Comorbidity across childhood-onset neuropsychiatric disorders

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Cover illustration: Pia Moberg

Det finns saker som man måste vara fackman för att inte förstå.

Hjalmar Söderberg

To Paula and Sara

ABSTRACT

Background: Attention-Deficit/Hyperactivity Disorder (ADHD), and Autism Spectrum Disorders (ASDs) have clinically found to be more comorbid with each other and with other psychiatric conditions than previously assumed. It is, however, difficult to capture the complexity of these comorbidities using current diagnostic systems, where exclusion criteria prevent simultaneous diagnosis. Thus, in order to describe this complexity and its consequences for the individual, it is important to describe actual comorbidity in different clinical contexts. **Aims:** The overall purpose of this thesis is to describe the prevalence and comorbidity between ASD and ADHD, and among them and other psychiatric conditions. Specific aims were to: describe comorbidity in a group of adult out-patients with ADHD and/or ASDs (Paper I); investigate the prevalence of personality disorders and describe the personality profiles of the same group (Paper II); describe psychiatric symptoms associated with aggressive behaviors in adult psychiatric patients (Paper III); describe comorbidity in a group of adolescents placed in special youth institutions (Paper IV); and to investigate whether comorbid ADHD and substance abuse is associated with a more negative outcome, that is, more criminal recidivism, health care needs, and untimely death (Paper V). **Methods and results:** Papers I and II were based on diagnostic and demographic cross-sectional data showing that ADHD and ASD overlap greatly with each other, and that there is a significant overlap between ADHD and bipolar disorder and between ASDs and psychosis. Personality disorder (PD) diagnoses are also common in these diagnostic groups, showing specific personality profiles associated with ADHD, ASD, and those with comorbid ADHD and ASD. In Paper III, aggressive behaviors were compared between a group of polyclinic psychiatric patients and a group of forensic psychiatric patients, and both groups reported similarly high scores on aggressiveness. Paper IV was based on cross-sectional data on institutionalized adolescents, which in Paper V was combined with longitudinal follow-up data. Psychiatric diagnoses in general, and of ADHD and ASD in particular, were high in this group, and criminal recidivism and health care use were overall very high. There were small differences between the groups with comorbid ADHD and substance abuse disorders (SUD), SUD only, and, no SUD in criminal recidivism, health care needs, and untimely death. **Conclusion:** Comorbidity between ADHD and ASD and other psychiatric diagnoses is common among psychiatric patients, and is in many cases associated with character immaturity, aggression, and PDs. Outcomes over time tend to worsening with increasing comorbidity, especially in cases with comorbid SUD and neuropsychiatric disorders. These complex states constitute diagnostic and treatment challenges for psychiatry and its classic divisions between child and adolescent versus adult psychiatry, mental illness versus PD, and psychological versus medical interventions.

SAMMANFATTNING PÅ SVENSKA

Bakgrund: De barndomsdebuterande psykiatriska tillstånden Attention-Deficit/Hyperactivity Disorder (ADHD) och Autismspektrumtillstånd (ASDs) har i den kliniska vardagen visat sig uppträda tillsammans med varandra och tillsammans med andra psykiatriska tillstånd i betydligt högre utsträckning än vad man tidigare har antagit. Det har också varit svårt att med hjälp av de nuvarande diagnostiska systemen fånga den mångfasetterade bild som många patienter uppvisar. Mot denna bakgrund har det framstått som viktigt att undersöka och beskriva både förekomsten av komorbiditet i olika kliniska sammanhang och dess konsekvenser för individen.

Syfte: Det övergripande syftet med denna avhandling har varit att i olika patientgrupper undersöka och beskriva förekomsten av och samsjukligheten mellan ADHD och ASDs och tillstånd som har visat sig vara vanligt förekommande tillsammans med dessa. Mera specifikt har syftet med de ingående studierna varit att: (1) beskriva den psykiatriska komorbiditeten i en grupp vuxna patienter med ADHD och/eller ASD, (2) undersöka förekomsten av personlighetsstörningar och beskriva personlighetsprofiler i en grupp av vuxna patienter med ADHD och/eller ASD, (3) att beskriva psykiatriska symtom förenade med aggressivt beteende hos vuxna psykiatripatienter, (4) att beskriva den psykiatriska komorbiditeten hos en grupp ungdomar placerade i särskilda ungdomshem och (5) att undersöka huruvida samtidig ADHD och beroendetillstånd bidrar till ett mer negativt utfall avseende återfall i kriminalitet, vårdbehov och för tidig död i en grupp ungdomar placerade i särskilda ungdomshem.

Metod: Avhandlingens två första arbeten (Paper I, II) utgår från tvärsnittsdata kring patienter från en öppenpsykiatrisk utredningsenhet med inriktning på neuropsykiatriska frågeställningar där omfattande bakgrundsdata tillsammans med detaljerad psykiatrisk diagnostik har samlats in. I Paper I redovisas data avseende förekomst dels av ADHD och ASD men också kring förekomst av komorbiditet avseende bipolär sjukdom och psykossymtom. I Paper II redovisas förekomst av personlighetsstörningar beskrivna utifrån DSM-IV axel II-diagnoser och specifika personlighetsprofiler beskrivna med hjälp av personlighetsinventoriet The Temperament and Character Inventory (TCI). I avhandlingens tredje arbete (Paper III) har gruppen som redovisats i Paper I-II jämförts med tvärsnittsdata från en grupp rättspsykiatriskt utredda patienter med avseende på förekomst av aggressivt beteende i ett livstidsperspektiv mätt med självskattningsformuläret Life History of Aggression (LHA). Slutligen redovisas i avhandlingens fjärde och femte arbeten (Paper IV-V) dels förekomst av och komorbiditet mellan diagnoser (Paper IV), och dels inverkan av ADHD och samtidigt missbruk på utfallet i ett antal olika kriminologiskt

intressanta och vårdrelaterade variabler hos en grupp ungdomar placerade på olika ungdomshem i Västsverige (Paper V). I Paper V har tvärsnittsdata kombinerats med longitudinella uppföljningsdata.

Resultat: Paper I visar att det finns ett betydande överlapp mellan ADHD och ASDs, men också att det finns ett lika betydande överlapp mellan ADHD och bipolär sjukdom och mellan ASDs och psykossjukdom. Paper II visar att förekomsten av personlighetsstörningsdiagnoser i denna grupp var mycket hög och att det finns specifika personlighetsprofiler enligt TCI associerade till ADHD (höga värden i temperamentfaktorn Novelty Seeking) och ASDs (låga värden i Novelty Seeking och Reward Dependence). Båda grupperna utmärkte sig vidare av markörer för personlighetsstörning i TCI (låga värden i karaktärsfaktorerna Self-directedness och Cooperativeness). Enligt Paper III har patienter inom en öppenpsykiatrisk mottagning samma grad av självrapporterad aggressivitet skattad med LHA som en grupp patienter som genomgick rättspsykiatrisk utredning i samband med våldsbrott. Aggression mätt med LHA visade sig också ha högst korrelation till hyperaktivitetssymtom inom ADHD och förekomsten av uppförandestörning. LHA-poängen var dessutom negativt korrelerad med GAF-värden (låga GAF-värden korrelerade till höga värden i aggressivitet) och till förekomst av autismsymptom. Paper IV visar dels att det finns en mycket hög förekomst av psykiatrisk sjuklighet generellt bland institutionsplacerade ungdomar (om man räknar bort missbruk och uppförandestörning i denna grupp så har 73% minst en diagnos och 41% minst 2 diagnoser) men också att förekomsten av ADHD (47% uppfyller denna diagnos) och ASDs (17% uppfyller denna diagnos) är kraftigt förhöjd i denna grupp jämfört med normalpopulationen. Det fanns vidare ett stort överlapp dels mellan ADHD och ASDs och dels mellan dessa tillstånd och andra psykiatriska diagnoser. Slutligen visar Paper V att återfallsfrekvensen i brott liksom sjukvårdskonsumtionen överlag är mycket hög i denna grupp, men att det var små skillnader mellan grupperna med ADHD och missbruk (ADHD+SUD), enbart SUD respektive ingen SUD. Utöver detta förelåg även indikationer på att individer i denna grupp går en för tidig död till mötes i betydligt högre utsträckning än vad fallet är för samma åldersgrupp i normalpopulationen.

Slutsats: Förekomst av ADHD och ASDs liksom komorbiditet dem emellan och andra psykiatriska diagnoser är vanligt bland vuxenpsykiatriska patienter i öppenvård, rättspsykiatri liksom ungdomsvård. Ofta är problematiken associerad med karaktärsomognad, aggressivitet och personlighetsstörningar. Utfallet över tid verkar också påverkas negativt med ökad grad av komorbiditet, speciellt vid komorbiditet mellan missbruk och neuropsykiatrisk problematik. Dessa komplexa tillstånd medför diagnostiska och behandlingsmässiga utmaningar för psykiatrin och dess indelning mellan å ena sidan barn- och ungdomspsykiatri och å andra sidan vuxenpsykiatri, mellan

psykiatrisk sjuklighet och personlighetsstörningar, och mellan psykologiska och medicinska interventioner. Denna indelning avspeglar i många fall bristfälligt detta problematiska utvecklingsförlopp samtidigt som den till viss del också motarbetar förståelsen av och förutsättningarna för att utreda och behandla denna problematik i ett livstidsperspektiv i dessa patientgrupper.

LIST OF PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

I.   Stahlberg, O., Soderstrom, H., Rastam, M., & Gillberg, C. (2004). Bipolar disorder, schizophrenia, and other psychotic disorders in adults with childhood onset AD/HD and/or autism spectrum disorders. *J Neural Transm,* 111(7), 891-902.

II. Anckarsäter, H., Stahlberg, O., Larson, T., Hakansson, C., Jutblad, S. B., Niklasson, L., et al. (2006). The impact of ADHD and autism spectrum disorders on temperament, character, and personality development. *Am J Psychiatry, 163*(7), 1239-1244.

III. Hofvander, B., Ståhlberg, O., Nydén, A., Wentz, E., degl'Innocenti, A., Billstedt, E., et al. (2011). Life History of Aggression scores are predicted by childhood hyperactivity, conduct disorder, adult substance abuse, and low cooperativeness in adult psychiatric patients. *Psychiatry Res,* 185(1-2), 280-285.

IV. Ståhlberg, O., Anckarsäter, H., & Nilsson, T. (2010). Mental health problems in youths committed to juvenile institutions: prevalences and treatment needs. *Eur Child Adolesc Psychiatry,* 19(12), 893-903.

V.   Ståhlberg, O., Boman, S., Robertsson, C., Kerekes, N., Anckarsäter, H., Nilsson, T. (submitted). A comparison between youths committed to juvenile institutions with comorbid substance abuse (SUD) and ADHD versus SUD without ADHD respective those without SUD: Few differences in outcome in a follow-up study on criminal behaviour and health care use.

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CONTENTS

ABBREVIATIONS

AD   ADHD, predominantly inattentive type

ADAD   Adolescent Drug Abuse Diagnosis instrument

ADHD   Attention-Deficit/Hyperactivity Disorder

AN   Anorexia nervosa

ASD(s)   Autism spectrum disorder(s)

ASDI   The Asperger Syndrome (and High-functioning Autism) Diagnostic Interview

ASPD   Antisocial personality disorder

ASSQ   Autism Spectrum Screening Questionnaire

AUC   Area under the ROC curve

BN   Bulimia nervosa

BPD   Borderline personality disorder

CD   Conduct disorder

CO   Cooperativeness

DAMP   Deficits in attention, motor control, and perception

DSM-IV   Diagnostic and Statistical Manual of Mental Disorders, 4th edition

DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ED	Eating disorder
ESSENCE	Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examination
FSIQ	Full-Scale Intelligence Quotient
GAF	Global Assessment of Functioning
HA	Harm Avoidance
HD	ADHD, predominantly hyperactive-impulsive type
ICD-10	International Classification of Diseases 10th edition
IQ	Intelligence Quotient
J-TCI	Junior Temperament and Character Inventory
LD	Learning disorder
LHA	Life History of Aggression
MR	Mental retardation
NPV	Negative predictive value
NS	Novelty Seeking
OCD	Obsessive-compulsive disorder
ODD	Oppositional defiant disorder

P	Persistence
PD	Personality disorder
PDD-NOS	Pervasive Developmental Disorder Not Otherwise Specified
PIQ	Performance Intelligence Quotient
POI	Perceptual Organization Index
PPV	Positive predictive value
PSI	Processing Speed Index
RD	Reward Dependence
ROC	Receiver Operating Characteristics
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SCID-II	Structured Clinical Interview for DSM-IV Axis II Personality Disorders
SD	Standard deviation
SD	Self-Directedness
SiS	Swedish National Board of Institutional Care
SPSS	Statistical Package for the Social Sciences
ST	Self-Transcendence
SUD	Substance abuse disorder

TCI   Temperament and Character Inventory

VIQ   Verbal Intelligence Quotient

WAIS   Wechsler Adult Intelligence Scale

WISC   Wechsler Intelligence Scale for Children

1 INTRODUCTION

1.1 Comorbidity

1.1.1 Definition and history of the concept

Most clinicians have noticed that certain diagnoses seem to occur more frequently together than alone, creating recognizable patterns or clusters. This is referred to as comorbidity even in psychiatry and psychology, which generally avoid terms such as disease and morbidity. The crucial issue is whether such aggregations of diagnoses reflect *true* (stemming from some common etiological factor behind distinct entities) or *artifactual* (caused by some confounding correlation between pseudo-related entities or poorly delineated diagnostic criteria) comorbidity. The study of such patterns can tell us important things about the nature of disorders and the validity of our diagnostic systems.

The concept of comorbidity was first presented and problematized by Feinstein in an article on pre-therapeutic classification of comorbidity in chronic diseases[1]. The goal of the article was to show the importance of selecting groups as homogenous as possible when evaluating different treatment strategies. In this perspective, comorbidity is regarded as a confounding factor that could bias evaluations, because uncertainty about the comparability of individuals in different treatment groups could lead to statistical errors in the evaluation of treatment outcomes in these groups. Feinstein defined comorbidity as "any distinct clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study"[2].

In the field of medicine, comorbidity is ideally described as co-occurrence of disease on the symptomatic, pathophysiological, and etiological levels. In psychiatry, with few exceptions (such as Huntington's chorea), this is rarely the case. Psychiatric comorbidities are instead based on the descriptive level, with no knowledge about etiological factors. Therefore, comorbidity in psychiatry is the co-occurrence of disorders. In this thesis, psychiatric comorbidity is examined on the phenotype level, beginning with disorders of

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[1] Feinstein, 1970
[2] Feinstein, 1970

childhood. Clarification of the phenotypic presentations of mental health problems may therefore be a necessary step before further progress in identifying underlying mechanisms is possible.

1.1.2 Different types of comorbidity

First[3] described three types of psychiatric comorbidity:

1) true comorbidity, which is relatively rare in psychiatry since we do not know enough about the underlying pathophysiology to be able to determine whether the observed disorders are truly etiologically distinct;

2) artifactual comorbidity, which is an effect of the way the diagnostic systems are designed, arising when diagnostic entities are split into numerous, non-validated, non-specific, and narrow disorders, rather than being grouped together in fewer, more broadly defined categories; and

3) spurious comorbidity, which arises when many disorders share the same symptoms. More broadly defined disorders sometimes contain the criteria for more narrowly-defined disorders (e.g. autism and Asperger's syndrome). Insistence on routines may lead to a diagnosis of an autism spectrum disorder or of obsessive-compulsive disorder (OCD). One way the developers of the diagnostic systems have dealt with spurious comorbidity is to introduce exclusion criteria among disorders or to use hierarchies of diagnoses that prohibit certain diagnoses in the presence of another specified diagnosis.

Angold and co-workers[4] developed and refined the concept of psychiatric comorbidity by suggesting the following distinctions:

a) **homotypic comorbidity** between disorders within a diagnostic group (e.g. major depression and dysthymia);

b) **heterotypic comorbidity** between disorders from different diagnostic groups (e.g. depression and conduct disorder);

c) **concurrent comorbidity** between disorders present at the same time; and

d) **successive comorbidity** between disorders which do not overlap in time.

Different categorical diagnostic systems have been developed to reduce the effects of artifactual comorbidity. Clarkin & Kendall[5] described two principles guiding the choice of exclusion criteria:

a) if the observed symptoms can be explained by an organic disorder, no other diagnosis that includes the symptoms of that organic disorder can be assigned (e.g. Alzheimers disease and memory disorder);

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[3] First, 2005

[4] Angold, Costello, & Erkanli, 1999

[5] Clarkin and Kendall, 1992

b) if a pervasive disorder has overlapping symptoms with a less pervasive disorder, the diagnosis of the less pervasive disorder cannot be assigned (e.g. autistic disorder and Asperger's disorder).

First[6] also listed four types of mutually exclusive relationships used in the DSM and the ICD between:
1) disorders at different Kraepelinian hierarchical levels (e.g. schizophrenia is higher in the hierarchy than depression, and therefore takes precedence over a diagnosis of depression);
2) disorders with the same manifestation but differences in duration or time of onset (e.g, a duration exceeding 6 months favors the diagnosis of schizophrenia over schizophreniform disorder);
3) disorders whose definitions nested, one within the other, and differ mainly in breadth (e.g. the definition of Asperger's disorder is included in that of autism, so an individual diagnosed with autism, which takes precedence, also meets the criteria for Asperger's disorder;
4) disorders whose significant symptoms overlap (e.g. schizophrenia and dysthymia).

1.1.3 Alternative terms

One alternative term suggested for comorbidity is **co-occurrence**, which denotes the simultaneous presence of two or more diagnoses in one individual. Those diagnoses do not need to be correlated in the total population, and the term does not necessarily imply any relation between the diagnoses in the individual. Co-occurrence simply denotes two or more disorders happening together, not whether they were caused by one or more common etiological factors. (For an overview see[7]). Another suggested expression is **co-variation**, which indicates that certain disorders occur together more often than expected by chance (i.e. comorbidity in the sense used here) or that dimensionally assessed problems or traits correlate. **Multimorbidity** has also been used to describe the co-occurrence of diseases within one person without any reference to an index condition or a common etiology.

Despite these limitations and methodological issues, in this thesis the term comorbidity is used and defined as the simultaneous or sequential presence of two or more (related or unrelated) conditions in the same individual manifested in the form of DSM-IV diagnoses.

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[6] First, 2005
[7] Kaplan, et al., 2006

1.1.4 Clinical groups vs. population-based studies

The study of comorbidity in clinical groups (assuming not all individuals in the population become clinical cases) offers little information about the occurrence of comorbidity in the general population. To be able to say something about the incidence and comorbidities of different conditions in different populations, population-based research approaches are necessary. Clinic-referred groups often have more pronounced symptomatology, and therefore studies based on such groups often result in biased estimates of prevalence and incidence of comorbidity in the general population. The study of comorbidity in clinical groups has the advantage of making connections and phenomena more clear. Comorbidity, more difficult to detect in large samples due to diagnostic difficulties and costs, can be shown, further studied, and used to create hypotheses on a more general level when studied in smaller, well-defined clinical samples.

1.2 Disruptive behavior disorders

Three disruptive behavior disorders usually diagnosed before or during adolescence are defined by the DSM-IV: Attention-Deficit/Hyperactivity Disorder (ADHD), oppositional defiant disorder (ODD) and conduct disorder (CD)[8]. Impulsivity is a core feature of all these disorders, and its comorbidity with other impulsive/compulsive disorders is considerable[9].

Some results show ADHD and CD to be associated with adult antisocial aggression. Whether ADHD, alone[10] or mediated through comorbid CD[11], is causal in this trajectory into antisocial aggressive behavior is a matter of controversy however.

1.2.1 Attention-Deficit/Hyperactivity Disorder

The core feature of Attention-Deficit/Hyperactivity Disorder (ADHD) is a reduced span of attention in combination with hyperkinesia and impulsivity[12]. Compromised executive functions (e.g. control over attention, activity, and impulses) may lead both to a deficient cognitive grasp of consequences and to disinhibited behavior. The attention dysfunction is not necessarily constant; some individuals may concentrate relatively well or even hyperfocus on tasks

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[8] Quay and Hogan, 1999

[9] Kessler, et al., 2006, Kessler, et al., 2006

[10] Mannuzza, Klein, & Moulton, 2008, Young and Thome, 2011

[11] Mordre, et al., 2011, von Polier, Vloet, & Herpertz-Dahlmann, 2012

[12] Gillberg, 1995

they find rewarding in a structured environment, but have great difficulty focusing their attention on less thrilling tasks. The DSM-IV separates ADHD with both attention deficits and hyperactivity/impulsivity from ADHD pre-dominated by one of the symptom clusters (AD vs. HD). ADHD is often combined with motor coordination problems and/or perceptual dysfunctions. This constellation has often been referred to as DAMP (deficits in attention, motor control, and perception) in Scandinavia (for an overview see[13]).

The childhood prevalence of ADHD is approximately 5-8%[14] with a reported male to female ratio of 3:1[15].

1.2.2 Oppositional defiant disorder, conduct disorder

ODD and CD are diagnosed by behavioral characteristics: ODD by hostile and oppositional attitudes, especially towards adults, and CD by cruel, outward-directed aggressive and destructive acts. ODD is seen as a precursor to CD, and according to the DSM-IV cannot be diagnosed in an individual who meets the criteria for CD. Since most of the CD criteria are classified as crimes in adults, it is debatable whether CD is a true mental disorder or merely early-onset criminal behavior. Early-onset CD (around the age of 10) is almost always a complication of another neuropsychiatric disorder, such as ADHD[16]. Teenage-onset CD is more often "pure" and may develop in otherwise healthy individuals, generally in the context of oppositional or criminal peer groups, often complicated by substance abuse, adjustment disorders, and mood disorders[17].

The prevalence of ODD and CD change from childhood to adolescence (ODD become less and CD more prevalent, partly because of the mutually exclusive criteria for these disorders). A wide range of estimates for prevalence have been reported; Maughan and co-workers[18] reviewed several studies and gave results from their own large national representative study including 5212 boys and 5226 girls. In this study the prevalence of ODD across all ages was reported to be 1.4% for girls and 3.2% for boys. The corresponding figures for CD were 0.8% and 2.1% respectively.

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[13] Gillberg, 2003

[14] Barbaresi, et al., 2002, American Psychiatric Association, 2000

[15] American Psychiatric Association, 2000

[16] Loeber and Farrington, 1994

[17] Lahey and Loeber, 1997

[18] Maughan, et al., 2004

1.2.3 Outcome and prognosis

It has been shown that the rate of persistence among those adults still fulfilling all criteria for ADHD is about 15%, while another 40-60% of adults who had ADHD as children go into partial remission[19]. A more recent study[20], however, found in a population-based sample that the proportion of individuals whose ADHD persisted from childhood into adulthood was 29%. The risk for death by suicide in adults with childhood ADHD was also shown to be significantly higher than in controls in that study.

Hyperactive children followed into young adulthood have been shown to have significantly more difficulties functioning adaptively in major life activities throughout their lives than community controls[21]. They had poorer educational performance and attainment, higher frequency of being fired, lower job performance, fewer close friends, earlier parenthood, and higher incidence of sexual transmitted diseases.

As a function of age, symptoms of hyperactivity become less obvious than symptoms of inattentiveness as hyperactivity and impulsivity are more likely to decline than inattention[22].

A study showed an increased risk of involvement with the juvenile justice system for adolescents with ADHD[23], and the same increased risks for involvement in antisocial behavior and for lifetime arrest records have been shown for adults with ADHD in numerous studies (see e.g.[24]). A review[25] of the literature on the childhood background of antisocial personality disorder (ASPD) showed that at least half of children with hyperactivity develop ODD, about a third develop CD, and that about half of children with any of these combinations develop ASPD in adulthood.

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[19] Faraone, Biederman, & Mick, 2006

[20] Barbaresi, et al., 2013

[21] Barkley, et al., 2004

[22] Biederman, Mick, & Faraone, 2000, Lahey, et al., 2005, Larsson, Lichtenstein, & Larsson, 2006

[23] Bussing, et al., 2010

[24] Mannuzza, Klein, & Moulton, 2008

[25] Hofvander, et al., 2009

1.3 **Autism spectrum disorders**

1.3.1 **History and basic description**

Autism spectrum disorders (ASDs) are the collective name of a set of neurodevelopmental disorders (in clinical practice autistic disorder, Asperger's disorder, and pervasive developmental disorder not otherwise specified [PDD-NOS], are referred to this spectrum) which all share impairments in social interaction and communication and a pattern of repetitive and restricted behaviors. The term spectrum refers to the broad variety, and different levels of severity, of symptoms within this collection of diagnoses. Until 1970 there was still uncertainty and controversy about how to classify autism; it was seen as a variant of schizophrenia until Kolvin[26] highlighted the distinction between autism and schizophrenia as two distinct conditions in 1971. (In the DSM-II, autism was still included in the category of schizophrenia, but later broken into 2 separate categories in the DSM-III, first published in 1980). In the DSM-IV, the different subtypes of autism were categorized under the concept of Pervasive Developmental Disorder (Autistic Disorder, Rett's Disorder, Childhood Disintegrative Disorder, Asperger's Disorder, and Pervasive Developmental Disorder Not Otherwise Specified).

There has been a clear rise in the reported prevalence of ASDs worldwide over the last decades[27]. Most authors attribute these effects to methodological refinement[28] or see them as a reflection of better detection and earlier diagnosis[29]. Other suggested causes include a change in the interpretation of the diagnostic criteria and a diagnostic substitution in which symptoms that were once attached to other diagnoses are now described as symptoms within the autism spectrum[30].

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[26] Kolvin, 1971

[27] Hansen, Schendel, & Parner, 2015

[28] Posserud, et al., 2010, Zaroff and Uhm, 2012

[29] Brugha, et al., 2011, Perkins and Berkman, 2012

[30] Isaksen, et al., 2013

From once being described as an extremely rare condition (0.4‰[31]), ASDs are now estimated in nearly 1%[32], but numbers as high as 2.6% in a 7–12-year-old South Korean community sample have been reported[33]. The male to female ratio is about 4:1[34]. This male preponderance is more pronounced in groups with normal or high Full-Scale Intelligence Quotient (FSIQ).

1.3.2 Outcome and prognosis

A considerable proportion of individuals with ASDs fulfill diagnostic criteria for neurological[35] (e.g. epilepsy, speech and language disorders, chronic sleep problems) and psychiatric[36] (e.g. ADHD, OCD, depression, anxiety, eating disorders [ED]) comorbid disorders. At least one additional psychiatric disorder in 70–75% of children and adults with autism and two or more comorbid psychiatric disorders in approximately 40% of children with ASDs have been reported[37]. The presence of intellectual disability has been shown to significantly reduce adaptive capacity and autonomy in individuals with ASDs[38].

Although a few individuals with autism do achieve autonomy with increased age, most remain dependent throughout their lives, as clearly shown in several studies[39]. The outcomes in these studies were poor or very poor (severe handicap, no independent social progress) in 58% of cases, while 41% had fair, good, or very good outcomes (employed or higher education, independent living if over 23, steady friends and/or relationship). Childhood IQ was positively correlated with better adult outcome, as was the presence of verbal communication at age 6. Other studies have reported even larger proportions of good to fair outcomes (e.g. 50% in[40]). A review[41] showed that studies report 3–25% of individuals losing their ASD diagnoses as they grow up. Relatively high intelligence, receptive language, verbal and motor imitation, motor development, earlier age of diagnosis and treatment, and a diagnosis of PDD-NOS were reported as predictors for recovery, while the presence of seizures, mental retardation, and genetic syndromes were associated with persistence of

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[31] Lotter, 1966

[32] Lai, Lombardo, & Baron-Cohen, 2014

[33] Kim, et al., 2011

[34] American Psychiatric Association, 2000, Fombonne, 2005

[35] Gillberg and Billstedt, 2000, Gurney, McPheeters, & Davis, 2006

[36] Ghaziuddin and Zafar, 2008, Simonoff, et al., 2008

[37] Ghaziuddin and Zafar, 2008

[38] Matson, et al., 2009

[39] Billstedt, Gillberg, & Gillberg, 2005, Howlin, et al., 2004

[40] Eaves and Ho, 2008

[41] Helt, et al., 2008

symptoms in this review. A recent study[42] implied a positive outcome for a subgroup of cognitively able (i.e. Verbal Intelligence Quotient (VIQ) < 70) children with ASDs who participated in early interventions. By 19 years of age 9% of the participants had overcome the core features of ASD and no longer fulfilled the criteria for a diagnosis.

1.4 ADHD-ASD comorbidity

Although none of the DSM or ICD criteria for ASDs and ADHD are overlapping, and in fact a primary diagnosis of ADHD is possible only if the ADHD symptoms are not better accounted for by another diagnosis (such as ASDs), it has been obvious for a long time that a considerable group of persons with ADHD also have autistic-like difficulties (social interaction, language/communication, inflexibility) and that participants with ASDs have ADHD-like symptoms (inattention, emotional disturbances, impulsivity, oppositional behavior), even to the point where criteria for both diagnoses are met. Kadesjö and Gillberg[43] concluded that pure cases of ADHD are the exception rather than the rule. Murray[44] reported the prevalence of ADHD in participants with ASDs to be in the range of 41–78% in different studies. Likewise ASD symptoms have been shown to be common in participants with ADHD. Reiersen and co-workers[45], for example, reported approximately one third of the children with ADHD to also have symptoms indicating a probable ASD.

1.4.1 Learning disorders and mental retardation

In the literature, especially the older, the concepts learning disorders (LDs) and mental retardation (MR) sometimes have been used interchangeable and sometimes LD has been used as superordinate to MR. The concept of LDs is understood as a discrepancy between a person's level of expected achievement and their performance in one or several important areas of life (e.g. reading, calculation, communication). In this thesis the two concepts are used interchangeable defined as MR, which is to be understood as an IQ < 70 consistently presented in IQ tests combined with dysfunction in at least two different areas (cognitive, social, language, motor, etc.). The onset of these problems must be traceable to childhood (before 18 years of age).

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[42] Anderson, Liang, & Lord, 2014
[43] Kadesjö and Gillberg, 2001
[44] Murray, 2010
[45] Reiersen, et al., 2007

In a US community-based representative sample, 44% of participants with ADHD had comorbid LD and 43% of participants with LD had comorbid ADHD[46]. In that study boys were more likely than girls to have any of the conditions and about twice as likely as girls to have ADHD-LD comorbidity. DuPaul and co-workers[47] reviewed 17 studies conducted between 2001 and 2011 on comorbidity between ADHD and LD. The rate of LD in students with ADHD was found to range between 8% and 76%, with a mean of 45%. The wide range was explained by the different criteria for LD applied across studies.

In the early days of autism research and for some time, it was claimed that the majority of affected children also had MR, but supporting data was rare and difficult to evaluate due to variations in diagnostic criteria and different diagnostic instruments. Today, it is widely accepted that individuals with ASDs may be found on the whole spectrum of IQ, from genius to severely impaired, but that the overlap with LD increases rapidly from Asperger's disorder and PDD-NOS to autistic disorder. LD prevalence rates of about 75% are commonly found in studies of people with autistic disorder[48], while recent studies focused on the broader concept of ASDs show lower prevalence rates, between 25% and 40%[49]. In cases of ASDs that are associated with known medical pathologies, a majority of children also have LD, especially in "syndromic" ASDs such as Fragile X syndrome. Here, it is worth noting that all genetic aberrations associated with autism can also give rise to LD[50].

Comorbid LD among people with ADHD and/or ASDs has essential effects on their mental health and global everyday functioning. Several studies have shown that individuals who have both ASDs and LD also have higher rates of other mental health problems[51], for example ADHD[52], episodic psychiatric disorders (most commonly major depression[53], disruptive disorders [25%], and anxiety disorders [22%][54]). The higher the IQ, the more developed and elaborate is a person's speech and language, while low to very low IQs are related to the absence or particularly late onset of verbal and nonverbal communication and to abnormalities such as echolalia, idiosyncrasy, and

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[46] Pastor and Reuben, 2008

[47] DuPaul, Gormley, & Laracy, 2013

[48] Ghaziuddin, 2000

[49] Chakrabarti and Fombonne, 2005, O'Brien and Pearson, 2004

[50] Betancur, 2011

[51] LoVullo and Matson, 2009

[52] McCarthy, 2007

[53] Bradley and Bolton, 2006

[54] Dekker and Koot, 2003

neologisms[55]. Finally, a low IQ is also associated with more stereotypies such as flicking, wiggling fingers, and hand flapping, while more complex repetitive behaviors, interests, and rituals are more common in higher-functioning people.

1.4.2 Oppositional defiant disorder, conduct disorder, and antisocial personality disorder

Children with ADHD face a dramatically increased risk of developing CD. Criteria for CD or ODD are met by a third of 10-year-olds and by approximately half of 15-year-olds with ADHD[56]. This problem combination increases the risk both of persisting ADHD and the development of ASPD. Approximately 50% of the affected children will develop persistent criminality, substance abuse, or psychosocial maladaptation[57]. Even if exact conclusions based on the results from longitudinal studies are rendered somewhat difficult by the use of different inclusion criteria, follow-up periods, and outcome measures, the overall findings roughly correspond to other epidemiological data: 25% to 50% of juvenile and adult offenders suffer from ADHD[58]. It has also been claimed that children with ADHD who do not develop childhood antisocial behaviors still run an increased risk of adult criminality and/or substance abuse[59], but this is a contested claim as their prognosis does seem to be much better.

There is a clear connection between ODD and CD; it has been shown in longitudinal studies[60] that 82% of clinically referred boys with CD also had been showing previous signs of ODD and that 47% of the boys with ODD eventually progressed to fulfill the criteria for CD.

Cross-sectional studies from forensic psychiatry[61] and among young adult criminal offenders[62] have indicated considerable prevalences (between 7% and 20%) of ASDs. In Swedish prison settings, the prevalence was reported to be 11%[63]. However, a prospective population-based longitudinal study following

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[55] O'Brien and Pearson, 2004

[56] Lahey and Loeber, 1997

[57] Hart, et al., 1995, Hechtman, Weiss, & Perlman, 1984, Rasmussen and Gillberg, 2000, Satterfield, Hoppe, & Schell, 1982

[58] Dalteg, Gustafsson, & Levander, 1998, Eyestone and Howell, 1994, Rasmussen and Gillberg, 2000

[59] Mannuzza, Klein, & Addalli, 1991, Mannuzza, et al., 1993

[60] Frick, et al., 1994, Lahey, et al., 1995

[61] Siponmaa, et al., 2001

[62] Fazel, et al., 2008

[63] Billstedt and Hofvander, 2012

children diagnosed with ASDs in childhood found no increased risk for later criminality[64], a finding that was mirrored in the follow-up of Hans Asperger's original cohort, which found no overrepresentation of criminality[65]. Autistic traits have been associated with delinquency and reported to predict childhood arrests[66] and CD[67], but whether this reflects co-variation with ADHD or a specific aspect of callous-unemotional traits that may[68] or may not[69] be "autistic-like" is not yet known.

1.4.3 Substance abuse disorders

A recent review[70] showed a higher risk for children with ADHD than for children without ADHD to develop alcohol use disorder, cannabis use disorder, psychoactive substance use disorder, drug use disorder (non-alcohol), and nicotine use by young adulthood and/or by middle adolescence. Wilens[71] reported that 17% to 45% of adults with ADHD also had alcohol abuse or dependence, and 9% to 30% had drug abuse or dependence. The lifetime risk for substance abuse disorders (SUD) in participants with adult ADHD is approximately 50%[72]. There have been suggestions, however, that the relation between childhood ADHD and subsequent SUD could be entirely[73] or partly[74] dependent on comorbid CD, and vice versa.

Knowledge about the comorbidity of ASDs and SUD is sparse and mainly anecdotal, indicating that alcohol and/or drug use is atypical in this group. However a handful of studies from the last years have addressed this question. A Danish study of a birth cohort supported the hypothesis of an inverse relation between ASDs and SUD, with a prevalence of merely 0.7% for alcohol-related disorders in ASDs[75]. Clinical studies, however, have shown a higher prevalence; 11% of individuals with ASDs had a lifetime substance dependence disorder (7% with alcohol, and 7% with drug dependence)[76], and a Dutch study found a total of 29% lifetime SUD in adults who sought treatment

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[64] Lundström, et al., 2014

[65] Hippler, et al., 2010

[66] Geluk, et al., 2012

[67] Lundström, et al., 2011

[68] Soderstrom, et al., 2005

[69] Jones, et al., 2010

[70] Lee, et al., 2011

[71] Wilens, 2007

[72] Bukstein, 2008

[73] Biederman, et al., 2008, Biederman, et al., 1997

[74] Barkley, et al., 2004, Katusic, et al., 2005

[75] Abdallah, et al., 2011

[76] Lugnegård, Hallerbäck, & Gillberg, 2011

for ASDs[77]. Another clinical study supported a very low (3%) lifetime prevalence of substance use in people with ASDs, in this case adolescents at the higher-functioning end of the autistic spectrum[78]. People with comorbid diagnoses of ASDs and SUD also either had a diagnosis of ADHD[79] or showed risk factors commonly found in people with comorbid ADHD and SUD (e.g. beginning smoking early in life, experiencing more adverse family events, having more parental SUD, and being less mature in character[80]). It thus seems that people with more typical ASDs (speech and language difficulties, developmental problems, and troubles with social interaction) are less prone to use alcohol and drugs, while those with coexisting ADHD-like behavior problems have a higher risk for developing abuse of alcohol and/or drugs. A clinical observation is that substance abuse in some people with ASDs may be easier to treat through their autistic rigidity rather than through ordinary addiction treatment.

1.4.4 Affective/mood disorders

Children and adults with ADHD have been shown to be at higher risk for comorbid mood disorders than participants without ADHD[81]. The relative risk (the ratio of the risk in the exposed group, in this case the ADHD group, divided by the risk in the unexposed, non-ADHD group) for children with ADHD to develop depression was 8.0 in the study. Some of the prevalent symptoms in mood disorders overlap with symptoms of ADHD (e.g. psychomotor agitation, restlessness, concentration, and attention problems). Faraone and Biederman[82] argued that ADHD and major depression share familial risk factors. Several studies have since replicated these findings[83].

To diagnose depression, clinicians rely on verbal statements from the patient (often assessed on self-report scales) and clinical assessment of changes in body language and facial expressions. Since introspection, verbal and nonverbal communication of thoughts and feelings are restricted or altered in ASDs, reliable diagnoses of depression are more difficult to achieve in this group. Nevertheless, Hans Asperger's[84] and Leo Kanner's[85] original descriptions included observations of what seemed to be depressive symptoms

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[77] Sizoo, et al., 2010
[78] Santosh and Mijovic, 2006
[79] Santosh and Mijovic, 2006
[80] Sizoo, et al., 2009, Sizoo, et al., 2010
[81] Larson, et al., 2011
[82] Faraone and Biederman, 1997
[83] Cole, et al., 2009, Spatola, et al., 2007
[84] Asperger, 1944
[85] Kanner, 1943

in their patients. Epidemiological studies covering more than 16 000 individuals reported a 10-fold higher incidence of depression in individuals with ASDs compared to those without[86]. It is more common in adults than in children, and in older rather than younger adults. Depression that is etiologically related to ASDs would, however, be more likely to arise in the first half of life, when adjustments are made more difficult by the autism-related deficits.

While it seems obvious that the dysfunctions of ASDs may lead to depression and other mood problems, there is also evidence for shared etiologies behind the disorders that may confound a phenotypical understanding of the link. The incidence of mood and anxiety disorders in relatives of patients with ASDs (with onset prior to the birth of the participant with ASDs) are higher than in both the general population and in families with children who have disabilities other than ASDs[87].

1.4.5 Anxiety disorders

A review[88] reported 15% to 35% of children with ADHD also to have significant anxiety symptoms, even if they pointed to some studies with prevalences as high as 50%. Michielsen and co-workers[89] showed that the comorbidity of ADHD and anxiety often seen in children and adolescents remains into adulthood in patients with a diagnosis of ADHD. Children with comorbid ADHD and anxiety have been reported to have specific neurocognitive problems (decreased impulsivity, increased inattention, longer reaction times, reduced working memory) as well as worse social and academic outcomes[90]. In fact, these findings have been so prominent that a separate subgroup of ADHD with anxiety, separate from the group with ADHD alone, has been proposed[91]. In clinical work the distinction between symptoms stemming from anxiety and symptoms produced by ADHD is an everyday question that still needs to be solved.

The question whether anxiety seen in individuals with ADHD is caused by the difficulties and failures they often face, or whether anxiety and ADHD occur independently has implications for treatment. In the first scenario it might be more efficient to treat the ADHD symptoms first to see whether this also

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[86] Lundström, et al., 2011

[87] Bolton, et al., 1998

[88] Schatz and Rostain, 2006

[89] Michielsen, et al., 2013

[90] Bloemsma, et al., 2013

[91] Jensen, Martin, & Cantwell, 1997, Nigg, Goldsmith, & Sachek, 2004

produces improvement in the anxiety symptoms, while in the latter scenario it might be wise to treat the two conditions independently, and even at the same time. Some studies (e.g.[92]) have found that relatives of participants with comorbid ADHD and anxiety had higher levels of anxiety than relatives of participants with ADHD alone. This could imply that ADHD and anxiety are in fact separate disorders, independently inherited, that should be treated separately.

Leo Kanner[93] recognized substantial symptoms of anxiety in some individuals in his original description of the autistic syndrome. Anxiety was even included as a core autistic symptom in the DSM-III, but it has been removed from the DSM-IV. Instead, the DSM-IV cautions against the diagnosis of some subtypes of anxiety disorders (e.g. generalized anxiety disorder) in participants with ASDs if the symptoms might be better accounted for by the ASDs itself.

A review suggested that the prevalence of anxiety in youth with ASDs is higher than in the general population, and that participants with ASDs experience similar levels of anxiety to those found among groups with clinically diagnosed anxiety disorders[94]. Forty to fifty percent of patients with ASDs have been diagnosed with anxiety disorders[95]. Among the different subtypes of anxiety disorders, specific phobias, social anxiety, and generalized anxiety disorder have frequently been reported as the most common in combination with ASDs[96].

In adults with OCD, 20% had been shown also to have autistic traits[97], and 8% of children with AS and PDD-NOS had OCD[98], while other studies have yielded prevalence figures in a wider range (from 6%[99] to 37%[100]). The prevalence of ADHD in children with OCD has been reported to approximately 10%[101].

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[92] Perrin and Last, 1996

[93] Kanner, 1943

[94] MacNeil, Lopes, & Minnes, 2009

[95] de Bruin, et al., 2007, Simonoff, et al., 2008

[96] van Steensel, Bogels, & de Bruin, 2013

[97] Bejerot, 2006, Bejerot, 2007

[98] Ivarsson and Melin, 2008

[99] de Bruin, et al., 2007

[100] Leyfer, et al., 2006

[101] Rutter, 2008

1.4.6 Eating disorders

The core features of ADHD (inattention, impulsivity, and hyperactivity) have been presented as characteristic for participants with eating disorders (EDs) as well. Impulsivity has been connected to binge-eating problems[102], attention problems to anorexia nervosa (AN) and bulimia nervosa (BN)[103], and hyperactive behavior, such as excessive exercise, with AN[104]. Surman and co-workers[105] found that females with ADHD were at significantly higher risk than controls to have EDs (as well as disruptive behavior, mood and anxiety disorders, and substance dependence). Biederman and co-workers[106] also showed that the lifetime risk of developing an ED is higher in girls with ADHD. Over a follow-up period of 5 years, girls with ADHD were 3.6 times more likely than controls to meet the criteria for any ED and 5.6 times more likely to fulfill criteria for BN[107].

ASDs and EDs, especially AN, share several symptoms. Although not explicitly included among the DSM-IV diagnostic criteria for ASDs, problems in relation to food intake and eating routines are very common in ASDs. (Interestingly, the hyper- or hypo-reactivity to sensory input included in the 1977 National Society for Autistic Children definitions of the syndrome of autism[108] were reintroduced in the DSM-5).

The prevalence of ASD symptoms have been proposed to be elevated in participants with EDs such as AN[109]. In several phases of independent clinical assessments, about 20% of participants with AN were consistently diagnosed with ASDs[110]. There is at least a subgroup among participants with ED who have the same restricted behaviors, insistence on sameness, social interaction problems and deviant neurocognitive profiles (impaired central coherence, impaired set shift ability, rigidity, and impaired theory of mind) as people with ASDs[111]. The converse question, whether EDs are overrepresented in participants with ASDs, has received less systematic study.

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[102] Rosval, et al., 2006, Waxman, 2009

[103] Bosanac, et al., 2007

[104] Hebebrand, et al., 2003

[105] Surman, Randall, & Biederman, 2006

[106] Biederman, et al., 2007

[107] Biederman, et al., 2006

[108] Ritvo and Freeman, 1977

[109] Råstam, 2008, Zucker, et al., 2007

[110] Wentz, et al., 2005, Råstam, Gillberg, & Wentz, 2003

[111] Huke, et al., 2013, Oldershaw, et al., 2011

1.4.7 Psychotic disorders

Attention problems are central to a wide range of diagnoses including psychotic disorders, and attention disturbances are considered core features of schizophrenia. A strong association between the negative psychotic-like symptoms and inattention symptoms, but no association with hyperactivity symptoms, was shown in a sample of 5318 individuals from the general adolescent population[112]. ADHD and schizophrenia have indeed been called two complex disorders of attention [113].

Studies reporting on comorbidity between ADHD and schizophrenia, however, are sparse. Some authors have suggested that ADHD constitutes a proneness to develop psychosis and schizophrenia[114]. First-degree relatives of participants with ADHD have been shown to be significantly more likely to have schizophrenia than non-ADHD controls. This indicates shared genetic factors between ADHD and schizophrenia[115].

The overlap between ASDs and psychotic disorders has been observed by clinicians and scientists for decades. In fact, the name "autism" is adopted from the self-absorbed, withdrawn behaviors of schizophrenic patients described by Bleuler in the early 20th century. Autism has even been proposed as a childhood precursor to adult schizotypal behaviors and its symptoms as "the earliest possible manifestation of childhood schizophrenia"[116].

In the DSM-IV, ASDs and schizophrenia are almost always considered to be mutually exclusive disorders, which has restricted the number of studies addressing the comorbidity of the two conditions.

The co-occurrence of non-affective psychoses in participants with ASDs was reported to range from 0% to 53% in a literature review[117].

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[112] Hurtig, et al., 2011

[113] Barr, 2001

[114] Keshavan, et al., 2003

[115] Larsson, et al., 2013

[116] Kanner, 1943

[117] Padgett, Miltsiou, & Tiffin, 2010

1.4.8 Personality disorders/personality traits

There are several overlapping criteria and clinically observed symptoms between personality disorders (PDs) (mainly in DSM-IV clusters B and C) and ADHD including impulsivity, oppositional behavior, and emotional dysregulation.

Odds ratios of PD in ADHD patients of 1.6, 3.1, and 6.5 for PD clusters A, B and C, respectively have been described[118].

Early clinical studies of children with ASDs reported an overrepresentation of specific personality patterns, alternately described as having Asperger's disorder, a schizoid PD, or a schizotypal PD[119]. There was a striking similarity in features between these diagnoses, especially with regard to lack of empathy, rigid adherence to restricted interests and behavior patterns, communication and interaction problems, and social withdrawal. Epidemiological research into the prevalence of coexisting ASDs and PDs (e.g. schizoid and schizotypal), however, is lacking, but more recent clinical research has shown distinct positive correlations between Asperger's disorder and schizotypal personality traits, especially in the area of social-interpersonal functioning, thus supporting a relation between Asperger's disorder and cluster A personality traits[120].

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[118] Miller, Nigg, & Faraone, 2007
[119] Wolff, 1991a, Wolff, 1991b
[120] Hurst, et al., 2007

2 AIMS

2.1 General aim

The overall aim of this thesis was to describe the actual comorbidity across childhood-onset neuropsychiatric disorders in different clinical groups.

2.2 Specific aims

(1) To define the psychiatric comorbidity in a group of adult patients with ADHD and/or ASDs (Paper I).

(2) To assess the occurrence of PDs and identify personality profiles in a group of adult patients with ADHD and/or ASDs (Paper II).

(3) To identify the psychiatric symptoms associated with aggressive behaviors in adult psychiatric patients (Paper III).

(4) To quantify psychiatric comorbidity in a group of adolescents placed in special youth institutions (Paper IV).

(5) To investigate whether comorbid ADHD and substance abuse are correlated with more negative outcomes with regard to criminal activity, health care needs, and possible early death in adolescents who have been institutionalized (Paper V).

3 PARTICIPANTS

This thesis uses information from the following non-overlapping data sets (no individual could have been included in more than one group): The Gothenburg Neuropsychiatric Genetic Study (NPG, n = 273, the "out-patient study group"), The Gothenburg Forensic Neuropsychiatry Project (n = 100, the "forensic study group"), and Clinical, Actuarial, and Treatment-related prognostic factors in SiS institutions (n = 110, the "adolescent study group").

Figure 1 shows in detail number of participants in each study group and how they were used in the different papers based on the inclusion criteria for each study and the available assessments.
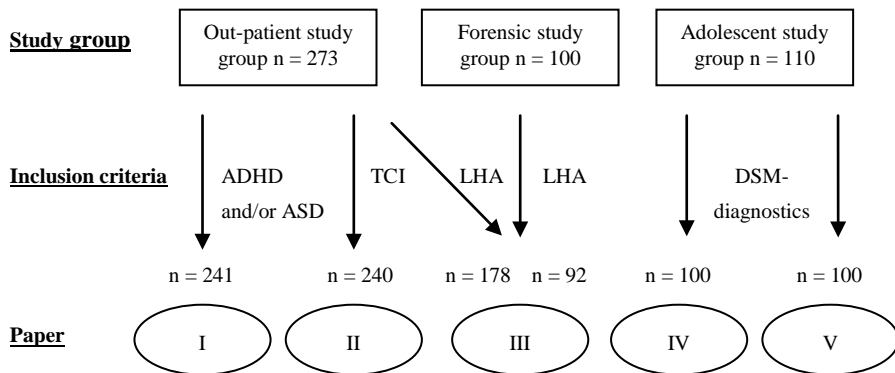
Figure 1. Contribution of participants from each study group to each paper.

3.1 The out-patient study group (Papers I–III)

A consecutive series of out-patients from the Adult Project conducted at the Child Neuropsychiatric Clinic in Gothenburg between January 2001 and April 2003 were recruited to the NPG study. All patients underwent an extensive multi-professional assessment on an out-patient basis. Patients provided clinical data and blood for genetic analyses aimed to establish a large, well-characterized, clinical case group for genetic studies.

The total study group consisted of 273 patients who gave informed consent to take part in the study. In Paper I, all 241 patients who had received a diagnosis

of ADHD and/or ASD were used. In Paper II, 240 participants with a complete Temperament and Character Inventory (TCI[121]) were included. Finally, in Paper III, 178 participants who had completed Life History of Aggression (LHA[122]) protocols were included. Table 1 provides a detailed description of the subgroups derived from the out-patient study group and used in Papers I-III.

Table 1. Basic characteristics of the subgroups derived from the out-patient study group included in Papers I-III.

	Subgroup included in Paper I	Subgroup included in Paper II	Subgroup included in Paper III
Inclusion criteria	ADHD and/or ASDs	TCI	LHA
Number of participants	241	240	178
Males (%)	135 (56%)	131 (55%)	98 (89%)
Females (%)	106 (44%)	109 (45%)	80 (11%)
Mean age (range)	31.5 (19–60)	32.3 (19–60)	32.5 (19–59)
Mean FSIQ[1] (range)	86 (42–134)	88 (42–134)	88 (42–134)
FSIQ ≤ 70	49 (23%)	45 (21%)	36 (21%)
71 ≤ FSIQ ≤ 85	49 (23%)	48 (22%)	40 (23%)
ADHD only	112 (46%)	100 (42%)	80 (45%)
ASDs only	80 (33%)	66 (28%)	45 (25%)
ASDs+ADHD	49 (20%)	47 (20%)	36 (20%)
Not ADHD, not ASDs	0	27 (11%)	17 (10%)

[1]Full-Scale Intelligence Quotient, 212, 218 and 172 patients in Papers I, II, and III respectively were tested with WAIS.

3.2 The forensic study group (Paper III)

One hundred consecutive perpetrators of severe interpersonal crimes (violent crimes in which the life of the victim had been threatened or taken [aggravated assault, aggravated unlawful threat, manslaughter, murder], arson, and sexual offences [rape, aggravated rape against an adult, sexual crime against minors]) referred for pre-trial forensic psychiatric investigation between October 1998

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[121] Cloninger, Svrakic, & Przybeck, 1993

[122] Coccaro, Berman, & Kavoussi, 1997

and February 2001 at the Department of Forensic Psychiatry in Gothenburg were included in the forensic study group. During four week-long in-patient investigations, participants underwent a broad range of clinical and neurobiological assessments conducted by psychiatrists, psychologists, forensic social workers and ward staff, with practically the same protocol as that used in the NPG study for evaluating childhood-onset neuropsychiatric disorders, other mental health disorders, personality, and aggression.

In Paper III, 92 participants from the forensic study group with completed LHA protocols were included. See Table 2 for a detailed description of the subgroup derived from the forensic study group that was included in Paper III.

Table 2. Basic characteristics for the subgroup derived from the forensic study group included in Paper III.

	Subgroup included in Paper III
Inclusion criteria	LHA
Number of participants	92
Males (%)	85 (92%)
Females (%)	7 (8%)
Mean age (range)	34.2 (17–76)
Mean FSIQ[1] (range)	91 (50–150)
FSIQ ≤ 70	17 (22%)
71 ≤ FSIQ ≤ 85	14 (18%)
ADHD only	29 (32%)
ASDs only	8 (9%)
ASDs + ADHD	8 (9%)
Not ADHD, not ASDs	47 (51%)

[1] Full-Scale Intelligence Quotient; 79 participants were tested with WAIS in the subgroup.

3.3 **The adolescent study group (Papers IV–V)**

The adolescent study group consisted of 110 adolescents committed to specialized, state-run, youth institutions in the South West of Sweden between September 2004 and February 2007. All participants were placed in institutions according to three separate laws:

a) Care of Young Persons (special provisions) Act (YPA)[123], applicable if the adolescent, due to his or her behavior or environment, is at risk of coming to harm;

b) Care of Young Offenders Act (YOA)[124], a law that allows courts of law to sentence offenders between the ages of criminal responsibility (15 years) and maturity (18 years) to incarceration in special youth institutions; and

c) The Social Services Act (SSA)[125], a law applied if the adolescent, due to his or her behavior or environment, is at risk of coming to harm and there is consensus between the authorities, the adolescent, and the parents that treatment is needed.

The placement was always the decision of a court of law. Inclusion in the study required that the referring authorities, the court or the Social Services, had requested psychosocial and psychiatric assessments. Adolescents scheduled for no more than a short stay at the institution on an emergency placement were thus not eligible.

All nine special juvenile institutions run by The Swedish National Board of Institutional Care (SiS) in the Swedish region of Västra Götaland were invited to participate in the study. Two of the four institutions that agreed to participate contributed 95 of a total of 103 consecutively committed adolescents meeting the inclusion criteria (rate of consent, 92%). The other two institutions contributed sporadic cases (n = 15), giving a total study group of 110 adolescents.

All participants underwent an extensive assessment using the same basic structure as in the out-patient and forensic study groups, with the alteration that the instruments and methods used were adapted to this younger age group. The assessments were all conducted by specially trained investigation teams,

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[123] SFS 1990:52 Swedish Codes of Statutes, 1990
[124] SFS 1998:603 Swedish Codes of Statutes, 1998
[125] SFS 2001:453 Swedish Codes of Statutes, 2001

and included a psychiatric evaluation by a specialist in psychiatry, an extensive assessment by psychologists including a neuropsychological assessment, and the collection of demographic and psychosocial background factors (including family situation, school achievements, and criminal and substance abuse history) by social workers.

Because only three of the 110 initially included participants were committed according to the SSA[126], these participants were excluded from further analyses. Seven other participants were excluded because of missing DSM-IV data. The final study group thus consisted of 100 participants (92 boys, 8 girls) with complete diagnostic records. The basic characteristics of the adolescent study group included in Papers IV and V are shown in Table 3.

Table 3. Basic characteristics for the adolescent study group included in Papers IV and V.

	Adolescent study group included in Papers IV and V
Inclusion criteria	DSM-IV diagnostics
Number of participants	100
Males (%)	92 (92%)
Females (%)	8 (8%)
Mean age (range)	16.2 (12–19)
Mean FSIQ[1] (range)	85 (45–121)
IQ ≤ 70	11 (11%)
71 ≤ FSIQ ≤ 85	30 (30%)
ADHD only	36 (36%)
ASDs only	6 (6%)
ASDs + ADHD	11 (11%)
Not ADHD, not ASDs	47 (47%)

[1] Full-Scale Intelligence Quotient, 92 participants were tested with WAIS or WISC

126 SFS 2001:453 Swedish Codes of Statutes, 2001

4 METHODS

4.1 Common procedures and measures

4.1.1 Data collection in Papers I–V:

In all study groups, the same principle of collecting information was used, with some adaptations to suit each specific group and clinical setting. The individual diagnoses were based on all available information including clinical status of the patient. Current symptoms were evaluated, as was retrospective information collected from the patients and their relatives to obtain a detailed picture of lifetime psychiatric health and developmental history. The diagnostic process included a lifetime perspective based on all available information received in previous medical records (including, when available, obstetric records, records from pediatric and child psychiatry, and school health services records) and social background files, clinical interviews, collateral interviews, self-rating scales, and information from different psychological tests. In all groups an extensive social investigation was also conducted. Table 4 gives an overview of the different methods and instruments used in the study groups included in each paper.

In the out-patient and forensic study groups diagnoses were assigned by two psychiatrists in consensus, while in the adolescent study group diagnoses were assigned in consensus after discussion by one or two of the consultant psychiatrists with the investigation team. Because the study groups consisted of either adolescents or adult patients, information on their developmental history, as well as lifetime occurrence of various symptoms, was collected retrospectively with multiple sources of information. To allow for a comprehensive description of comorbidity, DSM-IV criteria limiting the possibility of assigning multiple diagnoses were disregarded to allow a recording as complete as possible of all diagnostic criteria that were fulfilled.

Table 4. Description of the methods used in the different study groups presented in this thesis.

Measures used	Out-patient study group (n = 273)	Forensic study group (n = 100)	Adolescent study group (n = 100)
SCID-I	201	89	Not applicable
SCID-II	174	74	Not applicable
LHA	178	92	Not applicable
TCI / J-TCI	234	78	76
WAIS/WISC	241	81	92
DSM-IV checklist	263	100	100
ASSQ	185	86	Not applicable
ASDI	226	89	100
GAF	266	100	Not applicable
ADAD	Not applicable	Not applicable	100
Register data on crime	Not applicable	Not applicable	100
Register data on health care services use	Not applicable	Not applicable	100

4.1.2 The overall clinical diagnostic interview

In the out-patient and forensic study groups, The Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I[127]) was used to evaluate Axis I categorical diagnoses according to DSM-IV[128]. PDs were assessed in the majority of cases using the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II[129]) and, in some cases, a DSM-IV based clinical interview.

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[127] First, et al., 1997a
[128] American Psychiatric Association, 1994
[129] First, et al., 1997b

In the adolescent study group the Autism Spectrum Screening Questionnaire (ASSQ)[130], the Asperger Syndrome (and high-functioning autism) Diagnostic Interview (ASDI)[131], and ADHD DSM-IV checklists (in content equivalent to SCID-I) were used in most cases as a part of the normal assessment routine at the institutions together with a DSM-IV lifetime checklist especially developed for the project.

Since ADHD and ASDs are not assessed in the SCID-I, the following specific checklists addressing the DSM-IV criteria for these disorders were used:

a) ASSQ, a brief screening questionnaire for the identification of ASDs in people with normal intelligence or mild mental retardation, meant to be completed by lay informants;

b) ASDI, a structured clinical interview/observational manual for collecting information according to the 6 Gillberg & Gillberg criteria and assessing each criterion for a diagnosis of Asperger's disorder. All available information was used to determine which of the DSM-IV criteria that were fulfilled;

Syntaxes were written in SPSS to assign ASD diagnoses based on the number and distribution of the criteria fulfilled. A diagnosis of autistic disorder was assigned if the total number of fulfilled DSM-IV criteria was 6 or more, and the total number of fulfilled criteria in the A1 section (qualitative impairment in social interaction) of autistic syndrome was 2 or more, in the A2 section (qualitative impairment in communication) of autistic syndrome was 1 or more, and in the A3 section (restricted, repetitive, and stereotyped patterns of behavior, interests, and activities) of autistic syndrome was 1 or more.

A diagnosis of Asperger's disorder was assigned if the total number of fulfilled DSM-IV criteria was 4 or more, and the number of fulfilled criteria in the A1 section of autistic syndrome was 2 or more, and in the A3, 1 or more. A diagnosis of PDD-NOS was assigned if the total number of fulfilled DSM-IV criteria was 4 or more (irrespective of the distribution).

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130 Ehlers, Gillberg, & Wing, 1999
131 Gillberg, et al., 2001

Using a hierarchical structure, a diagnosis of autistic disorder or Asperger's disorder excluded PDD-NOS, and a diagnosis of autistic disorder excluded Asperger's disorder. To assess the pattern of comorbidity, the F criteria for Asperger's disorder (i.e. criteria for another pervasive developmental disorder or schizophrenia are not fulfilled) was disregarded.

An ADHD checklist for DSM-IV diagnostic criteria fulfilled in childhood and at the investigation time was compiled specifically for each project.

As with the ASD diagnoses, all available information was used to determine the criteria fulfilled for ADHD (combined type, AD, or HD). ADHD combined type was assigned if 6 or more criteria were fulfilled on both the DSM-IV A1 and the DSM-IV A2. AD and HD were assigned if 6 criteria or more were fulfilled only on the A1 or the A2, respectively. To assess the pattern of comorbidity, the E criteria for ADHD (i.e. the symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder, or are not better accounted for by another mental disorder) was disregarded.

4.1.3 Assessment of global functioning

In the out-patient and forensic study groups, social, occupational, and psychological functioning was assessed with the Global Assessment of Functioning (GAF[132]) scale. The GAF scale constitutes Axis V of the multi-axial assessment of the DSM-IV system. The scale ranges from 0 (lowest level of functioning) to 100 (highest).

4.2 Study-specific measures

4.2.1 Paper II: TCI

The Temperament and Character Inventory (TCI[133]) is a 240-item self-report questionnaire for personality traits. The respondent has to answer true or false to all of the 240 statements. The items are organized into 7 personality dimensions divided into four temperaments (Novelty Seeking [NS], Harm Avoidance [HA], Reward Dependence [RD] and Persistence [P]) and three character dimensions (Self-Directedness [SD], Cooperativeness [CO] and Self-Transcendence [ST]). The temperament and character dimensions are further divided into several subscales. Low scores in the character dimensions are taken as signs of character immaturity which is a prerequisite for diagnosing a

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[132] American Psychiatric Association, 2000

[133] Cloninger, Svrakic, & Przybeck, 1993

PD, where the configuration of the temperament dimensions (high or low) determines the type of PD. The raw scores were converted to T-scores with a mean of 50 and a *SD* of 10 according to published Swedish norm data[134]. A total raw score of 62 or more in SD and CO has been suggested to indicate character maturity[135].

4.2.2 Paper III: LHA

The Life History of Aggression (LHA[136]) is a questionnaire (self-rated, or rated by health professionals or collateral informants) covering 11 aspects of aggressive behavior, subdivided into 3 subscales: 1) aggression expressed towards others (temper tantrums, physical fights, verbal aggression, physical assaults on other people or animals, assault on property), 2) self-directed aggression (self-injurious behavior, suicide attempts), and 3) antisocial behaviors involving disciplinary action (school disciplinary problems, problems with supervisors at work, antisocial behavior with or without the involvement of the police). Each item is rated 0–5, with a maximum possible total score of 55 and maximum scores of 25, 20, and 10 on subscales 1, 2 and 3, respectively.

4.2.3 Papers IV and V: Psychological tests

The Wechsler scales (Wechsler Intelligence Scale for Children III [WISC-III[137]]) or Wechsler Adult Intelligence Scale third edition [WAIS-III[138]]) were used to assess the cognitive profiles in all study groups. The results collected by the psychologists reported in Paper IV concentrated on the neurocognitive profiles. The WISC and WAIS are frequently-used to assess cognitive functions and intellectual capacity in children and adolescents (WISC-III, 6-16 years) and adults (WAIS-III, 16–75 years). They consist of several subtests (14 in WAIS-III and 13 in WISC-III) designed to pinpoint a broad range of cognitive functions. The test scores are summed into composite scores of intelligence (full scale intelligence quotient [FSIQ], verbal intelligence quotient [VIQ], and performance intelligence quotient [PIQ]) and into index scores (in WISC-III, the verbal comprehension index [VCI], perceptual organization index [POI], freedom from distractibility index [FDI], processing speed index [PSI], and in WAIS-III the verbal comprehension index [VCI], perceptual organization index [POI], working memory index [WMI], and processing speed index [PSI]).

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[134] Brändström, et al., 1998

[135] Cloninger, 1994

[136] Brown, et al., 1982, Coccaro, Berman, & Kavoussi, 1997

[137] Wechsler, 1991

[138] Wechsler, 1997

4.2.4   Paper V: Assignment of groups

Based on whether or not they had a history of alcohol and/or other substance and/or a diagnosis of ADHD, the participants were assigned to 1 of 3 groups: substance use disorder group with ADHD (the SUD/ADHD group, n = 25), substance use disorder group without ADHD (the SUD group, n = 30), and the non-substance use disorder group (the non-SUD group, n = 45). In the last group, in 34 cases substance abuse was clearly ruled out and in another 11 cases the status was somewhat unclear, but none of the accessible information showed any sign of substance abuse. These 45 participants are referred to as the non-SUD group (n = 45). 22 participants (49%) in the non-SUD group had ADHD. The calculations of group differences were all based on this grouping principle.

4.2.5   Paper V: Data on criminality

In Paper V registered data on lifetime convictions in courts of law was requested from the Swedish National Council for Crime Prevention. The data received included dates of conviction(s), types of crime(s), sections of law applied in each case, type and length of sanction(s), and possible pre-trial forensic assessment. All convictions for patients were also requested from each court, providing information about single charges and circumstances of the crime(s). Using the date of conviction, the description of the sentence, or a combination of both, together with the date of inclusion into the study, each crime ending in a sentence was characterized as a crime committed prior to, concurrent with, or after inclusion in the study.

Every conviction following a previous conviction was coded as a relapse (participants with convictions thus could have 0, 1, or more than 1 relapses).

4.2.6   Paper V: Data on use of health care services

In Paper V all available data from the National Board of Health and Welfares National Patient Register and Cause of Death Register was also requested. The National Patient Register includes cause of visit to hospital, date, length of stay, and diagnoses given for all episodes of in-patient treatment, while the Cause of Death Register consists of data on death and its underlying cause. No data regarding out-patient treatment are available from this register. The variables include primary (ranging from 0 to 8) and secondary (ranging from 0 to 3) diagnoses according to The International Classification of Diseases- tenth edition (ICD-10[139]), date of treatment, length of hospital stay, type of treatment, and deaths. Episode length was coded as full days, with episodes

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[139] World Health Organization, 1992

shorter than 24 hours coded as one full day. Discharge diagnoses were first allocated to one of the broader ICD-10 categories based on the ICD-code and these categories were further collapsed into one of three categories: psychiatric, drug-related, or "other" diagnoses. In this way, 2 levels (primary and secondary diagnoses) and 3 sub-levels of diagnoses (psychiatric, drug-related, and other) were extracted from the data-file.

4.3 Analytical methods

The statistical methods used were either parametric or non-parametric depending on the sample size and whether data were normally distributed. All statistical analyses were performed using SPSS. In all analyses, two-tailed *p* values were used, commonly with a *p* equal to .05, but in cases where variables in regression analyses were identified, *p* equal to .10 was used.

In Paper I, groups were compared regarding differences in WISC/WAIS and GAF scores (continuous dependent variables) using Mann-Whitney U test, while the distribution of diagnoses (discrete dependent variables) were analyzed with Fisher's exact test.

In Paper II, the T-scores of the TCI temperament and character dimensions were compared to the expected population mean score of 50 with a *SD* of 10 by one-sample t-test. This test was used for the whole group as well as for the diagnostic subgroups.

In Paper III, the distribution of discrete variables among groups was tested with χ^2 tests, while the comparisons of continuous variables (age, FSIQ, different LHA scores) between groups were made with Mann-Whitney U tests. Spearman's rank correlations were used to test the co-variation between LHA scores and symptoms of childhood-onset neuropsychiatric disorders, FSIQ, and drug abuse. Multiple linear regression analysis models were used to identify clinical and demographical predictors for a high total LHA score. First all variables with $p < .30$ in the bivariate correlation analyses were tested in the regression analysis, and then one insignificant variable at a time was excluded until all the remaining variables had $p < .10$. The adjusted amount of explained variance (R^2) and standardized regression coefficients (β) were calculated with analysis of variance and t statistics respectively.

In Paper IV, χ^2 tests for independence (with Yates continuity correction) and Mann-Whitney U tests were used to test between-group differences in discrete and continuous variables respectively.

In Paper V, χ^2 test and Fisher's exact test were used to explore differences between groups on non-normally distributed discrete variables, and Kruskal-Wallis test was used for non-normally distributed continuous variables. ANOVA was used for normally distributed continuous variables. Correlations between variables were assessed with Spearman's rank correlation coefficient. Logistic regression analysis was used to identify factors associated with persistence in violence and general criminality and receiver operating characteristics (ROC) analysis was used to evaluate the predictive ability of single variables on persistence in criminality. The inflection points of the area under the ROC curve (AUC) were used to calculate specificity and sensitivity, the positive predictive value (PPV), and the negative predictive value (NPV) for each factor tested.

4.4 **Power analyses**

Because we used a descriptive study design in the groups included in this thesis, we did not have any pre-hoc defined primary or secondary target variables and we could not make any power estimates. Instead a strategy based on consecutive inclusion was used in order to include as many participants as possible in a given time-period without any pre-hoc plan of tests to use or questions to be answered. The overall purpose of the data collection was to produce the largest sample possible of well-diagnosed and clinically defined groups to provide rich comparative data, not to answer any pre-formulated research questions or to test specific hypotheses, but to carry out comparisons on clinically well-characterized diagnostic groups with a high ecological validity to further our understanding of patterns of comorbid symptoms and dysfunctional behavior among individuals with the studied diagnoses.

A power analysis gives an assumption of how likely a statistic test is to detect a given effect under the particular situation at hand and to decide on what sample size is needed to detect a given effect with a chosen precision and the other way round; how precise will the estimates be if a certain sample size is selected. This is of course of crucial importance if conclusions regarding a whole population is to be drawn from a small sample on a certain condition. We almost always are interested in reducing the sample size in order to gain time and money and in most cases it is not practically doable to sample the whole population.

Power analyses refer to address the risk of type II errors (the risk of false negative errors, β), while test of mass significance address the risk of type I errors (false positive errors, α). False negative errors occurs when we assume there is no difference or association between groups when there actually is one

(accepting a false null hypothesis) and false positive errors occur when we claim a difference to be present which in fact does not exist (rejecting a true null hypothesis). In clinical settings it is more fatal to make a type I error (for example stating that a certain medicine has effect while it in fact is useless or claiming a person with a disease to be healthy) and therefore the acceptance of type I errors are much lower than for type II errors (for example stating that a healthy person has a certain disease).

4.5 **Ethical aspects**

All studies in this thesis were approved by the Research Ethics Committee at the University of Gothenburg (Studies I, II, and III: Dnr L 446–98+Ö 586–99, Study III; Dnr L 400–98, and Studies IV+V: Dnr Ö 545–01). The participants received written and oral information about the studies and they all gave consent to use the data (or parts of it) for research purposes. For participants younger than 15 years of age, custodial consent was requested. The participants were also informed about their right to withdraw their consent at any time without any influence on their treatment process or, in the forensic and adolescent study groups, the outcome of their legal processes. No one received any financial compensation for participation. Finally, all data were handled with care and the actual working data sets were made anonymous by using codes instead of recognizable personal data. The original coded paper-versions of the data are still traceable to each individual according to a linking code key kept in a separate safety box.

The forensic and adolescent study groups presented particular concern from an ethical point of view since they were both patients and subjected to legal measures simultaneously. An informed consent requires decision competence and should be delivered freely without any form of pressure. The decision whether or not to participate in a research study under such circumstances may be influenced by the thought that participation might favorably influence their psychiatric evaluation, or conversely, that the data collected in the study might result in negative consequences.

These circumstances called for a clear separation between the process of the law, the process of collecting research data, and the process of performing clinical patient-oriented work. There is always a risk of conflict attending both to the research task and to the duty to do what is best for a potential patient when a researcher functions also as a clinician. It is an important and delicate matter to balance and maintain the participants' right to integrity and the potential scientific and societal gains of the study.

The potential disadvantages for the participants must be weighed against the potential advantages of gaining knowledge, knowledge that in the future can be used to help people in the same situation.

Given these considerations we took care to explain that the research results and the collecting of data would have no influence over decisions regarding the patients' psychiatric evaluation, discharge, or treatment.

4.6 **Gender aspects**

Both the forensic and adolescent study groups contained a low percentage of females ($< 10\%$), while the out-patient study group had a more equal sex ratio. All studies used a strategy of consecutive inclusion and the distribution of men and women reflects the overrepresentation of male participants in the forensic settings. The distributions are also typical for studies in this field. Of course, it would be desirable to obtain a better match between the number of women and men in future studies. To include a larger percentage of women would, however, require a significantly extended study period. In such studies, it would also be interesting to get a better understanding of the extreme over- and under-representation of certain aspects and variables connected to gender.

5 RESULTS

5.1 Prevalence and comorbidity between ADHD/ASDs and bipolar and/or psychotic disorders (Paper I)
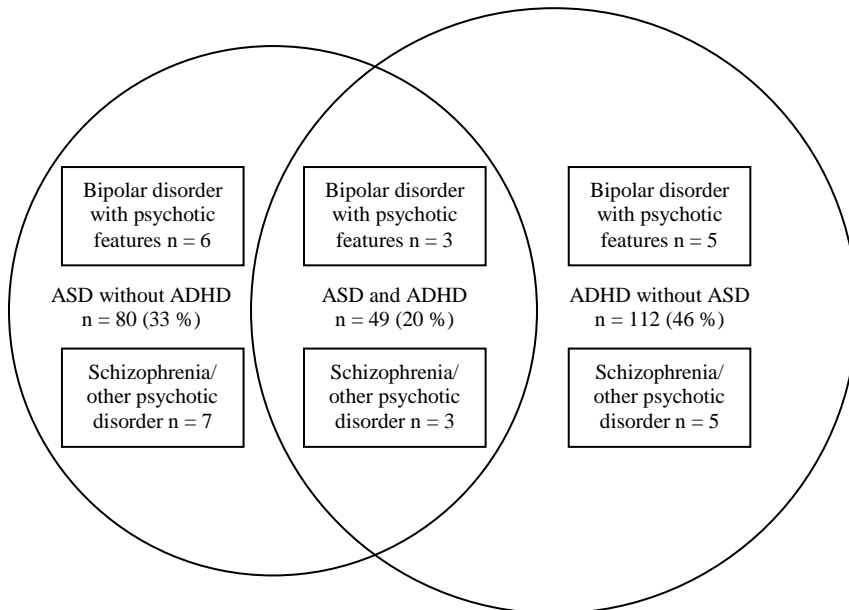
Figure 2. Distribution of diagnoses in the out-patient study group. Only participants with ASDs and/or ADHD are included.

Among 241 adults (135 men, 106 women) referred for assessment of possible childhood-onset neuropsychiatric disorders, 80 participants (33%; 50 men, 30 women) fulfilled DSM-IV criteria for ASDs, and another 112 (46%; 56 men, 56 women) fulfilled the criteria for ADHD. Of the 241 patients, 49 (20%; 29 men, 20 women) had both ADHD and ASDs. This means that 38% of the participants with ASDs also met criteria for ADHD, and that 30% of the participants with ADHD also met criteria for ASDs. A total of 161 participants (67%) had ADHD with or without comorbid ASDs, and 129 participants (54%) had ASDs with or without comorbid ADHD.

In addition, 14 of these participants also had a bipolar disorder with psychotic features, 4 had schizophrenia, and 11 had other psychotic disorders. Among

the participants with ASDs, 7% had bipolar disorder and 8% had a psychotic disorder. The corresponding figures for the patients with ADHD were 5% and 5% (see Figure 2 for a presentation of the distribution of these comorbid disorders). Participants with comorbid psychotic conditions had lower GAF scores than participants without such comorbidity.

Women more often displayed mood disorders and men more often schizophrenia or psychotic disorders.

5.2 Personality development in ADHD/ASDs (Paper II)

5.2.1 SCID-II

Participants with both ADHD and ASDs had the highest rates of DSM-IV PDs (85% fulfilled the criteria for at least 1 PD, compared to 42% in the group without ADHD or ASDs). Borderline PD (BPD) was most common in ADHD and obsessive-compulsive PD in ASDs. A total of 130 (75%) of the 174 participants for whom the SCID-II was completed met criteria for at least one PD, and 80 (46%) fulfilled criteria for more than one category of PD. Table 3 in Paper II gives a comprehensive description of the prevalences and distributions of PDs in the different ADHD and/or ASDs subgroups.

There were no significant differences in the distribution of men and women, the percentage of participants with MR, mean FSIQ, or mean age between the groups with (n = 44) and without (n = 130) PD.

5.2.2 TCI

Self-rated personality traits as measured by the TCI differed dramatically from those reported in the general population. The group with both ADHD and ASDs had significantly increased scores for the temperament dimensions Novelty Seeking (i.e. displayed more impulsivity, monotony avoidance, exploratory excitability etc.) and Harm Avoidance (i.e. were more prone to worrying, were more prone to avoiding uncertainty, had lower confidence, etc.), and significantly lower scores for Reward Dependence (displayed less social attachment and were more distanced from others). High Harm Avoidance, especially Fatigability, Asthenia, and Anticipatory worry, were also a prevalent finding in both the ADHD only group and the ASD only group. The different diagnostic groups had distinctive temperamental profiles: ADHD only was mainly associated with high Novelty Seeking, while ASDs only was associated with low Novelty Seeking and low Reward Dependence, especially in Sentimentality and Attachment. Patients who had both ASDs and ADHD had more ADHD-like temperaments and lower character scores than participants with ASDs only. The temperament and character T-scores for the different groups are presented in Table 5.

All groups also displayed extremely low scores for the character dimensions Self-directedness (internalized locus of control, maturity, goal orientation, responsibility) and Cooperativeness (tolerance, helpfulness, compassion, and high ethical principles), strongly indicating a high rate of clinically significant PDs. Only 35 participants (15%) had a total raw score of 62 or more on these character dimensions. Patients diagnosed with ADHD had even lower character scores than participants with ASDs.

Table 5. Description of T-scores in the temperament and character dimensions and the number of participants with character maturity in participants with ADHD, ASDs, ADHD plus ASDs, none of the disorders, and the whole group.

	ADHD only	ASD only	ADHD+ASD	No ADHD, no ASD	Whole group
	(n = 100)	(n = 66)	(n = 47)	(n = 27)	(n = 240)
NS[1], mean (± *SD*)	59.2 (10.9)**	45.8 (10.4)**	53.9 (11.7)*	50.6 (14.0)	53.5 (12.6)**
HA[2], mean (± *SD*)	63.4 (12.1)**	66.4 (11.6)**	62.1 (12.2)**	61.4 (11.4)**	63.7 (12.0)**
RD[3], mean (± *SD*)	46.2 (12.5)**	41.7 (12.6)**	45.7 (10.6)**	44.4 (12.4)*	44.7 (11.5)**
P[4], mean (± *SD*)	50.2 (10.1)	51.6 (12.6)	52.2 (10.2)	51.5 (10.2)	51.1 (10.8)
SD[5], mean (± *SD*))	29.0 (12.5)**	37.6 (12.8)**	33.1 (15.1)**	35.4 (15.6)**	32.9 (13.7)**
CO[6], mean (± *SD*)	35.2 (17.5)**	38.6 (16.4)**	35.3 (18.0)**	42.1 (14.1)**	37.0 (17.0)**
ST[7], mean (± *SD*)	55.1 (13.0)**	51.8 (14.2)	54.4 (12.9)*	50.0 (11.3)	53.5 (13.2)**
Character maturity[8] mean (± *SD*)	44.8 (12.9)**	49.9 (13.3)**	44.8 (13.8)**	53.0 (11.0)**	47.1 (13.3)**
Number of participants with character maturity[9] (%)	13 (13%)	11 (17%)	4 (8%)	7 (26%)	35 (15%)

[1] Novelty Seeking, [2] Harm Avoidance, [3] Reward Dependence, [4] Persistence, [5] Self-directedness, [6] Cooperativeness, [7] Self-Transcendence, [8] sum of raw scores for SD and CO, [9] sum of raw score for SD and CO ≥ 62 (indicating character maturity), * significant difference from the population mean (one-sample t-test) are indicated with * ($p < .05$) and ** ($p < .01$). Note: the *T*-score in the general population is 50 [$SD \pm 10$] on each dimension.

5.3 The relation of LHA scores and psychiatric disorders in adulthood (Paper III)

LHA total scores, as well as the Aggression and Self-directed aggression sub-scores, were all as high in the out-patient group as in the forensic group, while the Antisocial behavior sub-score was significantly higher in the forensic group.

In both groups, participants with ADHD had higher aggression scores than participants with ASDs. When calculated in the two groups together, aggression correlated most positively with the number of HD criteria met in childhood and with CD before age 15, and most negatively with the GAF scores.

In addition to the strong association between aggression score and ADHD, a negative correlation of aggression score with autistic traits in the out-patient study group contrasted with a positive correlation between aggression score and autistic traits in the forensic study group. Antisocial behavior was negatively correlated to autistic traits in the out-patient group, while a positive correlation was found in the forensic group. Conduct problems were strongly correlated with all LHA scores in both groups. For a more comprehensive presentation of univariate correlations, see Table 6.

Table 6. Correlations (Spearman's rho, two-tailed) between LHA scores, ADHD-scores, number of autistic criteria fulfilled and number of SCID-II criterion C fulfilled.

		Attention deficits	Hyperactivity	Autistic symptoms	Conduct problems
LHA Total score	Whole group	0.39**	0.48**	-0.07	0.65**
	Forensic group	0.41**	0.50**	0.33**	0.55**
	Out-patient group	0.41**	0.49**	-0.24**	0.74**
LHA Aggression score	Whole group	0.38**	0.48**	-0.06	0.55**
	Forensic group	0.38**	0.46**	0.27**	0.53**
	Out-patient group	0.38**	0.49**	-0.26**	0.66**
LHA Self-directed score	Whole group	0.13	0.19	-0.04	0.38**
	Forensic group	0.13	0.20	0.28**	0.27*
	Out-patient group	0.18*	0.21**	-0.04	0.48**
LHA Antisocial behavior	Whole group	0.34**	0.40**	-0.13	0.67**
	Forensic group	0.44**	0.50**	0.29**	0.56**
	Out-patient group	0.42**	0.44**	-0.20**	0.71**

* Correlation is significant at the 0.05 level
** Correlation is significant at the 0.01 level

In a linear regression model, conduct problems before the age of 15, childhood hyperactivity, drug abuse/dependence, and low Cooperativeness in TCI were found to be the most important clinical covariates of LHA total scores explaining 50% and 49% of the variance in the out-patient and forensic groups respectively.

5.4 Mental health problems in adolescents committed to juvenile institutions (Paper IV)

Forty-seven percent of the patients had ADHD (33% combined form, 11% AD and 3% HD) and another 17% had some kind of ASDs (5% autistic disorder, 5% Asperger's disorder and 7% PDD-NOS). Eleven percent fulfilled criteria for both ASDs (any form) and ADHD (any form). Twenty-three percent of those with ADHD thus had ASDs, and 65% of those with ASDs fulfilled criteria for ADHD.

When excluding drug abuse and CD, 73% of the participants fulfilled criteria for at least one major DSM-IV diagnosis, and 41% fulfilled criteria for at least 2 diagnoses.

In the group with ADHD (n = 47) 6 patients (13%) had MR, 6 (13%) had psychotic symptoms, 14 (30%) had depression, 6 (13%) anxiety disorder, 36 (77%) CD, and 25 (53%) SUD. The corresponding figures for participants with ASDs (n = 17) were 3 (18%), 6 (35%), 7 (41%), 6 (35%), 15 (88%), and 8 (47%), while the same figures for the group without ASDs and without ADHD (n = 47) were 5 (11%), 4 (8%), 4 (8%), 9 (19%), 35 (74%), and 25 (53%).

Overall, more than one in four (27%) of the participants had a severe mental disorder (ASDs, MR, and/or psychotic disorder) which would make them entitled to special assistance according to the Swedish legislation. The overall proportion of individuals in need of psychiatric specialist treatment (ADHD, ASDs, MR, psychotic disorder, and/or complicated depression) was 63%.

5.5 Comorbid ADHD and SUD, and longitudinal patterns of criminality and health care needs (Paper V)

5.5.1 Criminal pattern

The only differences found between the SUD/ADHD, SUD, and non-SUD groups in the baseline characteristics were the follow-up time in months (significantly longer follow-up for the SUD/ADHD group than the non-SUD group), gender (a dominance of males in the two groups of SUD/ADHD and SUD), substance abuse/dependence among primary relatives (the highest frequency was found in the SUD group and the lowest in the non-SUD group), and IQ (lower IQ in the non-SUD group than in the groups of SUD/ADHD and SUD).

There were almost no significant differences between the three diagnostic groups during follow-up in number of convictions and criminal behavior except for self-reported age of onset of criminality (the SUD/ADHD group reported almost 2 years earlier onset than the SUD and non-SUD groups), the total number of charges for criminal acts in all convictions (the SUD/ADHD group had on average more than double the charges of the non-SUD group), and the total number of criminal acts that were carried out alone (again, the SUD/ADHD group had more than double the criminal acts of the SUD and non-SUD groups).

5.5.2 Health care use

A total of 46 individuals (46%) received in-patient health care treatment during the follow-up period (mean number of days treated in hospital was 8.5 and the mean number of treatment episodes was 2.0). There was no difference among the 3 groups regarding number of days treated in hospital. The non-SUD group received significantly fewer drug-related diagnoses than the other 2 groups, but there were no other differences in the diagnostic panorama (psychiatric, drug-related, or other diagnosis) between the groups.

During the follow-up period, 2 patients were found to have died (one by suicide and one by unspecified intoxication poisoning). One of the deceased belonged to the SUD/ADHD group and the other to the SUD group. There was a much higher death rate in the total study group than in the same age group in Sweden during the years for which they were followed.

6 SUMMARY OF MAIN FINDINGS

1. ADHD and ASDs often coexist with each other, with other childhood-onset neuropsychiatric disorders, and with bipolar and psychotic disorders in adults (Paper I).

2. Participants with ADHD scored high in TCI Novelty Seeking and Harm Avoidance, while participants with ASDs score low in Novelty Seeking and Reward Dependence and high in Harm Avoidance. Both groups score extremely low in Self-directedness and Cooperativeness, corresponding to a PD according to the TCI. ADHD and ASDs often coexist with DSM-IV Axis II PDs, especially borderline PD in ADHD and obsessive-compulsive PD in ASDs (Paper II).

3. The levels of aggression measured by the LHA are as high in an out-patient group of patients referred for assessment of neuropsychiatric disorders as in a group of offenders referred to pre-trial forensic psychiatric investigation in connection with violent crimes. Total LHA scores are associated with the hyperactive component of ADHD, CD, SUD, and low scores of Cooperativeness, but not with ASD traits (Paper III).

4. ADHD and ASDs are highly prevalent among Swedish adolescents in special youth care, affecting at least one out of two (Paper IV).

5. The SUD plus ADHD group, the SUD group, and the non-SUD group are identical in almost every respect studied except in terms of substance abuse/dependence among primary relatives (highest frequency in the ADHD plus SUD group), IQ (lower IQ in the non-SUD group), and number of charges in each conviction (highest in the ADHD plus SUD group), as well as number of criminal acts carried out alone (highest in the ADHD plus SUD group). (Paper V).

7 DISCUSSION

The works included in this thesis focuses on the comorbidity between childhood-onset neuropsychiatric disorders and other psychiatric disorders as seen in different clinical patient groups of different ages. The overall prevalence of these disorders is high and the pattern of comorbidity is complex, cutting across different patient groups and affecting participants significantly.

7.1 Comments on main findings

7.1.1 ADHD-ASDs and major mental disorders

Paper I showed a considerable overlap between ADHD and ASDs in a group of patients referred for neuropsychiatric assessment (approximately one fifth of the participants had both ADHD and ASDs). Although much larger than would be expected from baseline population prevalence figures, this higher overlap is not surprising in a selected group of patients with a higher likely prevalence of these two disorders. Community-based[140] and clinical studies[141] have consistently shown a considerable overlap between these disorders, also supporting the notion that they share a true comorbidity. The data supporting a partly common heritability for these two conditions have grown to the point that the exclusion criteria have been removed in the new DSM-5[142]. A growing body of literature on this comorbidity has in fact shown a very unspecific symptomatology in early years in patients who later develop ADHD and/or ASD. This lack of early specificity is behind the newly minted concept Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examination (ESSENCE)[143] that is based on the fact that early signs of deviant development warrant early attention and a multidisciplinary and broad investigation, including assessment for ADHD and ASDs.

The second main finding in Paper I was a large overrepresentation of psychotic disorders in both the ADHD and the ASD group. Since the early 1970s, schizophrenia and psychotic disorders were considered incompatible with ADHD and ASDs, reflected in the mutual exclusion criteria in DSM-IV.

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[140] Leyfer, et al., 2006, Lichtenstein, et al., 2010

[141] Gadow, DeVincent, & Pomeroy, 2006, Goldstein and Schwebach, 2004, Rao and Landa, 2014

[142] American Psychiatric Association, 2013

[143] Gillberg, 2010

Since the publication of Paper I, several studies have supported comorbidity across ADHD, ASDs, and adult major mental disorders[144]. While the exclusion criteria for schizophrenia have been removed in the DSM-5 in a diagnosis of ASD, it still remains in the case of ADHD[145].

7.1.2 Personality

Findings in Paper II indicate that both ADHD and ASDs are characterized by certain specific temperament profiles in the TCI. These findings are in line with studies showing specific personality profiles in ADHD[146] and ASDs[147]. It was further found that both participants with ADHD and those with ASDs were characterized by extremely low scores on the two TCI character scales of Self-Directedness and Cooperativeness, reflecting a low level of character maturity. Hence the personality profiles in each of the ADHD and ASD groups expressed character immaturity, while participants with a combination of ADHD and ASDs had the most pronounced immaturity. It can be concluded that patients with both ADHD and ASDs are characterized overall by features consistent with what is expected in the PDs. This was further illustrated by the high prevalence of PDs measured by the SCID-II interviews. Some studies have argued that the personality profile of patients with both BPD and ADHD is characterized by character immaturity, while the profile of those with ADHD alone is not[148]. However, the majority of contemporary studies are in line with ours, indicating that character immaturity may be characteristic for clinical groups of participants with ADHD and/or ASDs[149].

7.1.3 Aggression

The high level of disruptive behaviors (criminality and aggression) found in patients with ADHD has been described repeatedly and has often been shown to be connected to comorbid CD and adult ASPD[150]. It has also been shown that ASDs combined with comorbid disorders such as psychotic symptoms,

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[144] Gadow, 2013, Padgett, Miltsiou, & Tiffin, 2010, Rapoport, et al., 2009, Skokauskas and Gallagher, 2010

[145] American Psychiatric Association, 2013

[146] Kerekes, et al., 2013, Nigg, et al., 2002, Ranseen, Campbell, & Baer, 1998

[147] Austin, 2005, Kerekes, et al., 2013, Wakabayashia, Baron-Cohen, & Wheelwright, 2006

[148] van Dijk, et al., 2012

[149] Faraone, et al., 2009, Garcia, Anckarsäter, & Lundström, 2013, Kerekes, et al., 2013, Sizoo, et al., 2009, Soderstrom, Rastam, & Gillberg, 2002

[150] Lundström, et al., 2014, Satterfield, et al., 2007

SUD, and ADHD, can constitute a problematic constellation with often stress-related aggression[151].

The findings in Paper III add to this knowledge by showing that the level of aggression measured by the total score on the LHA was equally high in a group of out-patients referred for neuropsychiatric assessment and in a group of participants convicted for violent crimes and referred to a pre-trial forensic evaluation. The only significant difference between these groups in LHA scores was a higher antisocial behavior subscale score in the forensic group. Furthermore it was found that the level of aggression was not connected to autistic traits in the outpatient group. This result is in line with some previous studies in which ASD symptoms were not associated on the group level with aggression, although subgroups may have exhibited increased levels of aggression[152]. Other studies have shown that there might be a connection between ASDs, aggression, and criminality, at least for a subgroup of people who have atypical autism, given that people with ASDs are overrepresented in high security hospitals and among offenders[153].

7.1.4 Institutionalized adolescents

The lifetime prevalence of ADHD in young offenders has been reported to be around 45%[154], comparable to the prevalence of 47% presented in Paper IV. This figure is thus consistent with international figures.

Since only a restricted number of studies specifically report the prevalence of ASDs in young offenders in general and in youth institutions in particular the figures presented in Paper IV have to be interpreted with caution. The 17% prevalence of ASDs in our study group is higher than the 8.3% reported in a group of Swedish adolescent criminal offenders referred to pre-sentence forensic psychiatric investigation[155] but very close to the 15% prevalence of PDD in another similar group of adolescent criminal offenders[156].

The high prevalence of psychiatric disorders among youths in special institutions found in Paper IV is in line with the findings of several previous studies[157]. A more remarkable finding was that the frequency of comorbidity

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[151] Långström, et al., 2009

[152] Ghaziuddin, Tsai, & Ghaziuddin, 1991, Lundström, et al., 2014, Palermo, 2004

[153] Soderstrom, et al., 2005, Scragg and Shah, 1994, Siponmaa, et al., 2001

[154] Young, et al., 2010, Rösler, et al., 2004

[155] Fazel, et al., 2008

[156] Siponmaa, et al., 2001

[157] Teplin, et al., 2002, Washburn, et al., 2008, Fazel, et al., 2008, Fazel, Doll, & Långström, 2008

was so high, not only in those with ADHD or ASDs, but in all participants. Among the participants without ADHD and ASDs (n = 47), 15 participants had two diagnoses and 12 had three or more diagnoses. The corresponding figures for participants with ASDs (n = 6) were 1 and 5, for those with ADHD (n = 36), 19 and 6, while the proportions of those with one, two, or three additional diagnoses among those with comorbid ASDs and ADHD (n = 11) were 3, 3, and 5, respectively.

The following diagnoses, in order from higher to lower, were the most frequent comorbid disorders in the group with ASDs: CD, ADHD, SUD, depression, anxiety, psychotic symptoms, and borderline intellectual functioning. For ADHD the most frequent comorbidities were (in order) CD, SUD, borderline intellectual functioning, depression, ASDs, anxiety, and, psychotic symptoms.

A high proportion of studies on the prevalence of psychiatric morbidity in young offenders have been conducted in the US and the UK, and the study groups have almost exclusively comprised detained youths. Differences in legal systems among most countries lead to selection differences in different studies. Our study group consisted of a mix of adolescents with (83%) and without (17%) a criminal history. The participants who were placed according to the YOA (by definition adolescents with a criminal record) had an overall lower prevalence of psychiatric disorders than the participants placed according to the YPA (participants not necessarily having a criminal history). Of participants in the YPA group, 23% had two disorders (ADHD and ASDs included) and 60% had three or more, while in the YOA group 18% had two and 32% had three or more. This difference probably reflects the courts' and social services' recognition of comorbidities and associated complexity when deciding under which act (YPA or YOA) to place different individuals.

7.1.5 Longitudinal follow-up of adolescents

The prevalence of SUD found in Paper V is as high as described in several studies of adolescents in custody or juvenile care, which have shown that conduct problems and attention problems are closely related to SUD. The results in Paper V are in line with such findings. Substance abuse and antisocial behavior have been shown to be the predominant risk factors for criminal behavior in adolescents in the general population, and the combination of ADHD and SUD has been shown to constitute a particularly disabling condition in regard to mental health and criminality[158].

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[158] Elonheimo, et al., 2007, Bihlar Muld, et al., 2013

Paper V also investigated whether a combination of ADHD and SUD is particularly risky for relapse into criminality among institutionalized adolescents. Although several studies have shown that SUD increases the risk of criminal recidivism in different clinical populations (e.g.[159]), this association received only limited support in the data described in Paper V. One possible explanation is that all participants in the studied groups, no matter whether or not they used drugs, were at the peak of the age-crime curve described by Blumstein et al.[160]. The effect of the age-related peak on criminality by far exceeds the effects of drug use.

Both health care use and untimely death in this group were found to be elevated over figures for the same age group in the general population, although they did not differ between the three diagnostic groups. This is in line with several international findings[161], as well as results from a Scandinavian study[162].

These results therefore add to the picture of adolescents as a vulnerable group with special health care needs, for whom special efforts must be undertaken if they are to be reached and any real improvements seen.

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[159] Dowden and Brown, 2002
[160] Blumstein, Cohen, & Farrington, 1988
[161] Barbaresi, et al., 2013
[162] Skardhamar and Skirbekk, 2013

7.2 **Conclusions**

1) The comorbidity found across different clinical groups implies that clinicians in psychiatry have to be prepared to recognize the diversity of psychiatric problems that characterize many of those who seek their services. The finding of comorbidity in so many psychiatric patients calls into question the orientation toward highly specialized units and calls for the development of units equipped to assess and treat all kind of psychiatric problem constellations.

2) Given the complexity in diagnostic panorama where comorbidity is the rule rather than the exception, it is necessary for treatment interventions to take an overall grasp identifying all treatment needs. This includes adopting a strategy in which each unique problem constellation is treated with the most effective and efficient method without losing the whole clinical picture out of sight.

3) Research on treatment must find methods to deal with and incorporate comorbidity in order to reflect clinical reality and to make real improvement in ecological validity.

4) The arbitrary division between child and adolescent psychiatry and adult psychiatry should be bridged.

5) There is an urgent need to develop a more efficient collaboration between child and adolescent psychiatry and adult psychiatry, school, social services, and other institutions to allow and encourage early identification of problems and implementation of support and interventions.

7.3 **Strengths and limitations**

In all studies in this thesis clinical background data was collected retrospectively and self-reported as part of the ordinary routines used in the study settings. Especially in adults, reliance upon such information in diagnosing childhood-onset disorders (e.g. ADHD and ASDs) constitutes a problem as there always is some risk of over- or underestimating the retrospective problems forming the basis of a diagnosis. One way we tried in our studies to avoid this problem was to combine information from different sources and to make a compound classification from all of the information taken together. All diagnoses were also assigned in consensus by more than one clinician in order to minimize the risk of bias.

In all 3 study groups, the attrition rates were low, which contributes significantly to the validity of the results and the possibility to draw conclusions. However, no formal assessment of differences between responders and non-responders was performed, which means there are some concerns about the representativeness of the participants.

The sample size in each study was modest for describing comorbidity in general, but studies with large sample sizes usually suffer from a lack of the diagnostic stringency and detail found in our study groups. The collection of detailed clinical data is, of course, time-consuming and expensive, so considerations about what sample size to accept are important.

We expected but were not able to replicate some previously reported findings (e.g. the effect of comorbid substance abuse on the criminality), which might be because our sample sizes were too small and thus led to an inability to detect significant differences. But it could also be the result of too much homogeneity in the groups on the assessed variables.

One of the main goals of this thesis was to assess and describe the comorbidity between childhood-onset neuropsychiatric disorders. These disorders are relatively rare in the general population. To get a picture of their comorbidity in the general population, large-scale longitudinal population-based studies would have to be conducted. These are time-consuming and expensive to carry out. An often used method when the goal is to describe prevalences of rare conditions is to describe the conditions in groups where the condition of interest is known or can be expected to be highly prevalent (case studies). A disadvantage of this method is that we cannot be sure that the participants assessed are representative of the general population. Most probably, there will be some kind of selection bias introduced when using case studies, as in this thesis, which will lower the external validity. On the other hand, the thorough and comprehensive diagnostic workup allowed in smaller groups such as the ones used in this thesis results in a high degree of clinical and ecological validity.

Paper I was published in 2004 and the findings were of interest and somewhat controversial at the time. Since then, a new version of the DSM has been published, in which definitions and diagnostic criteria for ADHD and ASDs were changed in line with the findings in this paper. However, the comparatively long period of time over which the papers were written constitute a limitation since knowledge changes quickly and can become

outdated as time elapses. However, Paper I represents what was in focus for research at that time and the findings have contributed to the present knowledge.

7.4 **Clinical implications and future research directions**

One consequence of the findings in this thesis is that diagnostic criteria need to take into consideration the overall comorbidity between different childhood-onset neuropsychiatric disorders and with other axis I clinical disorders. Changes of this kind have been made in the new DSM-5, in which diagnosis of ADHD and ASD can now be made simultaneously and is actually encouraged as a general practice. Although the clinical practice for some years has evolved to diagnose ADHD and ASDs simultaneously, this practice was not formally supported by the previous version of the DSM.

Further, findings in this thesis support the notion that the division between axis I and axis II (PD) disorders in DSM-IV is somewhat arbitrary and artificial and point to a close connection between childhood-onset neuropsychiatric disorders such as ADHD and ASDs and personality. By highlighting the importance of a comprehensive personality description to fully understand a patient, these findings also challenge the exclusion criteria that state that PDs should not be diagnosed when ASDs is better describing the problem constellation. DSM-5 has now developed a non-axial documentation of diagnoses, with separate notations for former axes IV (psychosocial and environmental problems) and V (Global Assessment of Functioning Scale). Axes I, II, and III have been abandoned for a non-axial classification to better reflect the clinical practice often used. DSM-5 is explicitly thought of as a living document ready to be revised more often than was the previous versions.

Findings in this thesis also point out the problematic division between child and adolescent psychiatry, in which questions and assessments of personality have traditionally been avoided in the former, while in the latter diagnoses of PDs have often been given without a thorough assessment of childhood-onset

neuropsychiatric disorders. Personality problems have been connected to an inability to comply with treatment[163], and it is therefore crucial to assess both specific diagnostic criteria and the presence of PDs.

The importance of screening for violent behavior in out-patient settings is also underscored by the findings that levels of aggressive behaviors (both self-directed violence and interpersonal violence and aggression) measured by the Life History of Aggression questionnaire were as high in an out-patient group referred for assessment of neuropsychiatric disorders as in a group of perpetrators of violent crimes referred to forensic psychiatric pre-trial investigation.

The high incidence of psychiatric problems in general, and childhood-onset neuropsychiatric disorders in particular, in special youth institutions shown in this thesis calls for several different considerations and changes. We need to be very clear about this psychiatric disorder panorama and provide youth institutions with psychiatric competence that can meet the different needs of the affected youths. We also have to develop and enlarge communication and cooperation between special youth institutions and child and adolescent psychiatry to meet these patients' complex needs. We might even have to introduce special units where psychosocial and environmental care can be combined with psychiatric care with high competence and accessibility.

The findings in this thesis are in line with, and in some sense precede, the changes made in DSM-5. The results show that comorbidity is the rule rather than the exception and that future research should be directed to search for the common underlying factors contributing to psychopathology. This further shows the importance of direct research, involving clinical practice, in describing and dealing with complexity, rather than trying to describe reality in arbitrary, incorrect, and simplified ways. The clinical implications of the findings are that we must develop methods and settings for both the description and treatment of the whole panorama of psychopathology. We also have to be prepared to make these decisions in a lifetime perspective and move away from the arbitrary division between child and adolescent psychiatry and adult psychiatry. This calls for developing more and closer cooperation between different occupational groups, professions, and perspectives to better meet the diverse needs of the concerned patients.

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[163] Purper-Ouakil, et al., 2010

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