Disorder

Historical perspectives

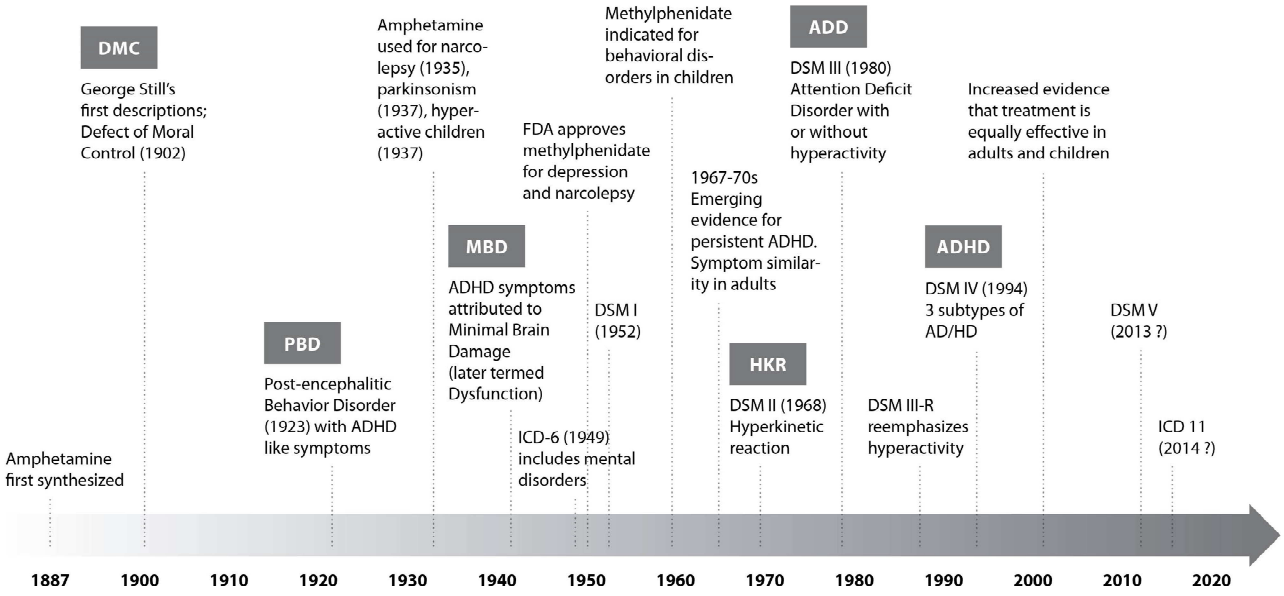
Attention-deficit/hyperactivity disorder (ADHD) is the diagnostic term currently used to designate a syndrome characterized by symptoms and problems related to attention deficits, hyperactivity and impulsivity. The syndrome has received different names and definitions during the last century. In 1789, the Scottish physician Alexander Crichton described a syndrome characterized by a "mental restlessness", in which the affected individuals showed an "incapacity of attending with a necessary degree of constancy to any one object", and which "almost always arises from an unnatural or morbid sensibility of the nerves, by which means this faculty is incessantly withdrawn from one impression to another". Crichton postulated that this condition "may be either born with a person or it may be the effect of accidental diseases" [1].

In 1902, the English paediatrician Sir George Still described a group of children with hyperactive, impulsive, often emotionally heightened and socially disruptive behaviour, with poor ability of sustained attention and who did not seem to adapt their behaviour in response as normally expected to reward and punishment. Still also postulated a biological origin to what he called a "morbid defect of moral control", which could be either congenital or acquired by disease in infancy [2].

Some decades after Still's description, in the wake of an epidemic outburst of viral encephalitis in the North of USA in 1917-18, the term "Post-Encephalitic Behaviour Disorder" (PBD) appeared. The term PBD referred to the clinical picture of children who were left with significant behavioural and cognitive sequela after surviving this brain infection. The syndrome was characterized by a combination of impaired attention and regulation of activity, impulsivity and social behaviour [3]. This observation led to a range of investigations of other possible causes of such a "brain damage syndrome", and associations were found with birth trauma, other brain

infections, head injuries, lead toxicity, and epilepsy [4]. The terms “Minimal Brain Damage” and later “Minimal Brain Dysfunction” (MBD) reflect the view around 1950 that this syndrome of hyperactivity/restlessness/inattentiveness was considered to be the consequence of some kind of brain abnormality, whether or not a history of brain damage was present.

Figure 1. Brief history of ADHD



In the following decades, the aspects of inattention and hyperactivity have been more or less emphasized in the diagnostic definitions: from Hyperkinetic Behaviour Syndrome [5] and Hyperkinetic Reaction of Childhood Disorder in the first official recognition of the diagnosis in the Diagnostic and Statistical Manual of Mental

Disorders, 2nd edition (DSM-II) in 1968, through Attention Deficit Disorder (ADD) with or without hyperactivity in the DSM-III in 1980, to the current Attention-deficit/hyperactivity disorder (ADHD), recognizing three different subtypes depending on the dominant symptom presentation (see Figure 1, brief history of ADHD).

Diagnostic criteria and subtypes of ADHD

Present diagnostic criteria for Attention-Deficit/Hyperactivity Disorder AD/HD are based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR), American Psychiatric Association, from 2000 [6], which is the diagnostic system used for mental disorders in the USA. In most European countries, the present official diagnostic system is the International Classification of Diseases, ICD-10 [7], where the diagnosis corresponding to AD/HD is named Hyperkinetic Disorder. The need for international standards, both in research and clinical practice, has led to the widespread use and adaptation of DSM-criteria also outside the USA.

The DSM-IV comprises 3 subtypes of AD/HD; AD/HD predominantly inattentive type, AD/HD predominantly hyperactive-impulsive type and AD/HD combined type, which require 6 of 9 symptoms of inattention, 6 of 9 symptoms of hyperactivity/impulsivity, or 6 of 9 symptoms from both categories (see Table 1). In addition, the category AD/HD Not Otherwise Specified (NOS) includes disorders with prominent symptoms of inattention or hyperactivity with impairment that do not fully meet the formal criteria. The list and grouping of symptoms are similar in the DSM-IV and the ICD-10 (except that the symptom “often talks excessively” is classified as a symptom of hyperactivity in the DSM-IV whereas it is listed among the impulsivity symptoms in the ICD-10). The main difference between the two systems is that the ICD-10 requires symptoms from both the inattentive (6 of 9), the hyperactive (3 of 5) and the impulsive (1 of 4) clusters for the diagnosis, whereas symptoms and impairment from inattention symptoms alone are sufficient for the diagnosis according

to the DSM-IV. Also, the ICD-10 is stricter in ruling out ADHD if other psychiatric disorders are present at the same time, i.e. if criteria for a mood or anxiety disorder are present, hyperkinetic disorder should not be diagnosed. The frequently occurring comorbidity with conduct disorder in children with ADHD is, on the other hand, regarded as a subtype in the ICD-10, where the term Hyperkinetic Disorders (F 90) includes the following specifications; Disturbance of Activity and Attention (F 90.0), Hyperkinetic Conduct Disorder (F 90.1), Other Hyperkinetic Disorder (F 90.8) and Hyperkinetic Disorder, Unspecified (F90.9).

Table 1. Diagnostic criteria of Attention-Deficit/Hyperactivity Disorder according to DSM-IV

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)

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision, American Psychiatric Association, 2000.

Prevalence of ADHD

ADHD is one of the most frequently encountered diagnoses in child psychiatry, with prevalence rates of 3-7 % in school-aged children, according to DSM-IV [6], and a recent pooled prevalence estimate of 5.3 % across studies worldwide [8]. However, reported prevalence estimates vary substantially between studies and countries (from less than 1 % to more than 20 %) [9]. Recent data from Norway estimate the prevalence of ADHD among 8-10 years old children to be 1.7 % [10]. The main explanation for this variation is probably differences in practice of assessment; i.e. ICD versus DSM criteria; parents or teachers used as informants; impairment criteria included or not, age range, gender, and type of population studied [9,11]. The prevalence rates are generally higher for DSM-based diagnoses, since all children diagnosed with ICD-10 hyperkinetic disorder will be included in the DSM-IV ADHD criteria, but not vice versa (i.e. ADHD predominantly inattentive subtype is excluded in ICD-10) [12,13]. A prevalence of 2-5 % thus represents a reasonable estimate of the prevalence of ADHD in children across populations.

Until recently, ADHD was considered to be a childhood disorder. In his description of The Hyperkinetic Reaction of Childhood Disorder in 1957, Laufer wrote that the disorder has a “good prognosis” and “often disappears after puberty” [5], and the DSM-II stated that “it usually diminishes in adolescence” [14]. Still, during the last decades, follow-up studies have shown that many children with ADHD continue to have impairing symptoms also in adolescence and adulthood. However, to what extent ADHD persists over the life span has not yet been established. In a meta-analysis of the earliest follow-up studies of children with ADHD, the actual proportions of children who retained an ADHD diagnosis at follow-up in late adolescence and young adulthood varied from 8-72 % [15]. Again, this variation appears to depend on methodological differences in the assessment of ADHD, including the use of different editions of the DSM at baseline and/or at follow-up. Persistence rates of ADHD have shown to be much higher when parent reporting is used, as compared to self-report from the young adults themselves [16]. In a recent review, Faraone and colleagues

confirmed the age dependent decline of ADHD diagnosis, and showed that the persistence rates depended much on the definition being used; from ~15 % persistence at age 25 years if maintenance of full diagnostic status was required (i.e. syndromatic persistence), to ~ 40-60 % persistence if partial diagnostic status with impairment was required (i.e. symptomatic persistence, corresponding to residual ADHD in the DSM-IV) [17]. With a prevalence estimate of 5 % in childhood, the deduced prevalence of ADHD in adults would range from less than 1 % for the full syndrome to about 2.5 % for the residual state of ADHD. These projected prevalence estimates are lower than found in recent cross-sectional studies of adult populations, which reported international prevalence rates of adult ADHD between 2.5 and 4.4 % [18-20]. Thus, the question may be raised whether ADHD seen in self-referred adults represents the same condition as ADHD seen in childhood [16].

Clinical aspects of adult ADHD

The diagnostic assessment of ADHD may be challenging for several reasons. First, according to current definitions, ADHD is a disorder that starts in childhood (see Table 1, criterion B). A diagnosis of ADHD in adulthood should therefore not be made unless there also is a childhood history of symptoms of ADHD. This may, however, be difficult to document retrospectively, because the recall and insight of own behaviour in childhood may be inaccurate, and because informants who were close to the person in childhood may be unavailable. Second, although diagnostic criteria for ADHD state that symptoms should be “maladaptive and inconsistent with developmental level”, they are based on symptoms and behaviour observed in children [21]. Follow-up studies of children with ADHD have shown that the course and pattern of symptoms change over time. While motor hyperactivity seems to attenuate during late adolescence and adulthood, attention problems are more persistent and may even increase [22,23]. The core symptoms may also have other manifestations in adults than in children and thereby be more difficult to recognize as ADHD symptoms. For example,

hyperactivity symptoms may be limited to fidgetiness or an inner feeling of restlessness rather than moving around, or to the inability to relax or sensation seeking behaviour and intolerance of boredom. Impulsivity and stimulation-seeking behaviour may have more serious consequences in adults than in childhood, such as reckless driving, terminating valuable relationships or quitting jobs without careful consideration. Attention problems in adults are often manifested as difficulties remaining focused in conversations or tasks, being easily distracted and having difficulties getting organized. Other typical features in adults with ADHD, not mentioned specifically in the DSM-IV, are procrastination and problems with time management. Underachievement and low self-esteem are often reported. These ADHD symptoms may actually be more impairing in adult life, when demands and expectations to one's self-organizing ability is increased relative to childhood, where the structure from school and parents may compensate for the lack of own, inner structure. As stated by Weiss et al., "It is exactly this difference between what is expected of children and what is expected of adults that makes it hard to diagnose adult ADHD using childhood criteria" [24].

In a comprehensive report on adult ADHD, Barkley et al. presented and compared data from two extensive studies on clinically referred adults with ADHD, and children diagnosed with ADHD followed to adulthood, respectively. They demonstrated the lack of sensitivity of current DSM-criteria for adults with ADHD, both regarding the formal cut-off of 6 of 9 symptoms from each symptom cluster, and the age-of-onset requirement of 7 years. Based on factor analytic models, they propose a novel set of diagnostic criteria for adults, which better delineate ADHD from the healthy population, and better distinguish the disorder from other clinical populations [16].

According to Barkley et al., and reflected in their proposed criteria, the core problem in ADHD is a deficit of executive function (EF), or more fundamentally, of response-inhibition. Executive functions may be broadly defined as "a set of neurocognitive processes that allow for the organization of behaviour across time so as to attain future goals" [25]. Thus, it is not the hyperactivity, often the most obvious symptom in children, but rather the distractibility, the impulsive decision making, and the impaired ability to

adjust their behavioural responses appropriately to a situation, which seem to best distinguish adults with ADHD from adults without ADHD.

Affect lability and emotional dysregulation

Adults with ADHD commonly present with additional symptoms to those required by the formal diagnostic criteria, but which may often be as impairing as the defined ADHD core symptoms. These symptoms, mainly related to affective lability or emotional dysregulation, were included in the earliest descriptions of ADHD in children [2,5] and are currently listed as associated features of ADHD in the DSM-IV. In their early reports on adults with persistent ADHD followed up from childhood, Wender and colleagues proposed a new set of diagnostic criteria aimed to better reflect the adult phenotype of ADHD [26]. These Utah-criteria require the presence and persistence of both motor hyperactivity and attention problems in childhood and in adulthood for the diagnosis, in addition to at least two of the following five symptoms/problems; mood instability (mood shifts that last for hours or at most a few days), disorganization or inability to complete tasks, hot temper (anger outbursts, easily irritated), emotional over-reactivity (difficulty dealing with ordinary stresses of life), and impulsivity (such as impulsive buying, other hasty business decisions, driving behaviour, initiation or termination of relationships). Wender and colleagues also developed the Wender Utah rating scale (WURS) as a tool for the retrospective assessment of childhood ADHD [27], emphasizing the importance of tracing symptoms back to childhood. Despite meeting a need for adult adjusted criteria for ADHD at the time, the use of the Utah criteria have been limited, probably because they fail to identify the predominantly inattentive subtype of ADHD, and because they may not adequately delineate ADHD from affective disorders [28]. The emotional aspect of ADHD however still reflects the clinical reality for patients with ADHD and their clinicians, and is associated with a more severe course and outcome of the disorder [25,29-31]. A topical question is how these emotional symptoms should best be understood; as an associated trait in a subgroup of patients (DSM-IV), as part of a

comorbid [32], or even primary affective disorder [33], or as a main feature of ADHD [25,34,35] (see Discussion of main findings).

Comorbidity and overlap with other psychiatric disorders

Attention-deficit/hyperactivity disorder frequently co-exists with other problems and psychiatric disorders, and this is particular true in adulthood. About 80 % of ADHD patients in clinical settings fulfil criteria for at least one, and approximately 50 % for at least two other DSM-IV diagnoses [16,36,37]. Comorbidity is also common in non-referred and community samples of adults with ADHD [16,19]. The most frequent co-occurring diagnoses are mood and anxiety disorders, substance use disorders (SUD) and personality disorders [19,38,39].

Mood (or affective) disorders are grouped into unipolar and bipolar disorders (BD), the first comprising depressions only, the latter characterized by alternations between depressive periods and periods of elevated mood and energy, i.e. mania (bipolar disorder 1, BD 1) or hypomania (bipolar disorder 2, BD 2). Attention-deficit/hyperactivity disorder and BD have several common features; they are both heritable disorders [40,41,42], their core symptoms involve a dysregulation of energy, activity, impulsivity, mood and attention [6], and both disorders often co-occur with other psychiatric disorders and problems [19,43-45], i.e. SUD [46-49] and anxiety disorders [50-52]. A main distinguishing feature between ADHD and BD is the periodicity of symptoms (state-like) in BD, contrasted to the chronic symptom course (trait-like) in ADHD. However, in recent years the concept of BD has been extended, including patients formerly diagnosed with unipolar depression [53]. There is now increasing evidence that affective temperaments, life-long dysregulation of mood, and other chronic symptoms are important parts of the phenomenology of the bipolar spectrum disorders (BSD) [54,55]. Another distinguishing feature between ADHD and BD is the age of onset, which typically is in late adolescence or young adulthood in BD, and before school age in ADHD. Interestingly, child psychiatrists are currently discussing the diagnostic criteria and phenomenology of BD in children, where the broadly defined juvenile BD seems to have more overlapping features and to be more

comorbid with ADHD than the narrow defined BD, which is based on the classical adult criteria for BD [56-58]. (For further discussion of this topic, see Discussion of main findings).

Substance use disorders (SUD) are frequently reported among adults with ADHD. In clinical samples of adults with ADHD, lifetime prevalence of alcohol abuse or dependence varies between 17 and 53 %, and for other drugs between 8 and 32 % [16,59-61]. In community-based samples, 15 % of adults with ADHD report a lifetime history for any substance use disorder compared to 6 % of adults without ADHD [19]. Symptoms related to substance misuse may be difficult to distinguish from primary ADHD symptoms, and ongoing substance use is a clinical challenge in the diagnostic assessment and the treatment of ADHD. The development of SUD in children growing up with ADHD seems to be partly mediated by the presence of symptoms of conduct disorder and of juvenile BD in adolescence. Comorbidity with SUD is further associated with antisocial behaviour and low functioning, including criminality, in adult life [59,62,63,64]. Some studies indicate that this malignant course of ADHD may be reduced by treatment with central stimulants (CS) in childhood [65], but more prospective studies are needed to clarify this important issue.

Anxiety disorders are also reported more often among children and adults with ADHD than in the general population [19,66,67]. Anxiety as a trait may be considered antagonistic to impulsivity, whereas anxiety and attention are closely related. The combination of ADHD and anxiety seems to be more linked to the inattentive subtype, to have a different cognitive profile and possibly also be caused by other risk factors, than the combined and hyperactive-impulsive subtypes of ADHD [16,52,68,69]. Differentiation between ADHD and anxiety may however be difficult in the clinical setting, especially since both disorders may appear early in life: Is the anxiety secondary to a disorganized and chaotic life due to a primary ADHD, or is the inability to concentrate and achieve secondary to a primary anxiety disorder? [70] In adults, some anxiety disorders (panic disorder, generalized anxiety disorder) have shown to be more specifically related to bipolar spectrum disorders [71]. This indicates a putative link between mood, anxiety and attention that may be relevant for ADHD.

In the multidimensional DSM, ADHD is classified as an axis I disorder, but the description of this long lasting trait is semantically close to the axis II personality disorders used in adult psychiatry [72]. Indeed, it has been shown that many children with ADHD as adults are diagnosed with personality disorders, in particular the cluster B personality disorders (i.e. antisocial and borderline) [38,73-76]. Features related to impulsivity and poor self-regulation (affect instability, lack of organization, impaired social relationships) are characteristics of both ADHD and borderline personality disorder (BPD), although not included in the current diagnostic criteria for ADHD. This may suggest that the axis II disorders arise as complications of insufficiently treated ADHD, but may also represent age dependent manifestations of common, overlapping traits.

Treatment

According to current guidelines, the first line treatment in mild to moderate cases of ADHD in children and adolescents is parent training/education programmes for carers and psychological and/or social skills training for the child or adolescent [77,78]. Psychosocial interventions should also be the first treatment for adults with ADHD with mild symptoms and impairment. Cognitive behavioural therapy (CBT) has shown to be effective in reducing persistent symptoms in adults after stabilization with medication [79,80].

For severe cases of ADHD in children (except preschoolers), and moderate to severe cases of ADHD in adults, medication is considered the first line treatment. Since the discovery of amphetamine's calming effect on hyperactive children in 1937, and the approval of methylphenidate for treatment of behavioural disorders in children in the beginning of the 1960s, central stimulants (CS) have been the drugs of choice in the treatment of ADHD/hyperkinetic disorder [81]. New developments in the pharmacotherapy of ADHD have so far mainly been related to alterations in composition and release properties of these CS [82]. Although CS are the most effective drugs in treating ADHD on a group basis [83], the more recently introduced non-stimulant drug atomoxetine has also shown to be effective and may be a useful

alternative for non-responders, or cases where stimulants should be avoided (e.g. ADHD comorbid with anxiety or SUD [84,85]). Other drugs that have been used less frequently include some antidepressants (buproprion, tricyclic antidepressants) and antihypertensives (clonidine, guanfacine) [86]. All of the above mentioned drugs act on the catecholaminergic system. In contrast, the widely used selective serotonin reuptake inhibitors (SSRI) in adult psychiatry do not have any documented effect in reducing core ADHD symptoms [87]. Despite the existence of effective treatment for reducing core symptoms of ADHD, there is still a need for studies that evaluate the long-term effects of pharmacotherapy on function and impairment, and studies on ADHD patients with comorbid disorders [88-90].

Neurobiology of ADHD

Brain regions and networks

ADHD is often considered a neurodevelopmental disorder, i.e. the symptoms and behaviour are caused by a disturbed development of the brain. Imaging of the brain with magnetic resonance techniques (MRI) has shown that children with ADHD on average have a reduced overall brain volume of about 3-4 % compared to control children [91,92]. The most prominent and consistent structural deficits in ADHD in children have been found in the frontal lobes (in particular the prefrontal cortex), the basal ganglia (striatum), and more recently also in the cerebellum, the anterior cingulate cortex and the corpus callossum [93-96]. Longitudinal studies have shown that normal maturation of the brain cortex is delayed by about 3 years in children with ADHD compared to controls [97], and cross-sectional studies have shown that cortical thickness is reduced in children, adolescents and adults with ADHD [98]. Deficits in response inhibition and of executive functions are, as mentioned, considered a core problem in ADHD [99]. Functional MRI has made it possible to localize these executive functions not only to the prefrontal areas of the brain, but also to fronto-striatal, and

fronto-subcortical-cerebellar networks. These areas seem to be underactivated in children with ADHD compared to controls during performance of tasks involving attention and disinhibition [100,101]. Differences in volume and shape of the hippocampus and the amygdala have also been found in children with ADHD, suggesting an involvement of the "emotional" limbic system in the disorder [102]. Although fewer in number, studies of adults with ADHD confirm these brain abnormalities [103-105]. Furthermore, it seems that the observed dysfunctions in children and adults with ADHD are not restricted to isolated brain regions but to compromised inter-regional connectivity- "the wiring"- between these areas [94,106,107].

Neurotransmitter systems

Several neurotransmitters seem to be involved in the pathogenesis of ADHD, of which the monoamines, and in particular the catecholamines have been the most studied. The main reason for this is that the central stimulant drugs methylphenidate and amphetamine act indirectly as dopamine (DA) and noradrenaline (NA) agonists, mainly by blocking the reuptake of DA and NA in the synapses [108-111]. The noradrenergic system is also the main target of the selective NA reuptake inhibitor, atomoxetine, a more recently introduced drug in the treatment of ADHD.
Dopamine is involved in the regulation of cognition, movement, reward and motivation, whereas NA is important for arousal and for sensory information processing, all considered central aspects of ADHD psychopathology. Dopaminergic neurons originate mainly in the brain stem and the hypothalamus. Their axons are connected to other brain regions by dopaminergic pathways, of which the mesocortical and the mesolimbic seem to be the most important in ADHD. The axons of the noradrenergic neurons in the locus coeruleus also project to various regions of the brain including the prefrontal cortex, the cingulate gyrus, the striatum, the amygdala and the hippocampus.

The monoamine serotonin is also involved in a variety of behaviour and brain functions, such as impulsivity, aggression, mood, cognition and sleep. Serotonergic

neurons originate in the raphe nuclei in the brain stem and project extensively throughout the brain in a diffuse modulatory system [112]. Serotonin as a neurotransmitter has been widely studied in mood- and anxiety disorders, but has so far received less attention in ADHD. However, there is evidence that serotonin may have a separate contribution to aspects of the ADHD phenotype [113,114]. Experiments on dopamine transporter (DAT) knockout mice have indicated that the calming effect of stimulants on dopamine related hyperactivity is mediated by serotonergic activity [115], and that serotonin modulates the effects of dopamine in the reinforcing/addictive elements of drug-taking behaviour [116]. A putative role of serotonin in ADHD thus would be through a disturbed balance and/or interaction with the other catecholamines within different regions of the brain [117-119]. Most of the serotonin in the body is however synthesised outside the brain, localized mainly in the gastrointestinal tract and blood platelets [120]. Importantly, the effects of serotonin on ADHD may extend beyond that of defective or altered neuronal signalling. Rodent data have shown that serotonin is crucial for normal embryonic brain development [121], and findings presented in this thesis suggest that low maternal serotonin production in pregnancy may have lasting effects on neuropsychiatric symptoms and behaviour (Paper IV). Still, the specific role of serotonin in the development of ADHD remains to be elucidated.

Risk factors of ADHD

Attention deficit/hyperactivity disorder is considered a complex trait disorder, with heterogeneity both in its clinical expression and etiological pathways. As early as in 1902, Still noted that the origins of the disorder could be congenital or acquired, either by disease in early infancy or by later trauma. Based on family, adoption and twin studies, it is now generally acknowledged that ADHD is of familial origin in most cases, with summarized data from twin studies reporting a heritability estimate of about 75 % [40], which is among the highest for psychiatric (and somatic) disorders.

Genetics

Inspired by the high heritability rates and putative monoaminergic dysfunction in several psychiatric disorders, numerous association studies on candidate genes have been performed on ADHD. The most studied candidate genes in children with ADHD are related to the dopamine system. Some significant associations across studies have been found for the dopamine transporter (SLC6A3/DAT1), the dopamine D4 receptor (DRD4) and the dopamine D5 receptor (DRD5) genes [122]. Other genes from the noradrenergic (DBH, SLC6A2/ NET, ADRA2A) and serotonergic systems (SLC6A4/SERT, HTR1B, TPH1, TPH2) have also been associated with ADHD in children [122]. However, results have been inconsistent and none of these findings have so far reached whole genome significance (defined to $P<5x10^{-8}$ when using 10^6 markers) [123]. Heterogeneity across studies may represent random variations and methodological differences. It should however be further explored, as it may also reflect differential involvement of genes in different subgroups of patients [122,124]. Whereas candidate gene studies are hypothesis driven, scanning of parts or the whole of the genome without predefined hypotheses may be useful to explore "new" associations of genes to a disorder. Linkage studies have identified several chromosomal regions associated with ADHD, some of which have been reported in multiple studies (5p13, 14q12, 17p11) [125]. The only chromosome region reaching genome-wide significance in a meta-analysis of all genome-wide linkage scans performed until 2008 (7 studies, 2084 individuals in total) was located on chromosome 16 (16q21) [125]. Interestingly, none of the more than 200 genes located within this region, had previously been considered as candidate genes for ADHD [125]. Six whole genome wide association studies (GWAS) have so far been published on ADHD (September 2010); five in children [126-130] and one in adults [131]. No single gene marker reached genome-wide significance in meta-analyses of these studies, and little overlap was found between the studies [123,132]. Again, none of the classical neurotransmitter candidate genes were on the list of the genes with strongest association to ADHD. The authors also compared a list of a priori defined candidate genes. Although none of them reached whole genome significance, there was a slight inflation of low p-values

among the candidate genes, which suggests that some of these genes may harbour a true association signal. The highest ranked gene in this meta-analysis of candidate genes (and the only gene overlapping between the GWAS) was the CDH13, which interestingly is located in chromosome 16, i.e. in the peak region from the meta-analysis of linkage studies of ADHD. The CDH13, which encodes a cell adhesion T-cadherin involved in cell motility and growth [133,134], has previously been associated to alcohol and drug abuse [135]. Thus, findings from GWAS have guided the attention towards new genes, some of which seem to be related to the development and function of the nervous system [132].

In view of the initial optimism, the rapidly evolving technology and the continuous efforts in genetic research on ADHD, the results in the search for a genetic underpinning of ADHD and other complex disorders have so far been disappointing. The polygenetic and multifactorial etiology, and the heterogeneous phenotype of ADHD (characteristics of complex trait disorders), is probably the main reason for the lack of identification of genes that confer a major risk. Common genetic risk variants (polymorphisms) may be difficult to identify because the effect of each gene variant is small (low penetrance) and may increase the risk for a disease only when interacting with other genetic or environmental factors. Importantly, if a strong association is found between a disease and single nucleotide polymorphisms (SNPs), the function of the gene may still be unknown. Rare gene variants (mutations) which each may be more strongly associated to the disorder (higher penetrance) are more difficult to study in association studies, because each variant is present only in a small number of individuals (Figure 2). However, if identified, they may be very useful in elucidating pathogenetic mechanisms of the disease since they may be linked more directly to the phenotype. Thus, whereas only weak associations were found between common variants of TPH1 or TPH2 in a recent large association study of adult ADHD [136], a study of functional, rare variants (missense mutations) within the same genes were found to be associated with ADHD (Paper IV). Likewise, Elia et al. studied rare copy number variants (CNV) in ADHD patients. They found that these variants were more likely to affect genes that have also been implicated in other neuropsychiatric disorders

(autism, schizophrenia, epilepsy). They thus concluded that rare CNVs could play an important role in impaired neurodevelopment, including ADHD [137].

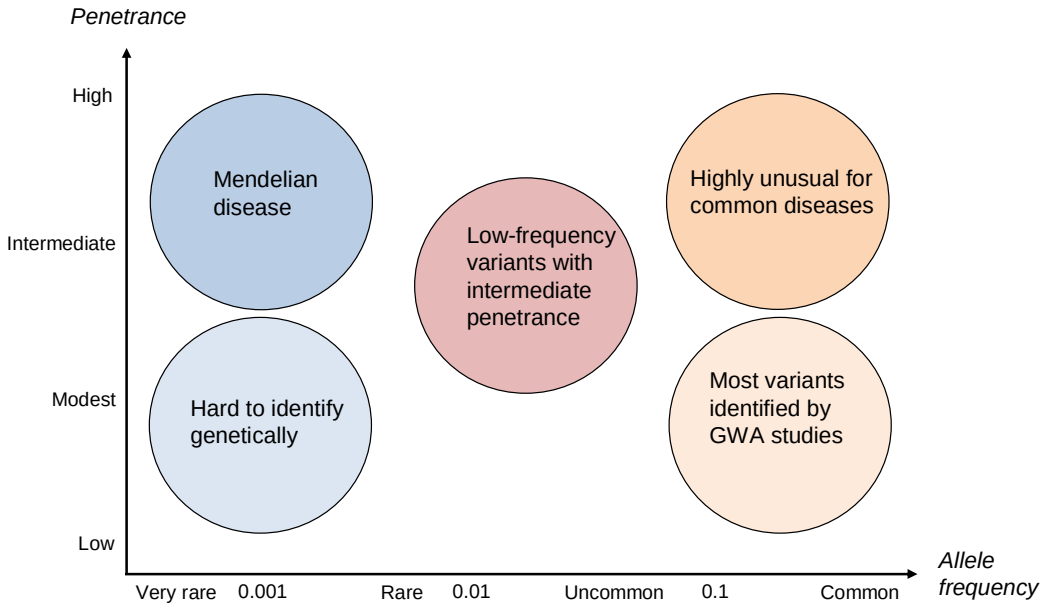


Figure 2: Disease susceptibility related to frequency of genetic risk variants. The genetic contribution in common (complex) diseases is typically based on the sum of several common gene variants acting together in increasing the vulnerability for the disorder. The effect of the individual gene is small, and is therefore difficult to detect in (genome wide) association studies. Figure adapted from McCarty et al., by permission from Macmillan Publishers Ltd: Nat Rev Genet, copyright 2008 [138].

Environmental risk factors

A heritability estimate of 75 % implies that at least 25 % of the etiology of ADHD is due to non-genetic (acquired, environmental) risk factors. Several environmental risk factors have been associated with ADHD, spanning from psychosocial stressors, to physical injuries or exposure to toxins to the brain [139,140]. Environmental risk factors may be 'shared' (by several individuals, siblings) or 'non-shared' (unique to the

individual). The ‘non-shared’ risk factors seem to be most important in the development of ADHD [141,142]. Environmental risk factors may further be classified as pre-, peri- or postnatal, depending on their period of influence relative to birth. Table 2 shows risk factors that have been associated with ADHD. Postnatal factors include brain trauma and infections (cf. post-encephalitic brain disorder, minimal brain damage), endocrine and metabolic disorders (thyroid dysfunction, phenylketonuria), toxins (PCB, lead), nutritional factors (deficiencies, additives, diet style) [143-147]. Psychosocial factors such as low social class, parental marital conflicts, maltreatment and emotional trauma during childhood, are also associated with ADHD, in particular when several such factors occur together [148,149]. Although they may increase symptoms and problems related to hyperactivity and inattention, further research is required before the role of acquired risk factors’ role in the etiology of ADHD can be established.

Pre- and perinatal environment

Pre- and perinatal factors are particularly attractive as “candidate” environmental risk factors for neurodevelopmental disorders because of their potential influence on the developing brain [150,151]. Several maternal life-style factors during pregnancy have been associated with ADHD in the offspring (Table 2), of which maternal smoking has been the most reported [152-155]. Growth retardation, preterm birth and low birth weight have also been widely studied and correlated to increased risk of ADHD and ADHD symptoms in later childhood [156-158] and adolescence [159,160]. Little is known, however, about these factors in relation to ADHD persisting to adulthood. Other interesting yet less studied factors are maternal somatic disease and metabolic or endocrine dysfunction, such as epilepsy (Paper III), thyroid dysfunction [161], phenylketonuria [162] and serotonin deficiency (Paper IV).

Table 2. Environmental risk factors that have been associated with ADHD

Prenatal risk factors	Alcohol in pregnancy
	Smoking in pregnancy
	Drug use in pregnancy
	Medication (thyroid medication)
	Maternal somatic conditions (epilepsy, thyroid disorder, phenylketonuria, obesity)
	Maternal stress during pregnancy
	Lead exposure
	Growth retardation
	Bleeding in pregnancy
	Protracted/complicated delivery
Perinatal risk factors	Low birth weight
	Preterm birth
	Low Apgar score
Postnatal risk factors	Cerebral trauma
	Infections (encephalitis, meningitis, otitis media)
	Nutritional factors (nutritional deficiencies, food additives, food sensitivities)
	Psychosocial adversities

Genes and environment

Since the impact of individual genetic and environmental risk factors in ADHD is only small or moderate in size, their contribution is likely through an additive and /or interacting effect in a multifactorial etiological model. This may be gene-gene, environment-environment, or gene-environment interactions, and the effect of one factor may be either mediated, or moderated, by the presence of the other factor. In the case of ADHD, gene-environment interactions have been found between; low birth weight (LBW) and the catechol-O-methyl-transferase gene (COMT) in predicting anti-social behaviour in children with ADHD [163]; maternal smoking in pregnancy and polymorphisms in dopaminergic genes (DAT, DRD4) [164] and the nicotinic receptor gene (CHRNA4) related to the combined subtype of ADHD, respectively [165]. Interaction between serotonergic gene variants (SERT, TPH2) and burden of life events seem to predict the presence of co-occurring personality traits and personality disorders in adult ADHD patients [72], and both dopamine and serotonin transporter genotypes may modify effects of maternal expressed emotions on emotional and conduct problems in children with ADHD [166]. These studies illustrate the possible benefits of studying limited phenotypic aspects of a complex disorder like ADHD, which may have different risk factor profiles. However, the exploratory nature of these studies calls for replications before conclusions can be made. Further functional and experimental studies are required before these risk factors can be considered true pathogenic factors [167].

Persistence of ADHD

Risk factors causing a disease are not necessarily the same as the risk or protective factors influencing the course of the disease over time [168]. Clinical studies have shown that the severity of ADHD (symptom severity, functional impairment) and the presence of psychiatric comorbidity and childhood adversities (including parental psychopathology) are associated with persistence of ADHD to adulthood[169-171]. Little

is known, however, about specific risk factors. Although it has been suggested that ADHD persisting to adulthood may be more heritable than ADHD that remits during adolescence [172], recent twin studies of adults have reported lower heritability rates than those found in child studies [173-175] (Larsson et al., unpublished data from Swedish sample of 15.000 twin pairs). Furthermore, recent large-scaled association studies of adults with ADHD have not been able to replicate the most established genetic findings from previous research in childhood ADHD relating to dopaminergic genes [132,176]. A study of serotonergic candidate genes in a combined sample of children and adults with ADHD revealed that some genes were associated only to adult ADHD (MAOB), others with the combined subtype of ADHD in both adults and children (5HT2A), and others again to adults and children with ADHD in general (DDC) [177]. It is not clear, however, whether these findings reflect differential effects of genes across the life span, methodological differences between studies, or differences in assessment of the ADHD phenotype in children and adults (self-report versus informant reports) [178].

Environmental risk factors have been less studied in adults with ADHD. Methodological challenges in the assessment of risk factors in adults include the fact that the number and hence the complexity of potential and interfering exposures will accumulate over time, and the problem of recall bias. Further research exploring potential differences between risk profiles of ADHD remitting in childhood versus ADHD persisting to adulthood would however be of interest.

The present study

The present study is part of the multi-disciplinary study "ADHD in adults in Norway; from clinical characterization to molecular mechanisms" initiated at the University of Bergen in 2004. The main motivation for conducting this study was a strong need for more knowledge about ADHD in adulthood, which appeared as a "new" diagnosis encountered in adult psychiatry at the time of the initiation of the study. The heterogeneity in the clinical presentation of adults with ADHD motivated both the primary clinical descriptions and the search for possible risk factors. The general aim of this study was to increase the understanding of this apparently prevalent, but often overlooked disorder.

Aims

I. Characterization of clinically diagnosed ADHD patients:
   - To describe occupational functioning among adults with ADHD, and to examine the effects of symptom profile and treatment on their functioning (Paper I)
   - To investigate the comorbidity and relationship between bipolar disorder (BD) and ADHD (Paper II)

II. Investigation of pre- and perinatal risk factors in adult ADHD:
   - To determine the association between complications in pregnancy and delivery and ADHD persisting to adulthood (Paper III)
   - To investigate the possible role of reduced serotonin production on ADHD related symptoms and behaviour (Paper IV)

Materials and methods

The present study is based on a cross-sectional case-control design of a nation wide sample of adults with ADHD and a population-based control sample. Paper IV additionally includes family members of ADHD patients, and Paper III uses a registry based nested case-control design.

Patients

We aimed at gathering a naturalistic patient sample as encountered in general clinical practice. Two main sources of patient recruitment were used; the registry of the former diagnostic committees (Expert Committees of Hyperkinetic Disorder) and clinicians (mainly psychiatrists) nationwide.

The Expert Committees of Hyperkinetic disorder /ADHD

The prescription of central stimulants (CS) for adults was legally restricted in Norway until 1997. From October 1997 to May 2005, adults (≥18 years) with ADHD/ Hyperkinetic disorder were allowed to receive CS only after a systematic and mandatory diagnostic evaluation by one of three regional diagnostic committees; i.e. the Expert Committees for Hyperkinetic Disorder/ ADHD [179]. Patients were referred to the committees by their psychiatrists, general practitioners or hospital doctors. Each of the diagnostic committees consisted of three to five clinicians (mainly psychiatrists and neuropsychologists), with special experience on diagnosing ADHD in children and adults. A few pioneering clinicians also diagnosed and treated adult patients with ADHD in addition to the committees (on special permissions).

Diagnostic assessment

The referral procedure to the expert committees required both thorough descriptions of the patient's current symptoms and functioning and informant information about childhood behaviour and functioning. Results from physical and psychiatric

examinations were also required. The expert committees then reviewed the patient's records to confirm, or disprove, the diagnosis of ADHD. A formal conclusion was made recommending or not recommending treatment with central stimulants, based on a confirmed diagnosis and the absence of contra-indications for such treatment (mainly psychosis or ongoing substance abuse). The diagnostic assessment was done according to the ICD-10 research criteria for Hyperkinetic Disorder, with two modifications; allowing the inattentive subtype as sufficient for the diagnosis and allowing the presence of comorbid psychiatric disorders as long as the criteria for ADHD were fulfilled and present before the appearance of the comorbid disorder. This diagnostic assessment strategy was chosen as a compromise between the fact that ICD-10 was the official diagnostic system used in Norway, and the need to have an assessment comparable with the international DSM-IV standards (O.B. Fasmer, personal communication).

The data from the Expert Committees of Hyperkinetic Disorder /ADHD were not primarily designed as a patient registry, but due to the compulsory referral system for adults considered for medical treatment for ADHD, it still constitutes a national cohort of adult ADHD patients. During almost eight years, the committees handled more than 5000 patient referrals, and nearly 70 % were recommended for treatment (n = 3397).

In May 2005, National Guidelines for Diagnosing Lifespan ADHD were implemented by the Norwegian Health Authorities. Since then the diagnosis and treatment of adult ADHD was handled by individual specialists in psychiatry and psychology without the direct involvement of the former expert committees.

Recruitment to the present study

Based on the address lists from the Expert Committees of ADHD/Hyperkinetic disorder, patients all across Norway were invited directly by posted mail to join the project. A total of 1700 invitations were sent to patients (mainly to those diagnosed after the year of 2000) from 2005 to 2007. By December 2007, 338 (19.9 %) of the invited patients had returned completed questionnaires and were included in the study. Clinicians (general practitioners, psychiatrists and psychologists) from all over the

country were also invited to recruit patients with a verified diagnosis of adult ADHD (mainly from out-patient clinics in the period from June 2004-September 2006).

The inclusion criteria for patients were:

1) A diagnosis of ADHD or Hyperkinetic Disorder received in adulthood confirmed by a clinician outside the project according to DSM-IV or ICD-10 criteria.

2) Age ≥ 18 years at the time of inclusion.

There were no formal exclusion criteria.

Patient recruitment to the project started in 2004 and is still going on at present time. The first 420 recruited patients were included in Paper I, the first 510 in Paper II, and the first 459 patients in Paper IV. The patient sample in the epidemiologic study in Paper III includes all patients from the registry of the Expert Committees who were found eligible for treatment with central stimulants and who were born between 1967 and 1987 (n = 2323). (Figure 3)

Controls

The control persons used in this study are individuals randomly recruited from the general population in Norway having the same age range as the patients (Paper I, II, IV), and a whole population cohort in Paper III.

The Medical Birth Registry of Norway (MBRN)

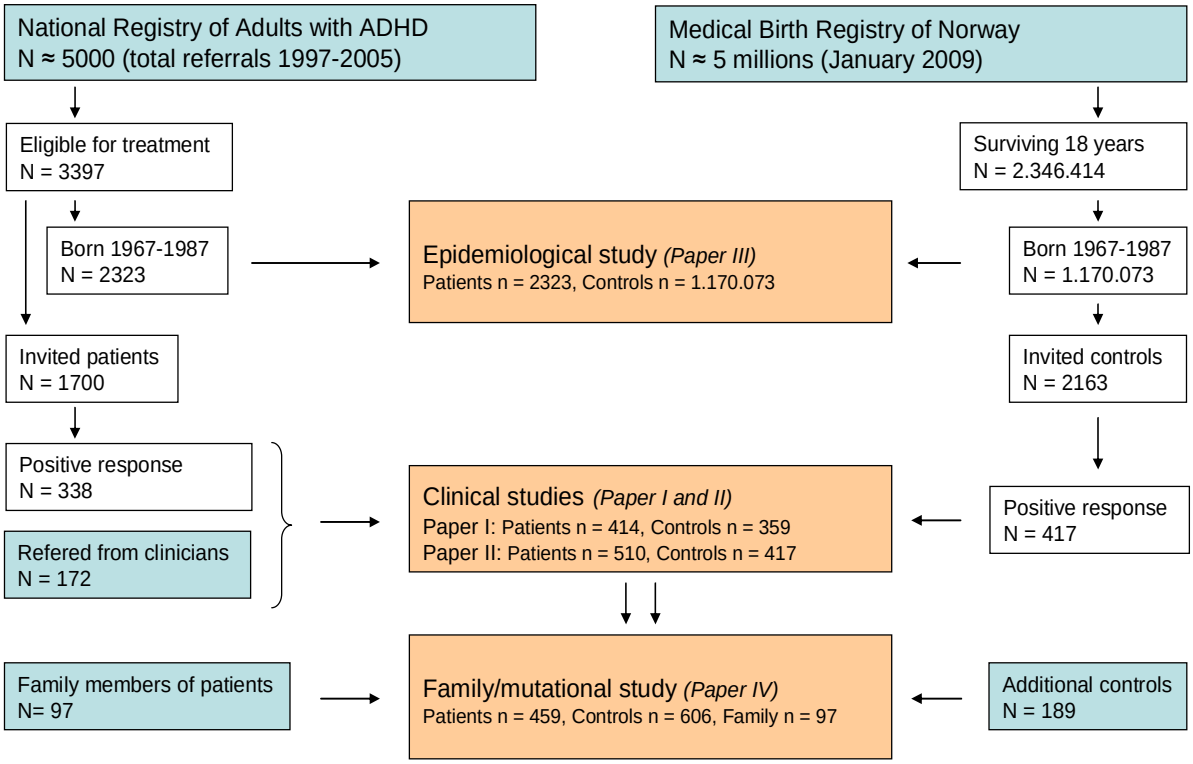
The MBRN is based on compulsory notification of all births in Norway from 1967. During January and March 2007, 2163 invitation letters were sent out to a randomly selected sample of the Norwegian population between 18 and 40 years old, using the MBRN as the basis. By December 2007, 417 of these (19.3 %) had responded with completed questionnaires and were included in the study. The control sample in the present study consisted of the first 359 recruited controls by this procedure in Paper I, and the first 417 in Paper II. In Paper IV, the sample of 606 controls additionally

included 189 controls recruited from other sources (friends of patients, n = 44, students n = 139, and 6 'other'). In Paper III, the control group consisted of the whole population born in Norway between 1967 and 1987, registered in the MBRN, and who had reached 18 years of age (n =1 170 073) (Figure 3).

Family members

Family members of patients were invited via patients (probands) to participate in the family study of the main project. The families included in Paper IV were families of probands with TPH 1 mutations, and in which at least three family members agreed to participate. Seven families with a total of 86 members were included.

Figure 3. Flow chart of included subjects in Papers I-IV



Questionnaires

All participants included in Paper I, II and IV filled in questionnaires for past and current ADHD symptoms, symptoms of bipolar disorder (BD), and questions about lifetime co-existent disorders and problems, as well as sociodemographic data including educational and occupational activity. A sample of blood or saliva was collected for further genetic analyses. No information was obtained directly from the patients or controls in the registry based study in Paper III.
The following self-report questionnaires were used in this study (Papers I, II, IV):

The Wender Utah Rating Scale (WURS): The WURS is designed to retrospectively assess symptoms and signs of ADHD in childhood. The version of the scale used in this study contains 25 items and has been validated by several investigators in different countries and populations. Each of the 25 questions is rated on a 5-point severity scale (0 = not at all/very slightly, 4 = very much).

The Adult ADHD Self Report Scale (ASRS): The ASRS is the World Health Organization's (WHO) rating scale for adult ADHD designed to measure current ADHD symptoms. It consists of 18 items based on DSM-IV symptoms/criteria for ADHD that are measured on a 5-point scale (0 = never/seldom and 4 = very often). The items 1-9 cover the symptoms of inattention; item 10-18 the symptoms of hyperactivity and impulsivity.

The Mood Disorder Questionnaire (MDQ): The MDQ is a screening instrument for bipolar spectrum disorders, BSD (i.e. BD I, BD II, BD not otherwise specified (BD NOS), and cyclothymia) for use in the general population and in psychiatric patient populations. The MDQ has been validated in both population-based and clinical samples [180,181]. The MDQ consists of 15 items; the first 13 questions are about lifetime symptoms of mania or hypomania, and the last two about co-occurrence of symptoms and ranking of functional impairment caused by the symptoms. Question 1-14 is answered by 'yes' or 'no', question 15 by a 4-point severity scale. A positive MDQ

score is defined as 7 or more ‘yes’ on the first 13 items, ‘yes’ on question 14 (co-occurrence of symptoms) and level ‘3 or more’ on question 15 (moderate to severe impairment).

The WURS, ASRS and MDQ have not yet been officially validated in Norway, but translated versions exist and are being used both in clinical practice and research [182]. The ASRS version used in this study is the same that was used by the Expert Committees of Hyperkinetic Disorder/ADHD. It was originally translated and re-translated (by an English-native employee of the Norwegian Department of Health and Social Welfare) and has later been evaluated by 4 experienced psychiatrists from our project group. The MDQ has been translated by a Norwegian psychiatrist (P. Bergsholm) and retranslated by an English-native psychologist, and is currently being used in clinical practice in Norway. The Norwegian WURS version has been used in earlier publications [182].

In addition, the patients answered 31 questions concerning sociodemographic factors including educational and occupational level, past and present medical treatment and lifetime history of comorbid disorders. They were also asked about the presence of ADHD and comorbid disorders in first degree family members. All patients were asked to give a form to their doctor (mainly psychiatrists) with questions regarding diagnosis and medical treatment. These questionnaires were specifically designed for this project (See Appendix for the Norwegian versions of the questionnaires).

Clinical interview

To assess the self-reported comorbidity on the questionnaire, a randomly selected subsample of patients living in the Bergen area (n=50, Paper II) was invited to a clinical interview. The interview took place at the out-patient section at the Department of Biological and Medical Psychology at the University of Bergen. The interview was based on the semi-structured module based Mini International

Neuropsychiatric Interview, the Plus version (M.I.N.I.-Plus) [183]. The M.I.N.I.-Plus assesses general psychopathology in adults by covering main axis 1-diagnoses according to both DSM-IV and ICD-10. Patients and controls were interviewed in a random sequence as part of the main project with the interviewers being blinded to the subjects' diagnostic status and self-report results. Two experienced psychiatrists performed the interviews (AH and MD, Paper II). After an initial phase of observing each other's interview directly behind mirroring windows, video-recordings of the interviews were performed when feasible. However, complete inter-rating measures were not available at the time of submission of this thesis.

Mutation analyses

As part of the main project, a blood or saliva sample was obtained from all participants (in Papers I, II and IV) after informed consent. DNA from saliva was extracted using the Oragene TM DNA Self-Collection Kit, and by standard methods from blood. Sequencing of the all exons and intron-exon regions of TPH1 (and TPH2) was performed for 457 (459) patients and 187 (179) controls to identify mutations (Paper IV). Further genotyping targeting the found mutations was performed for 86 (97) family members of ADHD patients. Protein expression in E. Coli and Human Embryonic Kidney (HEK) cells, and analyses of TPH1 mutants, were then performed to determine the impact of mutation on protein function.

Statistical analyses

Data were initially analysed to describe and compare frequencies and prevalence of different variables, using contingency tables (Chi-square tests, Fisher's Exact tests) for categorical variables and independent sample tests (Student T-tests) for non-categorical variables. Regression analyses (logistic and linear) were then performed to explore possible effects of different variables on defined outcome measures. A two-

tailed significance level of .05 was chosen for statistical significance. Odds ratios (OR) and relative risks (RR) were expressed with their corresponding 95 % confidence intervals (CI).

The statistical analyses were mainly performed using SPSS (Statistical Package for the Social Sciences, SPSS Inc, Chicago, IL, USA) version 14.01 (Paper I), version 15.01 (Papers II and IV) and PASW (Predictive Analytics Software, former SPSS) version 18.0 (Paper III). In addition, STATA (STATA Intercooled release 9 (Stata Statistical Software: Release 9, 2005, College Statin, TX: StataCorp LP)) was used for RR analyses in Paper III.

Ethics

An informed consent based on detailed written information about the project was obtained from all the participants included in Papers I, II and IV. All participants received NOK 250, - (~40$) upon return of questionnaires and spit or blood samples, and an additional NOK 500, - (~80$) if interviewed. Participants were not informed about results of individual genetic analyses. In the epidemiological study in Paper III included patients had provided a written, general consent that data from their records could be used in later research projects. Because the data in Paper III were treated anonymously, no further consent was required. The study was approved by the Regional Research Ethical Committee of Western Norway (IRB # 3 (FWA 00009490, IRB00001872), the Norwegian Directorate of Health and Social Services and the Norwegian Data Inspectorate.

Results

Paper I

Paper I is a clinical case-control study assessing occupational outcome among adults with ADHD. Clinically diagnosed ADHD patients (n = 414) and a population-based control group (n = 359) responded to questionnaires rating past and present symptoms of ADHD, comorbid conditions, treatment history and work status. Twenty-four percent of the patients reported being in work, compared to 79 % of the controls. Logistic regression analyses were performed to assess predictors of being out of work among the adult ADHD patients. We found that the combined subtype of ADHD, substance abuse, and a reported history of depression/anxiety were correlated to being out of work. Medical treatment, current or past, was positively correlated to being in work. Being diagnosed and treated with central stimulants during childhood was the strongest predictor for being in work as an adult (OR 3.2, p = 0.014), independently of psychiatric comorbidity, substance abuse and current treatment.

Paper II

Paper II is a clinical case-control study investigating the relationship between ADHD and Bipolar spectrum disorders (BSD). Clinically diagnosed ADHD patients (n = 510) and a population-based control group (n = 417) responded to questionnaires rating symptoms of ADHD, psychiatric comorbidity, sociodemographic data, and a screening questionnaire for BSD, the Mood Disorder Questionnaire (MDQ). A subsample of the patients was interviewed with a semi-structured interview (M.I.N.I Plus) to assess correlations between self-reported and interview based psychiatric diagnoses. We found that 50.6 % of the ADHD patients screened positive for BSD based on the questionnaire (MDQ), compared to 8.3 % of the controls. In comparison, the prevalence of BSD according to the DSM-IV based interview was 32 %. In the total study sample (n = 927), an ADHD diagnosis was the strongest predictor for screening

positive on the MDQ (OR = 5.0, p<0.001), but the correlation between dimensional symptom levels of ADHD and of BSD was strongest in the control group. Patients screening positive for a BSD had significantly more drug problems, higher ADHD symptom scores and lower educational and occupational levels. The findings illustrate the close relationship between some symptoms of BSD and ADHD in adults.

Paper III

Paper III is an epidemiological, population-based study of pre- and perinatal risk factors in ADHD. It is the largest study on pregnancy- and birth complications in ADHD ever performed, and the only on adults with ADHD so far. A patient cohort consisting of all adult ADHD patients approved for treatment with central stimulants in Norway between 1997 and 2005 and who were born after 1966 (2323 patients) was compared with the remaining of the Norwegian adult population born in the same time period, 1967-1987 (1.17 million controls) by data linkage with the Medical Birth Registry of Norway (MBRN). The associations between pregnancy- and birth complications and adult ADHD were calculated and adjusted for potential confounders. We found that preterm and extremely preterm births (<37 and <28 weeks of gestation) were associated with 1.3- and 5.0-fold increased risks of developing persistent ADHD, respectively. Similarly, birth weights <2500 g and <1500 g were associated with 1.5- and 2.1-fold increased risks, and 5 minutes Apgar scores<4 and <7 with 2.8-and 1.5-fold increased risks of persistent ADHD. We also found an association between maternal epilepsy (RR=1.7) and offspring oral cleft (RR=2.8) and ADHD in the adult offspring.

Paper IV

Paper IV is a translational study investigating the long-term effects of an impaired serotonin synthesis on the developing human brain. We studied the effects of missense

and nonsense mutations affecting tryptophan hydroxylase (TPH) enzymes responsible for serotonin production in maternal reproductive tissues (TPH1) and the brain (TPH2), respectively. Sequencing of the entire TPH1 and TPH2 genes in 646 Norwegian adults (ADHD patients, their relatives and control persons) identified 7 different TPH1 coding variants in a total of 38 persons. Functional studies showed that 6 of the variants had significantly decreased enzyme activity or stability in vitro compared to wild type TPH1. Subsequent family based analysis revealed that individuals born to mothers with TPH1 mutations reported 1.5- 2.5 times higher ADHD scores and related symptoms during childhood and as adults than controls ($p< 10^{-6}$), or individuals with fathers with the corresponding TPH1 mutations ($p<0.001$). This effect was independent of the children's own TPH genotypes, indicating that maternal serotonin production has profound long-term behavioural effects on their offspring. The study illustrates a novel approach of investigation of the consequences of genetic polymorphisms in psychiatry.

Discussion

Methodological considerations

The patient and control samples

A main strength of the present study is the large sample size of ADHD patients and controls and the fact that they were recruited from all parts of the country. In the epidemiological study (Paper III) we had access to a national cohort of adult ADHD patients; all adult patients found eligible for CS treatment for ADHD, and born after 1966, were included. This patient sample is, as far as we know, unique in its kind. Likewise, the control sample in this study is a national cohort consisting of the rest of the population born in the same time period. As the MBRN was established as early as in 1967 and covers the whole population with compulsory notification, it currently (2010) includes birth data on close to the entire adult population from 18 to 43 years. This allowed us to link our patient sample to the targeted age group.
Many different clinicians, who were not connected to the project, diagnosed the patients. The possible heterogeneity of the diagnostic assessment was compensated by the evaluation by one of the three Expert Committees. The studied patients thus represent a population-based naturalistic clinical setting, which is important for the external validity of the results. In other case-control studies of adult ADHD, patients are often diagnosed and recruited from one or a few specialized centres. Also, more strict inclusion criteria are often used, for example excluding patients with comorbid psychiatric disorders or substance abuse. These patient samples may be more homogeneous and have higher internal validity (diagnostic reliability), but the study results may be less generalizable to other clinical settings, which typically are very heterogeneous when adult ADHD is concerned.

However, the low awareness of adult ADHD and the relatively stringent referral system for treatment at the time, have probably excluded some affected individuals from being diagnosed, and hence displaced the relative distribution between cases and

controls in our population sample. This is confirmed by the low prevalence estimates of adult ADHD (< 0.2 %) in our sample compared to other population-based prevalence estimates. Caution is therefore still required before generalizing the results from Paper III to samples including self-referred adults with milder symptoms not requiring medical treatment for their ADHD.

In the clinical studies (Papers I, II, IV), our aim of gathering a naturalistic nation-wide sample of patients was limited by the relative low response rate among patients invited to the study. This may have biased our sample. Because we did not have information available to directly compare responding and non-responding patients, we do not know the direction or magnitude of this possible bias. Compared to the statistics from the national cohort of ADHD patients from the Expert Committee Registry ([184], Michael Lensing, personal communication), the patients willing to participate in our study were older (62 % versus 42 % over 30 years) and more often women (48 % versus 29 %). The nature of the disorder itself (poor sustained attention, disorganization and procrastination) may have affected the response rate of patients by reducing their ability to fill in and return the questionnaires. The most severely affected and dysfunctional patients could therefore be overrepresented in the non-responders group. In that case the effects related to the ADHD patients in this study would be underestimated. It may also be that patients with fewer symptoms and problems were less motivated to participate in the study than patients with more symptoms, in which case the effects would be overestimated. It remains difficult to compare this to other clinical studies, since response rates are often lacking in sample descriptions. Interestingly, the response rate among the controls in our study was very similar to that of the patients. The low response rate of the invited controls may be due to characteristics of our project. People could be less interested in ADHD compared to other disorders, such as cancer or cardiovascular disease, which may affect them later in life. Furthermore, people may have higher thresholds for participating in studies where DNA is required.

Reported measures

Self-report questionnaires

The clinical information on symptom profiles and comorbidity (Papers I, II, IV) was mainly based on self-report questionnaires. We did not have information about the time of diagnosis for each patient. We could therefore not assess how the time of diagnosis may have influenced the symptom severity reported at the time of inclusion into the study (information bias), or the interest in participating (selection bias). Most of the patients in our sample had been treated with CS, and most of them with good response. However, data on the course of treatment were too crude to allow for analyses on how the treatment affected ADHD symptoms. This may have biased our data towards lower current symptom scores (ASRS) among patients, and may thus explain the relatively large proportions of patients in our study with sub-threshold scores on the ASRS at inclusion. Furthermore, the retrospective nature of some of the questions entails the problem of recall bias. Inaccurate recall could result in lower or more negative scores, whereas biased recall due to attribution (e.g. increased relative awareness of ADHD-related symptoms in childhood after having been diagnosed with ADHD in adulthood) could yield higher or more positive scores among patients relative to controls. Data on childhood treatment was also based on self-report in this study (Paper I), but we expect that this information would be less influenced by recall bias. However, the finding that treatment in childhood is positively correlated to being in work as an adult should ideally be verified in long-term, prospective, controlled studies. Methodological challenges- both ethical and practical- complicate the feasibility of such studies. Therefore, more open-labelled, observational studies are needed to explore this important finding and other predictors for long-term outcome of treatment of childhood mental disorders [185].

The questionnaires have not influenced the diagnostic status of patients, since the diagnosis of ADHD/Hyperkinetic disorder was required before inclusion and confirmed on a separate form by the patient's doctor. Other lifetime diagnosed disorders were, however, reported by the participants themselves, by responding 'yes'

or ‘no’ to questions like: “Do you have, or have you ever had, bipolar disorder?“. The gold standard for diagnostic assessment of psychiatric disorders is the clinical interview performed by an experienced clinician, and psychiatric disorders should never be diagnosed exclusively by self-report questionnaires. Assessment by interview is, however, still influenced by the personal judgement of the clinician in the decision of whether symptoms and impairment criteria are fulfilled [186]. Self-reported disorders and problems may be valuable in reflecting the patients’ problems as they would be encountered in a clinical setting. The prevalence of self-reported comorbid psychiatric disorders and problems in the present study were comparable (often higher), to other clinical samples of adults with ADHD [36,44,61,187]. The trend towards higher prevalence rates found in our study may be due the less stringent nature of self-reported diagnoses, or it may be due to a selection bias of our patients towards a more severely affected and /or less homogeneously defined sample. The self-report findings were however satisfactorily correlated to standard blinded diagnostic assessment in the interviewed subsample of patients (Paper II).

Registry based measures

In the epidemiological study (Paper III), data were extracted from population-based registries, with the Medical Birth Registry of Norway as the main source. Based on compulsory notification, this registry has collected information on all births, live and still, from 16 weeks’ gestation since 1967. A standardized notification form collects data on demographic variables, maternal health before and during pregnancy, complications during pregnancy and delivery, and pregnancy outcomes which include vital status of the newborn and congenital anomalies (See Appendix). The midwife and/or the physician attending the birth are responsible for completing the notification form.

In Norway, all live births are also notified to the Directorate of taxes in a parallel civil system for registration of births. The national identification number of the newborn is generated and a new record is established in the Central Population Registry. All

records of the MBRN are routinely matched to those of the Central Population Registry, with mutual updating of files. Births in the Central Population Registry that are not notified to the MBRN are actively sought from delivery units, ensuring complete medical notification of all live born infants in the country. Selection bias of controls is therefore not a likely problem in this study (Paper III).

The quality of the different variables of interest in this study varied. Birth weight is known to have good quality with little missing data (0.2 % in the inclusion period of the present study, K.K. Melve, personal communication). Gestational age was based on the mother's reported last menstrual period, and is known to be less accurate. Ultrasound based gestational age is not reported in the MBRN before 1998. Due to the uncertainty of menstrual dates, we validated gestational age by calculating birth weight Z-scores for each gestational week [188]. Births with Z-scores greater than 4.0 were excluded when analysing gestational age due to the misclassification. In the time period of this study, 5.3% of the births in the MBRN had missing values for gestational age, and 0.4% was misclassified.

Information about Apgar scores has not yet been formally validated in the MBRN. They are available only from 1978, and could therefore not be studied for the whole sample. Most of our patients were, however, born in the latest part of the studied time-period, and, hence included in the analyses on Apgar scores. Preliminary validation data on maternal epilepsy has so far shown satisfactory results (personal communication, I. Borthen). Whereas certain anomalies, such as heart defects, were underreported in the first time period of the MBRN, oral clefts have shown satisfactory ascertainment during the entire Registry period [189].

Differential information bias between cases and controls may have occurred for those variables that are self-reported. For example, reports of menstrual dates by mothers of ADHD patients were generally more uncertain than for other mothers. Although it was not possible to verify the presence and direction of these potential information biases, we believe that, in general, they have most likely lead to underestimation of effects.

Association does not necessarily imply causality. Unmeasured and unknown factors may be associated to both the exposure and outcome variables in a way that would alter the found association if they were accounted for in the analyses. The roles of confounders relevant for the present study are mentioned in the Discussion of the main findings.

Translational research - the value of combining different methodological approaches

Large scale epidemiological studies are invaluable in providing evidence for associations and generating new hypotheses about risk factors for diseases. Other approaches like experimental animal studies, or functional molecular studies will often be necessary to elucidate pathogenetic mechanisms and the exact relation between putative risk factors and disease. However, as research methodologies evolve and become more specialized, it becomes increasingly challenging to communicate across disciplines. An overriding aim of the main project "ADHD in adults: from clinical characterization to molecular mechanism" was to apply a multi-disciplinary approach, i.e. combining people and their competences from different research areas, in the common focus of investigating clinical and pathophysiological aspects of adult ADHD.

Despite massive efforts and rapid advances in technologies, the search for susceptibility genes for ADHD- and most other complex trait disorders- has so far not succeeded in explaining the bulk of observed heritability of the disorder (see Introduction). This "missing heritability", and new approaches to uncover the underlying genetic architecture of complex diseases, is presently being hotly debated [190]. Nearly all published molecular genetic association studies on mental disorders are based on studies of common genetic markers, most of them with no apparent functional role; i.e. they rely on indirect associations between test markers and an unknown disease variant in its chromosomal vicinity. It has recently been proposed

that the accumulated effects of many different rare variants may confer a stronger risk to common, complex trait disorders [191,192]. These rare variants may be difficult to detect, but when detected, they may be more informative in establishing a plausible causal association between genetic variants and impaired function related to the disorder. Furthermore, most genetic studies of psychiatric disorders focus on a single diagnosis or a limited number of symptoms, although it becomes increasingly recognized that susceptibility genes may have more general effects on brain function and be involved in different clinical syndromes. Finally, and importantly, the typical mode of inheritance investigated in genetic studies, i.e. how DNA variants segregate with phenotypes, may not be the only model accounting for disease susceptibility, but other models of disease susceptibility and transmission are generally not accounted for in genetic studies.

Our study on the effects of maternal serotonin biosynthetic capacity and offspring behaviour (Paper IV) is unusual in many aspects, and illustrates an alternative approach to identify susceptibility genes, and pathomechanisms. Here we attempted to detect and functionally characterize all gene variants, which could have a direct effect on the protein level (i.e. of TPH). We thus studied many different mutations within the gene, with individual allele frequencies of approximately 0.1 %, most of which had an impact on the enzyme function using in vitro assays. In the phenotype approach, we collected information on various symptoms and problems, including dimensional measures on both ADHD and mood disorders. This allowed us to detect possible effects on brain development that were not limited to specific diagnostic entities. Finally, the main model examined in Paper IV was the transmission of a trait based on maternal genotype irrespective of the individual's (offspring's) own genotype. Although transgenerational effects on behaviour have been robustly demonstrated in animal models, molecular studies in human mental disorders have been sparse. Parent-of-origin effects have, however, recently been highlighted as interesting approaches to pursue in order to reveal the genetic architecture of complex disorders [193].

Together, the integration of clinical, genetic and molecular approaches in Paper IV, allowed us to formulate specific pathophysiological hypotheses that have hardly been

addressed in previous studies. However, considering its moderate sample size and still limited availability of clinical data, the study also illustrates some of the challenges of human behavioural genetics.

The different methods and sample selections used across the papers in this thesis also give an advantage in elucidating the posed research questions. For example, in the investigation of pre- and perinatal risk factors' role in ADHD, Paper III provides evidence of an association between disturbed foetal development and ADHD. The data does, however, not allow causal conclusions to be made about pathogenetic mechanisms [194]. Paper IV indicates that one such mechanism could be mediated by impaired serotonin production in the early intrauterine environment [195]. In the investigation of the relation between ADHD and other psychiatric symptoms and problems, the results in Paper II showed that the majority of our adult ADHD patients had co-existent affective symptoms and that the combination of ADHD symptoms and a high load of affective symptoms increased the risk of reported drug problems and other impairment (Paper I). In Paper IV, we found that reduced serotonin production in embryonic development may be a causal factor for this phenotype, since symptoms of ADHD, bipolar disorder and impulsive drug related behaviour were all increased in offspring to mothers with TPH1 mutations. Together, and by different means, these studies thus contribute to more coherent knowledge about a clinically important group of adult ADHD patients.

Discussion of the main findings

Functional impairment in adult ADHD

The ongoing debate about ADHD either being a distinct disorder or just a normal variant of human behaviour is partly due to the non-specificity of symptoms of ADHD, in which most people will recognize themselves from time to time. The threshold for getting a diagnosis of ADHD is, however, dependent on the chronicity of

symptoms over time and the impairment caused by these symptoms in several important aspects of life, such as school, work, interpersonal relations etc. We found that only 24 % of the adults with ADHD in our study (mean age 34 years) were employed at the time of inclusion in the study. About half of the patients were receiving a disability pension or were under rehabilitation. Although ADHD is known to be associated with lower socio-economic status and educational level than controls, the proportion being out of work was surprisingly high compared to results from other (few) existing studies on the topic [16]. In their follow-up study of hyperactive boys (average 7 years), Manuzza et al. found that as much as 90 % of the 85 probands were gainfully employed as adults (average 24 years) [196]. In a large cross-sectional study of clinically referred adults, 73 % of adults diagnosed with ADHD were currently employed, not differing statistically from control samples [16]. There may be several reasons for this. First, as discussed earlier, the patients in our study may represent a more severely affected group compared to other samples of adults with ADHD. Indeed, the patients recruited to the present study, i.e. representing the period of the mandatory referral to the expert committees, were, as a group, less often in work than patients recruited later (after 2007), both in our material (24 % versus 41%), and as confirmed by other studies [61]. Second, national differences in societal structure may account for some of the difference. The welfare system in Norway is quite developed and may provide for people who in other countries would be engaged in some kind of work although struggling, underachieving or not functioning properly, for example frequently changing jobs.

The combined subtype of ADHD was associated with lower occupational outcome in our study. This group also had higher frequencies of reported alcohol and drug problems, comorbid affective disorders and treatment for other psychiatric disorders. This finding is consistent with other studies reporting that the combined subtype is associated with the poorest outcome among adults with ADHD [197,198].

The finding that treatment, particularly treatment in childhood, was strongly associated with an increased probability of being in work in adulthood (Paper I) is an important finding that has not been clearly shown before. Follow-up studies of children with ADHD have rather found that treatment was associated with a more negative outcome,

although this was probably due to the confounding effect of increased symptom severity in children who received treatment [169]. It has, however, been shown that treatment with CS may be protective against later substance abuse [47], which is in line with our findings. Although educational and occupational levels were highly correlated in our study, treatment in childhood did not seem to significantly affect the educational level attained. Symptom severity in childhood was the main risk factor of having the lowest level of education. This may be because adults with ADHD who were not recognized in childhood have been able to compensate their lower functioning until the demands of self-organizing are increased, or the external supporting structure decreased, as discussed earlier.

ADHD and bipolar disorder- comorbidity or shared phenotypes?

Comorbidity simply refers to the presence of two or more disorders occurring together. In somatic medicine, comorbidity usually refers to two or more distinct diseases (i.e. clinical entities with a known etiology or pathogenesis) being present together at the same time [199]. In psychiatry, where the term disorder is used (i.e. clinical entities without a known etiology or pathogenesis), the nature of this co-occurrence may, however, range from independent disorders occurring together by chance, to co-occurrence of disorders sharing some common or correlated underlying etiology, or it may simply represent an artefact of overlapping phenotypes [200,201]. Disorders succeeding each other in time, i.e. lifetime comorbidity, may include situations in which the presence of one disorder is a risk factor for the other, or the two disorders may represent different developmental expressions of a common underlying vulnerability [202].

The relationship between ADHD and bipolar disorder is not fully understood. One reason why this relation is difficult to investigate is the lack of a uniform understanding of the two disorders' phenotypes in a developmental perspective. Parallel to the case of ADHD in adults, criteria for bipolar disorder are not adapted to

the juvenile or childhood onset form of bipolar disorder. Another reason is that the core symptom of BD - mood dysregulation- is also part of the common adjuvant symptoms of ADHD (see Introduction). These symptoms may be distinguished quantitatively, i.e. by periodicity and duration of mood swings, and to some extent also qualitatively, i.e. irritability versus hot temper. Still, the clinician is given room in his or her interpretation and decision-making about whether the mood symptoms in this particular individual seem more bipolar-like or ADHD-like. We thus applied a commonly used screening tool for bipolar disorder (MDQ) in our study, without telling the participants what they were screened for. According to standard cut-offs for this questionnaire (MDQ-positive) half of our ADHD patients (50.6 %) screened positive for a BSD compared to 12 % reporting a known bipolar disorder in the same sample. Using a broader cut-off (MDQ7positive), more than 70 % of the patients screened positive on the MDQ. This gap between the presence of symptoms of BD and of diagnosed BD illustrates two important points: First, symptoms of bipolar disorder are highly frequent in adults with ADHD, while a diagnosis of BD not necessarily is. Second, the prevalence of BD diagnosis is highly dependent on the subtype or definition of BD being used. Although this may seem logical, the clinical consequences may be difficult to follow and may depend on the clinician's viewpoint or experience in diagnosing the two disorders. A positive screen on a questionnaire should never be sufficient to make a diagnosis, but should be confirmed or disapproved by a comprehensive patient interview. As ADHD is not included in standard interviews of psychopathology for adults, a diagnosis of ADHD, which we have shown is a strong predictor for screening positively for BD, will not be confirmed unless it is thought of a priori by the clinician. The large variations in prescription of central stimulants between different counties in Norway (data from the Norwegian prescription database available from: http://www.reseptregisteret.no/) and between different states in the USA [203] indicate that traditions and attitudes in diagnosing and treating ADHD still may play a role in defining the disorder.

Comorbidity studies have found very varying prevalence of BD among adult ADHD patients, from rates around 1 %, i.e. similar to the general population [16] to elevated rates ranging from 5 to 47 % (for review see Wingo et al. 2007 [204]). The prevalence of

BD in our interviewed sample varied from 8 to 32 % according to the definition of BD used, and this illustrates some of the challenges in assessing the relationship between the two disorders. ADHD does not seem to be particularly difficult to distinguish from the clearly episodic BD1. However, the recent widening of the bipolar spectrum includes more chronic clinical pictures of (brief) recurrent depressions, alternating or co-occurring with elevated or dysphoric mood swings, and often complicated by substance abuse. It is this bipolar spectrum beyond BD1 that really challenges the distinction between ADHD and BD, and also some personality disorders, in particular borderline personality disorder (see Introduction and Paper II) [205,206]. Interestingly, recent studies have shown that a positive score on the MDQ frequently is correlated to these other psychiatric disorders also in the absence of a diagnosed BD [207,208].

Another issue emerging from the findings in Paper II, is the question whether the bipolar-like symptoms should be considered an inherent part of the ADHD syndrome, a distinct subtype of ADHD, or co-occurring symptoms qualitatively distinct from core symptoms of ADHD. The fact that most patients had a high load of symptoms of BD without having a BD diagnosis indicates that the measured bipolar symptoms are an inherent part of the ADHD syndrome and not an artefact of misdiagnosed BD. Also, the presence of bipolar symptoms is clinically important since it is associated with more impairment than ADHD without such symptoms. This is in line with other studies showing that emotional symptoms and problems affect the outcome of ADHD negatively (more behavioural problems, substance abuse, less capable of working). It is currently being debated whether emotional lability should be included in the formal diagnostic criteria of ADHD. Because it is the majority, and not a minority of patients that report such symptoms, we think it is appropriate to consider these symptoms as an inherent part of the ADHD syndrome in adults.

The role of pre- and perinatal factors in the etiology of ADHD

Paper III and IV of this thesis provide evidence- by different means- that pregnancy and birth related factors are associated with the development of ADHD and related symptoms and behaviour later in life.

The epidemiological study (Paper III) shows an association between various pregnancy and foetal factors (low birth weight, growth restriction, preterm birth, low Apgar scores, maternal epilepsy in pregnancy) and ADHD in adults. Low birth weight (LBW), as well as other indirect measures of a suboptimal prenatal environment, are known to increase an individual's risk for disease in later life [209,210]. Although LBW has already been shown to be associated with ADHD in children [156,157], our study is the first to show such an association in adults with ADHD. This is important added knowledge to the discussion on developmental aspects of ADHD since it presently remains unclear whether ADHD persisting to adulthood is caused by the same factors as ADHD remitting in childhood or adolescence. Our findings that preterm birth is associated with ADHD in adulthood extend findings from childhood studies [157]. Further, the association with low Apgar scores support experimental and imaging studies suggesting reduced cerebral blood flow in foetal life (in particular to the basal ganglia) as a putative pathogenetic mechanism in ADHD [211,212].

Systematic reports on maternal smoking are not available in the MBRN for births before 1987. We could therefore not adjust our results for maternal smoking. This clearly is a limitation in our study, considering the large amount of literature pointing to an association between smoking in pregnancy and ADHD [152,213]. However, recent studies with innovative designs capable of separating genetic and environmental influences, question the nature of this relation, suggesting that it may not be causal, but genetically mediated [214,215]. If this is the case, adjusting for maternal smoking would not necessarily alter our results.

The associations in our sample between maternal epilepsy and ADHD, as well as between infant oral cleft and ADHD, are new findings. The epidemiological nature of the study only allows us to speculate about possible causal mechanisms underlying

these associations. Thus, maternal epilepsy may be linked to ADHD in the offspring through various pathways; direct effects of hypoxic states during epileptic seizures in pregnancy; a common genetic vulnerability for the two disorders as in the case of 16p11.2 duplication [216]; or direct (teratogenic) or indirect effects of anti-epileptic drugs on the foetus. The latter may possibly be mediated through low maternal folate status, which has recently been shown to be associated with behavioural outcomes in human offspring, presumably due to an effect on brain development [217].

Likewise, the association found between infant oral cleft and ADHD may depend on common genetic or environmental risk factors affecting the development of both these apparently different phenotypes. The use of folic acid in pregnancy has recently been shown to be associated with oral cleft in the offspring [218]. Our epidemiological data point to foetal growth restriction as a risk factor for ADHD, independent of LBW and preterm birth. Foetal growth restriction may be caused by several factors, both maternal (placental dysfunction, poor nutrition, psychosocial stress, smoking in pregnancy, or altered hormonal status) and infant related (congenital malformations or genetic syndromes). Animal studies have indicated that serotonin plays an important role in embryonic morphogenesis by regulating developmental processes even before it starts acting as a neurotransmitter [219,220], including effects on the formation of craniofacial and palatal structures [221,222]. Altered serotonin levels in intrauterine life could thus be linked to both neurobehavioural symptoms as in ADHD, and to oral cleft.

Furthermore, studies of TPH1 knock-out mice have shown that normal embryonic development in mice is more dependent on maternal serotonin production than that of the embryo itself [121]. Paper IV represents a first attempt to replicate and explore the potential relevance of this latter finding in a sample of humans. Although it was not possible to study a real knock-out-effect (since all our TPH1 mutations were heterozygous), functional studies showed reduced enzyme function in vitro for nearly all the studied TPH1 mutations, indicating that serotonin production is impaired in mutation carriers. We found higher levels of ADHD symptoms (both inattentive and hyperactive/impulsive symptoms), mood symptoms, and impulsive drug related

behaviour in adult offspring of mothers with TPH1 mutations, compared to offspring of fathers with TPH1 mutations, and a control population without mutation, independent of the offspring's genotype. Our findings thus confirm those from the mice studies by Côté et al. concerning the importance of maternal serotonin production for development.

Clinical implications of these findings should include increased awareness regarding the use of agents that alter serotonin levels during pregnancy. At present, TPH-blocking agents are being developed for use in gastrointestinal disorders like irritable bowel syndrome [223], which is frequently reported among young women [224]. In view of our findings, caution should be made before administering such agents to pregnant women.

Selective serotonin reuptake inhibitors (SSRI) are widely used antidepressants, also among pregnant women, although concern is increasingly raised regarding their possible adverse effects on the foetus [225]. These effects includes congenital heart defects [226], pulmonary hypertension, foetal growth restriction [195], preterm birth [227,228], as well as neonatal withdrawal syndrome, and increased need for intensive care in the newborn child. Animal studies have shown that exposure to SSRI in utero may increase depression/anxiety-like traits in the adult offspring, i.e. the "SSRI paradox" [229]. Possible long-term effects of prenatal exposure to SSRIs on human neurodevelopment are, however, still unclear [230], but it has been suggested that deviations in either direction from optimal serotonin levels, during critical periods of developmental, may produce dramatic and long-lasting alterations in the organism [231].

Recent studies have shown that impaired serotonin production affects insulin-production in pregnant mice, suggesting a possible risk factor for gestational diabetes [232]. Interestingly, although the difference did not reach statistically significance, maternal diabetes was more frequent among ADHD mothers than among control mothers in our epidemiological study (Paper III). Together, findings from this work (Paper III and Paper IV) emphasize that factors influencing the intrauterine environment, with impaired serotonin production as one proposed pathway, may have

lasting cognitive and behavioural consequences extending beyond specific diagnostic boundaries.

Conclusions

- Adults with ADHD had lower educational levels and far lower participation in occupational life compared to the general population.
- Among adults with ADHD, a diagnosis and treatment of ADHD in childhood was associated with an increased probability of being in work in adulthood.
- ADHD was often comorbid and overlapping with the broadly defined bipolar spectrum disorders.
- Emotional lability was an important and impairing part of the symptom profile in a majority of adults with ADHD, and was associated with more severe ADHD symptoms, more alcohol and substance use, and lower occupational functioning.
- Unfavourable conditions in pregnancy and delivery, expressed by low birth weight, preterm birth, growth restriction and low Apgar scores were associated with increased risk of developing ADHD persisting to adult life.
- Impaired maternal serotonin production was associated with an increased risk of ADHD like symptoms and behaviour in adult offspring, independently of offspring's own serotonin biosynthetic capacity

Future perspectives

A main issue ensuing from the work of this thesis is the importance of exploring boundaries between psychiatric diagnoses and the value of using cross-diagnostic approaches when studying putative risk factors of diseases. The developmental perspective of psychiatric disorders is also a topical issue that should be emphasized in future research.

The close relationship between ADHD and bipolar symptoms demonstrated in Paper II warrants further research. Emotional dysregulation is increasingly recognized as an inherent and impairing feature of ADHD. These problems are often interpreted as being qualitatively different from the mood swings typical of bipolar disorder, but- as shown by our work- this difference may be less clear in the interface between the broadly defined bipolar spectrum disorders and ADHD in adults, or- as shown by others- between juvenile bipolar disorder and ADHD in children [57]. A follow-up of the findings of Paper II should include assessment of past and current ADHD symptoms in future studies of bipolar patients, in particular BD II and beyond, to further explore the interface between these diagnoses. Developmental aspects of the relation between ADHD and bipolar disorder should ideally be addressed in long-term, prospective studies of children followed to adulthood.

As long as the clinical interview remains the gold standard of 'well-defined' psychiatric diagnoses, there will continue to be disagreement about the validity of 'newer' diagnoses, as well as subthreshold and borderline cases. These 'well-defined' diagnostic categories may also actually impede research aiming at understanding the pathogenesis of psychiatric disorders. A dimensional approach to psychiatric symptoms across formal diagnostic entities may be more fruitful in reflecting the full spectrum of disorders and yielding information of underlying risk factors, which do not necessarily follow the boundaries of current diagnostic categories. This is illustrated by the findings in Paper IV, where impaired maternal serotonin production seems to be associated to a phenotype including cognitive deficits, mood symptoms

and impulsive behaviour, rather than to a formal diagnosis of ADHD. As attempted in Paper IV, in the search of genetic causes for ADHD and other complex disorders, there should be more emphasis on functional studies of putative genes of interest, in order to move from associative to causative relationships and thus to advance the understanding of the etiology of the disorder.

In our epidemiological study on pre- and perinatal risk factors (Paper III) we did not have access to symptom profiles and comorbid diagnoses for the whole patient cohort that was studied. We have, however, initiated a study on our clinically recruited patient sample, to investigate if the associations found with e.g. low birth weight and maternal epilepsy are specific to subgroups of ADHD patients, e.g. the predominantly inattentive subtype. This may guide us towards more specific pathogenetic explanations between risk factors and disease, and eventually influence psychiatric diagnostic classification towards a more etiologically based understanding. We are also planning an epidemiological study within the Norwegian Medical Birth Registry comparing a national cohort of children versus adults with ADHD to investigate more directly possible differences in pre- and perinatal risk factors for ADHD across the life-span.

Finally, and related to Paper I, I would like to emphasize the importance of assessing the functional impairment of disorders, and of studying how treatment and other interventions influence functional rather than pure symptomatic aspects. Obviously, more long-term studies from naturalistic/observational settings are needed to assess the real efficiency- not only short-term effects- of treatment and the role of early interventions in ADHD and other mental disorders in childhood [185].

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Errata

Page 9: 3rd paragraph; 6th sentence: "..national cohort of 2123 adults.." should be "..national cohort of 2323 adults.."

Page 39: The following sentences *"The families included in Paper IV were families of probands with TPH1 mutations, and in which at least three family members agreed to participate. Seven families with a total of 86 members were included."* should be replaced by *"The families included in Paper IV were families of probands with TPH mutations, and in which at least three family members agreed to participate. Eight families with a total of 97 members were included."*

Reference 24 and 70 should be identical and listed only once (24)

Reference 132 *"Franke B, Neale BM, Faraone SV. Genome-wide association studies in ADHD. Hum Genet 2009; 126(1): 13-50."* should be replaced by *"Franke B, Vasquez AA, Johansson S, et al. Multicenter Analysis of the SLC6A3/DAT1 VNTR Haplotype in Persistent ADHD Suggests Differential Involvement of the Gene in Childhood and Persistent ADHD. Neuropsychopharmacology. Nov 4 2009."*

Reference 136 *"McKinney J, Johansson S, Halmoy A, Dramsdahl M, Winge I, Knappskog PM, Haavik J. A loss-of-function mutation in tryptophan hydroxylase 2 segregating with attention-deficit/hyperactivity disorder. Mol Psychiatry 2008; 13(4): 365-367."* should be reference 187 *"Johansson S, Halmoy A, Mavroconstanti T, et al. Common variants in the TPH1 and TPH2 regions are not associated with persistent ADHD in a combined sample of 1,636 adult cases and 1,923 controls from four European populations. Am J Med Genet B Neuropsychiatr Genet. Mar 8 2010;153B(5):1008-1015.*

Reference 184 should be identical to reference 179; *"Aanonsen NO, Lensing MB, Prietz R, Gørvell P, Sandven I, Ljøner L. Utprøvende behandling med sentralstimulerende legemidler til voksne med hyperkinetisk forstyrrelse/ADHD. Rapport til Sosial-og helsedirektoratet. Erfaringer fra prøveperioden oktober 1997 til august 2003. Ullevål universitetssykehus, 2004."* and listed only once.