AD/HD and autism spectrum disorders in adults

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In theory there is no difference between theory and practice. In practice there is.

Jan L. A. van de Snepscheut/
Yogi Berra

To Ebba and Truls

Contents

Abstract

Background: Attention deficit/hyperactivity disorder (AD/HD) and autism spectrum disorders (ASDs) are early-onset, but often life-time impairing, neurodevelopmental disorders. They are highly overlapping and seem to carry considerable risks of negative outcomes, psychiatrically and psychosocially. Childhood hyperactivity is a known risk factor for early-onset conduct disorder (CD), but details concerning the associations between neurodevelopmental problems, aggression, and antisocial personality disorder (ASPD) in adult age are still uncertain. The current diagnostic subdivision of the ASDs is based on children, while the adult characteristics, including patterns of comorbidity and psychosocial adversities, have been less studied, especially in subjects without concomitant intellectual disability. **Objectives**: The overall aim of this thesis was to describe the adult outcome of AD/HD and ASDs. Specific aims were to: (1) review prospective, longitudinal studies of the adult outcome of childhood hyperactivity, equivalent to AD/HD, with special regard to ASPD, (2) investigate the relationships between AD/HD, ASDs, and different types of aggressive behaviours, (3) describe the clinical presentation, including personality development and psychosocial outcome, in normal-intelligence adult subjects with ASDs. **Method**: The first paper is a systematic meta-analysis of published studies. The subsequent studies are descriptive analyses of common clinical assessment protocols from consecutive groups of adults either referred for clinical evaluations of childhood-onset neuropsychiatric disorders, for forensic psychiatric investigations, or recruited to a population-based, longitudinal study of teenage-onset anorexia nervosa (AN). **Results**: Childhood hyperactivity increases the risk for CD, which is found in at least one-third of all hyperactive children, forming the starting point for the development of aggressive antisociality in adulthood in about half of cases with the combination of hyperactivity and CD in childhood. Support for the hypothesis that childhood hyperactivity, in the absence of early CD, carries a risk for adult ASPD, is still lacking (*Paper I*). Both conditions are, however, predictors of aggression in adults, together with substance-related disorders and poor development of the character trait Cooperativeness. ASD traits or symptoms did not generally predict aggression but may be associated with unique violent offences (*Paper II*). Among subjects with normal-intelligence ASDs, life-time psychiatric comorbidity was very high, and measures of outcome indicated low psychosocial functioning. AD/HD was common in all ASD subject categories studied with the notable exception of subjects with AN, none of whom had AD/HD. ASPD and substance-related disorders were more common in patients with an atypical ASD as compared to Asperger´s disorder or autistic disorder. Among all adults diagnosed with an ASD, less than half led an independent life and comparatively few had ever had a long-term relationship. Female subjects more often reported having been bullied at school than male subjects (*Paper III* and *IV*). **Discussion and conclusions**: Childhood-onset neuropsychiatric conditions such as AD/HD and ASDs are relevant for adult psychiatric phenotypes but insufficiently studied. Current classifications suffer from the hiatus between child- and adolescent psychiatry and adult psychiatry and future diagnostic concepts ought to be longitudinal with a life-time perspective on cognitive and emotional development and a patient-centred focus rather than fragmented into complex patterns of "comorbidities".

Key Words: AD/HD; Autism spectrum disorders; Comorbidity; Behaviour disorders; Outcome

Svensk sammanfattning

Bakgrund: Uppmärksamhetsstörning med hyperaktivitet och impulsivitet (AD/HD) och autismspektrumstörningar (ASDs) är neuroutvecklingsrelaterade psykiatriska tillstånd som debuterar tidigt i livet och påverkar individens fungerande genom livet. Dessa diagnosgrupper överlappar påtagligt sinsemellan och med andra psykiatriska tillstånd. Hyperaktivitet i barndomen är en känd bakgrundsfaktor till uppförandestörning i barndomen (CD), medan det fortfarande är oklart vilken roll neuroutvecklingsrelaterade problem i övrigt spelar för aggressivitet och antisocial personlighetsstörning (ASPD) i vuxen ålder. Kunskapen om hur ASDs ter sig i vuxna kliniska grupper och hur de förhåller sig till viktiga utfallsmått som aggressivitet och psykosocialt fungerande är fortfarande begränsad. **Syfte**: Det övergripande syftet för denna avhandling har varit att undersöka det psykiatriska och psykosociala utfallet av AD/HD och ASDs. Specifika målsättningar var att: (1) genomföra en litteraturöversikt över prospektiva, longitudinella studier där hyperaktivitet i barndomen, motsvarande AD/HD, följts upp i vuxen ålder, med särskilt fokus på utvecklingen av ASPD, (2) undersöka förhållandet mellan AD/HD, ASDs och olika former av aggressiva beteenden, (3) beskriva den kliniska bilden, inklusive psykosocialt fungerande, hos vuxna normalbegåvade personer med ASDs. **Metod**: Avhandlingens första arbete (*Paper I*) utgår från en systematisk meta-analys av den vetenskapliga litteraturen. De därpå följande arbetena (*Paper II*, *III* och *IV*) är deskriptiva analyser av kliniska data, insamlade antingen i konsekutiva, vuxenpsykiatriska grupper där forskningspersonerna remitterats till neuropsykiatriska utredningar alternativt rättspsykiatriska undersökningar eller ingått i en longitudinell, populationsbaserad grupp bestående av individer med tonårsdebuterande anorexia nervosa (AN). **Resultat**: Minst en tredjedel av alla hyperaktiva barn utvecklar uppförandestörning i barndomen, och hälften av barn med denna problemkombination går vidare till ASPD eller kriminalitet i vuxen ålder. Vi fann inte stöd i dagens vetenskapliga litteratur för antagandet att hyperaktivitet i barndomen, i frånvaro av uppförandestörning, medför en ökad risk för utveckling av ASPD i vuxenlivet (*Paper I*). I en vuxenpsykiatrisk grupp utgör emellertid både hyperaktivitet och CD i barndomen oberoende variabler i en prediktionsmodell för aggressivitet, tillsammans med drogmissbruk och låga poäng på karaktärsskalan Cooperativeness. Autistiska symptom bidrog inte till prediktionen av aggressivitet, men kan vara relaterade till enstaka våldshandlingar (*Paper II*). En mycket hög psykiatrisk samsjuklighet konstaterades hos vuxna normalbegåvade individer med ASDs (*Paper III* och *IV*). AD/HD var vanligt i denna grupp med undantag för de individer, företrädelsevis kvinnor, som hade samtidig AN i anamnesen. Bland de studerade individerna med ASDs var ASPD och missbrukrelaterade tillstånd överrepresenterade hos dem med atypiska former av ASDs. I ASD gruppen var erfarenheter av mobbing under uppväxten mycket vanliga, särskilt hos de kvinnliga deltagarna i studien. Mindre än hälften av gruppen levde i ett självständigt boende och förhållandevis få hade haft ett långvarigt kärleksförhållande. **Diskussion och slutsatser**: Neuroutvecklingsrelaterade problembilder som AD/HD och ASDs är av betydelse för vuxenpsykiatrin men är otillräckligt studerade. Den nuvarande psykiatriska diagnostiken försämras som en konsekvens av uppdelningen i barn- och vuxenpsykiatri, och måste utvecklas mot patient-centrerade beskrivningar av problembilder i ett longitudinellt perspektiv, istället för att fångas i överlappande definitioner av störningar.

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I may not have gone where I intended to go, but I think I have ended up where I intended to be.

Douglas Adams

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List of papers

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

I: Hofvander B, Ossowski D, Lundström S, Anckarsäter H (2009). Continuity of aggressive antisocial behavior from childhood to adulthood: The question of phenotype definition. *International Journal of Law and Psychiatry* 32:224-234.

II: Hofvander B, Ståhlberg O, Nydén A, Wentz E, Degl'Innocenti A, Billstedt E, Forsman A, Gillberg C, Nilsson T, Råstam M, Anckarsäter H. (submitted). Trait aggression in adult psychiatry is predicted by childhood hyperactivity, conduct disorder, adult substance abuse and low cooperativeness.

III: Hofvander B, Delorme R, Chaste P, Nydén A, Wentz E, Ståhlberg O, Herbrecht E, Stopin A, Anckarsäter H, Gillberg C, Råstam M, Leboyer M. (2009). Psychiatric and psychosocial problems in adults with normal-intelligence autism spectrum disorders. *BMC Psychiatry* 9:35.

IV: Anckarsäter H, **Hofvander B**, Billstedt E, Gillberg IC, Gillberg C, Wentz E, Råstam M. (manuscript). The sociocommunicative deficit subgroup in anorexia nervosa: clinical symptoms, autism spectrum disorders, neurocognition, personality, and prognosis in a population-based, longitudinal study.

Papers I and *III* were reprinted with permission from the publishers.

Abbreviations

AD	Autistic Disorder
AD/HD	Attention Deficit/Hyperactivity Disorder
AD/HD-C	AD/HD - combined subtype
AD/HD-HI	AD/HD - predominantly hyperactive/impulsive subtype
AD/HD-IA	AD/HD - predominantly inattentive subtype
ALC	Autistic-like conditions
AN	The longitudinal Gothenburg Anorexia Nervosa project
AS	Asperger´s disorder
ASD	Autism spectrum disorders
ASDI	Asperger Syndrome/high functioning autism Diagnostic Interview
ASPD	Antisocial personality disorder
CD	Conduct disorder
CO	Cooperativeness
DIS-CAT	The Early-onset behaviour DISorders across diagnostic CATegories study
DSM-IV	The Diagnostic and Statistical Manual of Mental Disorders 4th edition
EF	Executive function
FNP	The Gothenburg Forensic Neuropsychiatry Project
FSIQ	Full scale intelligence quotient as measured by the Wechsler scales
GAF	Global Assessment of Functioning
G & G	Gillberg & Gillberg criteria for Asperger syndrome/high-functioning autism
HA	Harm Avoidance
HFA	High functioning autism
HKCD	Hyperkinetic conduct disorder
HKD	Hyperkinetic disorder

ICD-10	The International Classification of Diseases 10th edition
LHA	Life History of Aggression
MR	Mental retardation
NPG	The Gothenburg Neuro-Psychiatry Genetics project
NS	Novelty Seeking
OCD	Obsessive-compulsive disorder
OCPD	Obsessive-compulsive personality disorder
ODD	Oppositional defiant disorder
P	Persistence
PD NOS	Personality disorder not otherwise specified
PDD NOS	Pervasive developmental disorder not otherwise specified
P.A.R.I.S.	The Paris Autism Research International Sibpair study
PIQ	Performance Intelligence Quotient
RD	Reward Dependence
SCID-I	Structured Clinical Interview for DSM IV – axis I disorders
SCID-II	Structured Clinical Interview for DSM IV – axis II disorders
SD	Self-Directedness
ST	Self-Transcendence
TCI	Temperament and Character Inventory
ToL	Tower of London
ToM	Theory of Mind
TOVA	Test of Variables of Attention
VIQ	Verbal Intelligence Quotient
WAIS-R	Wechsler Adult Intelligence Scale – Revised
WAIS-III	Wechsler Adult Intelligence Scale – third edition

Introduction

Attention deficit/hyperactivity disorder (AD/HD) and autism spectrum disorders (ASDs) are psychiatric conditions with an early onset and functional impairments that, in most cases, persist throughout life (Biederman et al., 2000; Rasmussen & Gillberg, 2000; Billstedt et al., 2005; Cederlund et al., 2008). Patients with these diagnoses constitute large groups within child and adolescent psychiatric care (Kopp & Gillberg, 2003), and their presence in adult psychiatry has in recent years been brought to increasing attention (Faraone et al., 2006; Ghazziudin & Zafar, 2008). The disorders have considerable impact on health and quality of life, as manifested through academic failures, occupational disabilities (Galéra et al., 2009; Sobanski et al., 2007; Cederlund et al., 2008), risk of injury (Lee et al., 2008), high consumption of health care, both psychiatric and somatic (De Ridder & De Graeve, 2006; Knapp et al., 2009), and mortality (Mouridsen et al., 2008; Jokela et al., 2009).

This thesis is based on the idea that psychiatric diagnostic practices, both for research purposes and in the clinic, should account for all symptoms expressed, not only for those expected in a particular condition at a particular moment. Such a patient-centered, developmental approach would allow us to see a larger scope of treatment targets in our patients. In addition, in research, the notion is increasingly addressed that subclinical behavioural definitions or phenotypes are vital in our efforts to understand the aetiology of psychiatric disorders (e.g. Szatmari et al., 2007).

Nosology

Psychiatric classification has its roots in the botanical taxonomy of the 16th and the 17th centuries and the efforts of "experts" to define species, initially based on a few a priori essential features (Kendler, 2009). There were, however, various expert taxonomists who proposed different essential characters on which plants should be classified, some favouring fruits or reproductive structures, others the general growth patterns.

Centuries later, in the 19th and the early 20th centuries, psychiatry witnessed a profusion of suggested nosologies, each based on the perception of a different expert (e.g. Krafft-Ebing, Wernicke, Kraepelin, Bleuler), bringing to their classification wide clinical experience and a range of assumptions about what constitutes the fundamental features of a psychiatric illness. When Kraepelin focused on the course of illness, Bleuler assumed that the diverse features of schizophrenia were all manifestations of deeper abnormalities (Shorter, 2005), i.e. they emphasized different types of prominent features as validators to implement their own expert concept of the core nature of psychiatric disorders.

Criticizing the predominant, theory-based classification within psychiatry and aiming to validate some of Bleulers subdivisions of schizophrenia, Robins and Guze (1970) set up a number of criteria for validity to be used in the systematic study of diagnostic categories within psychiatry. Their method for achieving validity consisted of five "phases": 1. clinical description, 2. laboratory studies, 3. delimitation from other disorders, 4. follow-up study, and 5. family study. Through these "phases" homogeneity in diagnostic categories would be reached and form a basis for studies concerning aetiology, pathogenesis, and treatment.

Their now classical work on clinical validity has inspired hundreds of studies and several authors have added proposals for what should constitute proper entities or categories in psychiatry and its neighbouring fields (Kendler, 1990; Andreasen, 1995; Hyman, 2002). However, we are still a long way from an aetiopathogenic validation of the mental disorders in psychiatry, and researchers studying psychiatric conditions today do so in a state of "nosological insecurity" (Kendler & Zachar, 2008).

Comorbidity and the borders of disorders

Comorbidity refers to the co-occurrence over time, or concurrently, of two or more diseases/disorders, thought to be distinct, within an individual (Feinstein, 1970). This phenomenon is of scientific and clinical interest because it raises important questions about possible underlying mechanisms and has considerable impact on treatment and research, which are largely governed by the diagnostics. Epidemiological evidence of comorbidity in psychiatry has been noted repeatedly (Caron & Rutter, 1991). Basically, a number of reasons could account for two psychiatric disorders to occur simultaneously.

According to a list drawn by Rutter (1997), the artefactual reasons behind comorbidity include, first, a probable statistical over-representation in clinical samples. If each of the psychiatric conditions that are comorbid provides a reason for referral, and if only some people with each condition get referred, clinical samples will always contain a disproportionate number of individuals with comorbid disorders (the so called Berkson effect). Second, it is more likely for referral to occur with severe and complicated (including comorbid) disorders than with mild and simple ones (i.e. referral bias). Third, in what is called two-stage community studies, where subjects are selected for further assessments based on a certain score on some measure of general psychopathology, individuals with several different sorts of symptomatology will be more likely to qualify. Fourth, the prevailing system of classification of disorders may increase the likelihood of comorbidity through overlapping diagnostic criteria. This could be the case with, for example, distractibility, being present in both AD/HD and mania, or symptoms of social withdrawal, seen in schizophrenia, depression, social phobia, and the ASDs. Diagnostic subdivisions have become increasingly specific since the publication of the DSM-III-R (American Psychiatric Association, 1987). With an increase in "splitting" of nosological entities, patients who formerly had one diagnosis will perhaps meet criteria for two or three diagnoses. The solution to this problem in DSM and ICD has been the use of exclusionary criteria, where some disorders take precedence over others.

Over the last decades, representative population studies have provided strong evidence of "true" comorbidity within psychiatry when eliminating methodological factors as major causes of these findings (Angold et al., 1999a). There is growing consensus that several psychiatric disorders "belong together", with highly frequent co-occurrence, simultaneously and sequentially (e.g. Watson, 2005). Hence, diagnostic comorbidity, within and across the different "axes" set up in the DSM system to account separately for "personality", "somatic" and "psychosocial" disorders in addition to the conventional mental disorders, is increasingly being recognized as the norm rather than the exception.

Empirically "true" comorbidity could have several possible backgrounds. The different disorders could represent two or more manifestations of the same underlying condition. One reasonably accepted example of this would be bipolar disorder, which at times may be manifested by

depression, at times by mania, and sometimes by a mixture of both (Goodwin et al., 2000). A variant of this first explanation of comorbidity is that the two disorders represent different stages in the progression of the same underlying condition. Early-onset conduct disorder (CD) and antisocial personality disorder (ASPD) seem to illustrate this example fairly well (Lahey et al., 2005a). A third basis for comorbidity is provided by the situation in which the two disorders are derived from the same susceptibility factor(s) or from inter-correlated susceptibility factors (e.g. bipolar disorder and schizophrenia, Lichtenstein et al., 2009). A fourth possible reason behind observed comorbidity is that two comorbid conditions represent a valid condition on its own that is distinctive from the two disorders when they occur separately. The ICD-10 diagnosis of hyperkinetic conduct disorder (HKCD) is a result of support for the merging in some instances of hyperkinetic disorder and CD (World Health Organization, 1993). The fifth possibility is that the existence of one condition creates an increased risk that some other disorder(s) may develop. Again, the progression from hyperactivity into oppositional defiant disorder (ODD) and CD is a well-studied example, in which the roles of the different parts in the combined problem constellation still remain unclear (Rowe et al., 2002).

Categories or dimensions?

Whether psychiatric disorders are discrete clinical conditions or arbitrary distinctions along dimensions of functional impairment has been a long-standing issue (Kendell, 1975), and the debate is presently more vivid than ever (Widiger & Samuel, 2005). Both dimensional and categorical approaches do have their pitfalls (Angold & Costello, 2009), and alternative models (e.g. the prototype model, Jablensky, 2005) are also considered. Another related area of taxonomic/nosological dispute is so called sub-threshold conditions (e.g. Angold et al., 1999b; Shankman et al., 2009) and questions of "caseness" in relation to the boundaries between normality and psychopathology (Wakefield, 1992), which form one of the core issues of psychiatric nosology, not least when diagnostics are used in legal contexts or for the allocation of financial resources and support.

Angold and Costello (2009) pose a central question when asking why "good" disorders *have to* have sharply demarked boundaries. When the brain is the most complex organ we have, interacting with innumerable environmental variables, it is not surprising that psychiatric disorders have fuzzy boundaries. At this time, it seems a good guess that the forthcoming diagnostic labels will be moved further away from the theory-based categories but perhaps rely on criteria that are driven by clinical utility, where assertions on prognosis, treatment outcome and testable propositions about biological and social correlates will have their places (Kendell & Jablensky, 2003).

Course and continuity of disorders

Finding early predictors of later psychopathology and describing outcome are two of the main assignments of psychiatric research. Diversity of outcomes seems to be characteristic of psychiatric disorders at every age, and behaviour of one type is in many cases predictive of behaviour of an apparently different type in later age (Kim-Cohen et al., 2003; Angold & Costello, 2009). Age at onset is a factor of potential importance to sub-classification and prognostics of mental disorders, proposed, for example, in bipolar disorder (Leboyer et al., 2005), schizophrenia (Nicolson & Rapoport, 1999), and obsessive-compulsive disorder (OCD) (Chabane et al., 2005). In the field of disorders linked to antisocial behaviour, the most influential model in

recent years for understanding variability in later outcomes has been Moffitt's (1993) developmental taxonomy. It suggests that antisocial behaviours are displayed by two fairly distinct subgroups, differing in early risks and long-term outcomes, and distinguished by an age at onset early in life, well before adolescence and puberty, or a late onset during these periods ("life-course-persistent" vs. "adolescence-limited"). As yet, fairly little is known of the factors leading to constructive or destructive outcomes, but several separate or interconnected mechanisms for continuity and discontinuity in psychopathology have been proposed (Rutter et al., 2006).

In clinical psychiatric settings, comorbidity is associated with greater persistence, more severe symptoms, and worse prognosis as compared to mono-morbidity (e.g. Capaldi, 1992; Connor et al., 2003). In terms of underlying risk factors, studies suggest that psychiatric disorders in many cases share the same genetic risk factors, while specific, environmental features in some cases differentiate the disorders during development (Kendler et al., 2003; Plomin & Davis, 2009). Also, genetic differences between people seem to account for stability from age to age (Mill et al., 2006), whereas environmental factors may account for change (Plomin et al., 2008). Genetic sensitivity to environment (i.e. gene-environment interaction) has recently gained considerable attention (spurred by Caspi et al., 2002) as a possible factor influencing outcome in different disorders.

Psychopathology across the lifespan

Childhood conditions in adults

Important progress has been made over the past 15 years in our understanding of childhood-onset psychopathology and its development. A number of prospective and longitudinal studies collecting data from childhood to adulthood have made lifespan perspectives accessible for clinical psychologists and psychiatrists. The results of these studies (e.g. Costello et al., 1996; Wals & Verhulst, 2005; Moffitt, 2006; Cederlund et al., 2008), have shown that childhood psychopathology, formerly believed to wane or to be something people "grew out of", in most cases, persists into adulthood, though often not in the same shape as when it was first recognized (e.g. Barkley & Brown, 2008).

A main obstacle for patients, clinicians and scientists seeking to understand developmental pathways of mental disorders is formed by the divergent terminologies that are used in child- and adolescent psychiatry on the one hand, and in adult psychiatry on the other, emphasizing different aspects of mental problems, such as temperament, developmental aberrations, neuropsychological deficits, emotional problems, personality immaturity, communication problems, and productive symptomatology.

The detection of "childhood" disorders in adults has forced clinicians to question their diagnostic practices and widened the arsenal of treatments available to adult psychiatry. Likewise, the application of "adult-style" diagnostic criteria to children and adolescents has been quite successful in demonstrating that many adult disorders definitely occur in childhood (e.g. social phobia, major depression, and bipolar disorder, although with atypical features), starting much earlier than used to be thought even possible, while indicating that some others really are very

uncommon before later adolescence (e.g. panic disorder, "classical" mania, anorexia nervosa, and schizophrenia (Costello et al., 2006).

Neurodevelopmental disorders

The concept of "neurodevelopmental" or "child neuropsychiatric" disorders has long been proposed as a subcategory within the psychiatric and neurological classifications (e.g. Gillberg, 1995). Rutter and colleagues (2006) set up criteria defining neuropsychiatric disorders with childhood onset. First, they stated, neurodevelopmental disorders are characterized by aberrations in psychological abilities influenced by maturation. Second, the course of the disorder is not, unlike most other multi-factorial psychiatric disorders, marked by remission and relapses. Third, the impairment associated with the disorder persists into adulthood but is lessened with age. Fourth, these disorders involve some, specific or general, cognitive impairment. Fifth, neurodevelopmental disorders coincide with each other. Sixth, the genetic influence on the inter-individual variation in these disorders is generally strong. Finally, the sex ratio is most often highly skewed, with males being significantly more often affected.

Other, more liberal definitions of what constitutes a neurodevelopmental disorder would state that it is a disorder with a disrupted development of the brain's structure and function before full maturity and the defining features of the disorder are reached. By this definition, schizophrenia, for example, could qualify as a late-onset neurodevelopmental disorder (Weinberger, 1987).

Attention Deficit/Hyperactivity Disorder

AD/HD (American Psychiatric Association, 1994) is uncontestedly the most common neurodevelopmental disorder, affecting 3-5% of school-age children in population-based studies (Landgren et al., 1996; Kadesjö & Gillberg, 1998) and 7-12% of children if less severe symptoms are included (Biederman & Faraone, 2005). The DSM-IV (American Psychiatric Association, 1994) allows subgroups of symptoms to constitute a diagnosis, while the ICD-10 (World Health Organization, 1993) definition proclaims a single disorder (hyperkinetic disorder/HKD) and includes a more rigorous criterion for pervasiveness than does the DSM-IV diagnosis.

At first conceptualized as a disorder affecting males in mid-childhood (Willoughby, 2003), AD/HD is now recognized as a chronic disorder in both sexes. The aetiology is considered to be multi-factorial, but a unanimous literature describes a high familial aggregation (e.g. Faraone, 2004), the share of variance attributable to genetic factors across different environments estimated to about 76% (Faraone et al., 2005).

As seen in Table 1, the clinical features of AD/HD in the DSM-IV are inattention, hyperactivity, and impulsivity severe enough to cause impairment and suffering (American Psychiatric Association, 2000). Since, however, the diagnosis may be assigned if only one of the two broader symptom definitions is met, two persons with AD/HD may not share a single symptom, or very few actual problems. Regardless of the actual type of symptomatology, the diagnosis also requires an early onset of symptoms, a developmental extremity in relation to peers (given that these problems are ubiquitous in young children), and a cross-situational display, creating significant dysfunction in at least two different settings, such as school, family life, or peer interaction. Several studies have shown that the symptoms of AD/HD are highly affected by

situational factors such as the degree of environmental demands involving inhibition (Luk, 1985), fatigue (Zagar & Bowers, 1983) and adult supervision (Gomez & Sanson, 1994). The impairment criterion seems to have a dramatic impact on the epidemiological figures of the disorder (Wolraich et al., 1998; Wille et al., 2008), and the number or frequency of symptoms seems to have a weak relation to impairment (Gordon et al., 2006). Assessments also vary to a considerable extent with the choice of informants used in the assessment (Scahill & Schwab-Stone, 2000; Barkley et al., 2002).

Table 1. Diagnostic criteria for Attention-Deficit/Hyperactivity Disorder (DSM- IV)

A. Either (1) or (2):

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

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

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

Hyperactivity

- (a) often fidgets with hands or feet or squirms in seat
- (b) often leaves seat in classroom or in other situations in which remaining seated is expected
- (c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
- (d) often has difficulty playing or engaging in leisure activities quietly
- (e) is often "on the go" or often acts as if "driven by a motor"
- (f) (f) often talks excessively

Impulsivity

- (g) often blurts out answers before questions have been completed
- (h) often has difficulty awaiting turn
- (i) often interrupts or intrudes on others (e.g., butts into conversations or games)

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

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

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

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

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th ed (American Psychiatric Association, 1994)

The heterogeneity of AD/HD

According to DSM-IV, AD/HD is divided into three subtypes: the predominantly inattentive type (AD/HD-IA), the predominantly hyperactive/impulsive type (AD/HD-HI), and the combined type (AD/HD-C). Heterogeneity is thus built into the diagnosis. However, factor analytical approaches (e.g. Hartman et al., 2001) and latent class analyses (e.g. Rasmussen et al., 2002) have, at a dimensional level, confirmed a structure underlying the constituent symptomatology largely corresponding to the current DSM model. Still, estimates of the subtype prevalences have differed considerably across studies (Rowland et al., 2008) and subtype stability from childhood to adult age has been found to be relatively weak (Lahey et al., 2005b; Todd et al., 2008).

In some studies, the IA-domain has been associated with learning disabilities, academic underachievement, anxiety, and depression (Gaub and Carlson 1997a; Carlson et al., 2002) whereas the HI-domain seems to be aggregating with aggression and conduct problems (Lahey & Loeber, 1997; Milich, 2001). Based on some studies, girls with AD/HD are believed to have higher rates of AD/HD-IA than AD/HD-C (Gaub and Carlson 1997b; Biederman et al., 2002), but a couple of carefully screened samples have not confirmed this assumption (McBurnett et al., 1999; Hinshaw, 2002).

The persistence of AD/HD into adulthood varies considerably across studies (Mannuzza et al., 1998; Biederman et al., 2000). A recent meta-analysis (Faraone et al., 2006) reported that about 15% of identified children continued to meet full diagnostic criteria when followed into adulthood (i.e. syndromatic persistence) until age 25. If cases with partial remission were included, the persistence rose to approximately 65%. The lack of developmentally sensitive diagnostic criteria and cut-offs for adults in the DSM has been repeatedly implicated as one of the reasons behind the longitudinal attenuation of AD/HD (Barkley, 1997a; Faraone et al., 2000). For example, whereas childhood hyperactivity-impulsivity is manifested as ”running about or climbing on things” or the inability to stay seated, adolescent or adult hyperactivity-impulsivity may manifest as an inability to relax or to persist in sedentary activities (Wender, 1995). In the few trajectory studies reported so far, it seems as though the ratio between hyperactive-impulsive symptoms and inattentive symptoms changes over time, as the former symptoms decline or change in appearance with age whereas the latter remain more stable, possibly as a function of higher task demands in school (Hart et al., 1995).

Neuropsychological correlates

The central deficit behind the heterogeneous clinical picture of AD/HD has been described as executive dysfunction (Barkley, 1997b). Executive function (EF) is a broad construct referring to complex organizing of behaviour and various mental processes involved in the maintenance of appropriate problem-solving sets to guide future, goal-directed behaviour (Welsh & Pennington, 1988). It seems as though 35-50% of subjects affected with AD/HD-C have significant test-verified deficits in the EF area (Nigg et al., 2005), but deficits in this domain are not specific for AD/HD (Pennington & Ozonoff, 1996).

A wide range of other candidate neuropsychological sub-processes have been proposed in causal models of AD/HD, including dysfunctional state regulation (e.g. Sergeant, 1999), deficits in self-regulation (Nigg, 2000), or reward insensitivity (e.g. Haenlein & Caul, 1987). Impulsive behaviours have also been reconceptualised as a functional response aimed at avoiding delay (Sonuga-Barke, 2002). Coghill and co-workers (2005) suggested that inattention, but not

hyperactivity/impulsivity, is associated with deficient EFs and poor academic achievement, and that hyperactivity/impulsivity is more closely related to dysfunctions of reward mechanisms (e.g. Sonuga-Barke et al., 2003). Most probably, differences in comorbid symptom expression contribute to neuropsychological heterogeneity in subjects with AD/HD symptoms, and there are multiple neuropsychological pathways to AD/HD (e.g., Castellanos et al., 2006)

Recently, the model proposed by Zelazo and Mullers (2003) on the functional differentiations within the frontal cortices has attracted some attention. This conceptualization distinguishes between more purely cognitive, "cool" aspects of the EFs, associated with the dorsolateral frontal cortex, and "hot", or affective, aspects, associated with the orbital and medial prefrontal cortex. In this model, "cool" EFs are elicited by relatively abstract, decontextualized problems, such as most of the tasks tested so far in AD/HD. "Hot" executive functions are required for problems that are characterized by high affective involvement or demand flexible or appropriate appraisals of the emotional significance of stimuli. Deficits on tests of these demands have been associated with hyperactivity/impulsivity (Toplak et al., 2005) and with symptoms of opposition and conduct problems (Ernst et al., 2003) but not with symptoms of inattention.

Psychiatric and psychosocial outcome

Prospective findings provide ample evidence that AD/HD carries high psychiatric morbidity, on axis I as well as axis II, across the life course (Weiss et al., 1985; Biederman et al., 1993; Rasmussen & Gillberg, 2000; Fisher et al., 2002). In clinical settings, adults with AD/HD constitute a large group, though still in many cases undetected under the cover of other diagnoses. Among groups of adult psychiatric patients diagnosed with other psychiatric disorders, between 7% and 25% also meet criteria for adult AD/HD (Barkley & Brown, 2008), with the highest prevalences of comorbid AD/HD in patients with drug dependence, agoraphobia, dysthymia, and bipolar disorder. Persistence of syndromatic AD/HD has been proposed as a risk factor for the development of additional psychopathology (Miller et al., 2008).

In addition to these well-known complications, longitudinal data confirm that AD/HD also carries failure in high-school studies (Barkley et al., 2006), an adversity with long term effects on adult adjustment. Subjects with AD/HD also seem to have riskier sexual histories with earlier parenthood as a consequence (Barkley et al., 2006). Some studies suggest that persons with AD/HD have more children (Hansen et al., 1999) and, as Weiss and Hechtman (1993) have highlighted, married adults with AD/HD report more family dysfunction and poorer overall marital adjustment compared to control families. However, several of these negative outcomes, are mediated by, or most significantly worsened by, co-existing CD symptoms (Barkley et al., 2006).

Autism spectrum disorders

The pervasive developmental disorders (PDDs) in the DSM-IV are impairing developmental disorders characterized by aberrations in social interaction and communication and by stereotyped or repetitive behaviour patterns (Wing, 1981) estimated to affect about 1% of the general population (Kadesjö et al., 1999; Baird et al., 2006). The DSM-IV includes five PDDs: autistic disorder (AD), Asperger´s disorder (AS), Rett´s disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified (PDD NOS). Wing and Gould (1979) described what was later coined autism spectrum disorder (ASDs), delineating a

group of disorders of development with impairments from the triad of social interaction, communication, and imagination associated with a narrow, repetitive pattern of activities.

Though the ASD diagnosis does not conform directly to either the diagnostic category of the PDDs and its subgroups as described in the tenth edition of the ICD or the fourth edition of the DSM, this thesis will deal with AD, AS, and PDD NOS using the umbrella term ASDs.

Autistic disorder

AD or "classic autism", following the initial definition of Kanner (1943), is the most severe condition among the ASDs. As seen in Table 2, the diagnosis of AD requires problems in all three domains with a developmental delay in at least one area prior to the age of three. In most AD cases, there is no period of unequivocally normal development (American Psychiatric Association, 2000).

Table 2. Diagnostic criteria for autistic disorder (DSM- IV)

A. A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3).

(1) Qualitative impairment in social interaction, as manifested by at least two of the following:

- (a) marked impairment in the use of multiple non-verbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gesture to regulate social interaction
- (b) failure to develop peer relationships appropriate for developmental level
- (c) lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (by lack of showing, bringing, or pointing out objects of interests to other people)
- (d) lack of social or emotional reciprocity

(2) Qualitative impairments in communication, as manifested by at least two of the following:

- (a) delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
- (b) In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
- (c) stereotyped and repetitive use of language or idiosyncratic language
- (d) lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level

(3) Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:

- (a) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
- (b) apparently inflexible adherence to specific, non-functional routines or rituals
- (c) stereotyped and repetitive motor-mannerisms (hand- or finger-flapping or twisting or complex whole-body movements)
- (d) persistent preoccupation with parts of objects

B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play

C. The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th ed (American Psychiatric Association, 1994)

Asperger´s disorder

Although first described in Germany in the 1940s and later, AS did not appear as a diagnostic entity until the early 1980s, after being introduced by Wing (1981). Gillberg and Gillberg proposed a set of diagnostic criteria for Asperger *syndrome*, based on Asperger's first case histories, for the First International Conference on Asperger syndrome in 1988. These criteria were published a year later (Gillberg & Gillberg, 1989) and were followed by a more detailed set of operationalized criteria (Gillberg, 1991).

The six criteria (Table 3) comprise 20 different items. Diagnostic criteria for AS according to the DSM and ICD systems were not published until the 1990s (in the fourth edition of the DSM, DSM-IV, American Psychiatric Association, 1994 and the tenth edition of the ICD, ICD-10, World Health Organization, 1993). These criteria have been widely criticized (e.g. Miller & Ozonoff, 1997; Leekam et al., 2000), and there is still no consensus as to how AS should best be described.

Table 3: Diagnostic criteria of Asperger syndrome (Gillberg & Gillberg, 1989/1991)

All six criteria must be met for confirmation of the diagnosis

(1) Severe impairment in reciprocal social interaction (at least two of the following)
- (a) inability to interact with peers
- (b) lack of desire to interact with peers
- (c) lack of appreciation of social cues
- (d) socially and emotionally inappropriate behaviour

(2) Narrow interests (at least one of the following)
- (a) exclusion of other activities
- (b) repetitive adherence
- (c) more route than meaning

(3) Repetitive routines (at least one of the following)
- (a) on self, in aspects of daily life
- (b) on others

(4) Speech and language peculiarities (at least three of the following)
- (a) delayed development
- (b) superficially perfect expressive language
- (c) formal pedantic language
- (d) odd prosody, peculiar voice characteristics
- (e) impairment of comprehension, including misinterpretation of literal/implied meanings

(5) Non-verbal communication problems (at least one of the following)
- (a) limited use of gestures
- (b) clumsy/gauche body language
- (c) limited facial expression
- (d) inappropriate expression
- (e) peculiar, stiff gaze

(6) Motor clumsiness
- (a) poor performance on neuro-developmental examination

The DSM-IV criteria (Table 4) for AS require impairment in social interaction (as for AD) and restrictions in behaviour (as for AD) but absence of clinically significant delays in language or cognitive development or in the development of age-appropriate self-help skills, adaptive behaviour, and curiosity about the environment in the first three years of life. As opposed to the G & G criteria, where nine symptoms are required, the DSM-IV requires only three symptoms.

Table 4. Diagnostic criteria for Asperger's disorder (DSM- IV)

(A)	Qualitative impairment in social interaction, as manifested by at least two of the following: (1) marked impairment in the use of multiple non-verbal behaviours such as eye-to-eye gaze, facial expression, body postures, and gesture to regulate social interaction (2) failure to develop peer relationships appropriate for developmental level (3) lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (by lack of showing, bringing, or pointing out objects of interests to other people) (4) lack of social or emotional reciprocity
(B)	Restricted repetitive and stereotyped patterns of behaviour, interests, and activities, as manifested by at least one of the following: (1) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus (2) apparently inflexible adherence to specific, non-functional routines or rituals (3) stereotyped and repetitive motor-mannerisms (hand- or finger-flapping or twisting or complex whole-body movements) (4) persistent preoccupation with parts of objects
(C)	The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning
(D)	There is no clinically significant general delay in language (e.g., single words used by age 2 years, communicative phrases used by age 3 years)
(E)	There is no clinically significant delay in cognitive development or in the development of age appropriate self-help skills, adaptive behaviour (other than in social interaction), and curiosity about the environment in childhood
(F)	Criteria are not met for another Pervasive Development Disorder or Schizophrenia

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th ed (American Psychiatric Association, 1994)

High-functioning autism

Subjects meeting criteria for AD with a global intelligence within the normal range are sometimes referred to as high-functioning (HFA). There has been considerable discussion about the differences between AS and HFA (e.g. Gillberg, 1998). The distinction has partly evolved from alluded psychometrical differences, but empirical results from studies of this alleged difference have been contradictory (Szatmari et al., 1990; Spek et al., 2008), possibly due to small study groups and differences in diagnostic criteria. Some studies have found no or negligible differences between subjects with HFA and AS (Manjiviona & Prior, 1999). Ozonoff and colleagues (2000) argued that HFA and AS involve the same fundamental symptomatology but differ primarily in degree or severity of impairment.

Pervasive developmental disorder - not otherwise specified

PDD NOS applies when an individual fails to meet specific criteria for AD or another specifically defined PDD (Table 5). In the DSM-IV taxonomy, PDD NOS may be diagnosed in ''presentations that do not meet the criteria for AD because of late age at onset, atypical symptomatology, or sub-threshold symptomatology, or all of these,'' and includes conditions sometimes referred to as "atypical autism" or autistic-like conditions (ALC) (American Psychiatric Association, 2000). Since no specific items or scoring algorithms are provided, subjects with PDD NOS may have different combinations of symptoms and therefore by definition (or the lack thereof) constitute a very heterogeneous group (Walker et al., 2004).

Table 5. Diagnostic criteria for Pervasive developmental disorder – not otherwise specified (DSM- IV)

A severe and pervasive impairment in the development of reciprocal social interaction associated with impairment in either verbal or nonverbal communication skills or with the presence of stereotyped behavior, interests, and activities, but the criteria are not met for a specific Pervasive Developmental Disorder, Schizophrenia, Schizotypal Personality Disorder, or Avoidant Personality Disorder.

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th ed (American Psychiatric Association, 1994)

The empirical support for the validity of the ASD subtypes has been mixed (Lecavalier et al., 2009). Significant problems with diagnostic criteria have been noted with younger children (Stone et al., 1999) and AS (e.g. Gillberg & Gillberg, 1989). Along the same lines, PDD NOS, the most frequently diagnosed ASD, is the least well characterized and has been the subject of scant empirical attention (Towbin, 2005). There have been propositions for different dimensions to characterize the ASDs, e.g. a single dimension model (Constantino et al., 2004) or a two-partite model consisting of social-communicative and repetitive-restricted behaviours (Frazier et al., 2008).

The broader autism phenotype

A "milder" variant of autism, defined as sub-threshold difficulties from the autistic triad (i.e. learning difficulties, language and communication deficits, and social impairments) was proposed by Folstein and Rutter (1977). Examining the characteristics of relatives of individuals with autism, as many as 10% to 25% of siblings who did not meet criteria for ASDs demonstrated these broader phenotype impairments (Bolton et al., 1994). A study of personality traits in first-degree relatives of subjects with ASDs found them to be more anxious, impulsive, aloof, shy, sensitive, irritable, and eccentric than relatives of individuals with Down syndrome (Murphy et al., 2000). Difficulties with pragmatics or social language are often observed in individuals with ASDs and have been reported to aggregate also in their parents (Landa et al., 1992).

Neuropsychological correlates

There has been considerable research devoted to the various neuropsychological impairments thought to characterize individuals with ASDs (Tsatsanis, 2005), and some of these have even been proposed to describe the core impairment(s) of the ASDs. Baron-Cohen and colleagues (1985) suggested that the autistic phenotype could be explained in terms of a lack of Theory of Mind (ToM), referring to the ability to mentalize or to attribute mental states to others and to oneself. However, quite early it was found that children with ASD and high verbal abilities were able to pass these tests, and that subjects diagnosed as autistic were gradually more skilled at mentalizing with increasing age (Happé, 1995). Based on a paper by Damasio and Maurer (1978) that compared the symptoms of autism to those of patients with injuries to the frontal lobes of the brain, deficits in executive functions (EFs) was instead put forward as an explanatory theory of the triad of ASD symptoms. Since then, multiple studies have identified EF deficits in preschoolers, children, adolescents, and adults with ASDs (Ozonoff et al., 2005). Some researchers have suggested that executive dysfunctions are due to a primary deficit in inhibition (Hughes & Russel, 1993), while others have stressed the central role of flexibility impairments (e.g. Szatmari et al., 1990). However, this theory also conflicts with the "discriminant validity"

problem and the fact that no EF deficit is specific to the ASDs (Pennington & Ozonoff, 1996). A third prominent candidate for the role of core or primary deficit in the ASDs is the weak central coherence theory (Frith, 1989). Central coherence is the everyday tendency to process incoming information in context in order to produce Gestalts (Happé, 2005), i.e. pulling information together for higher-level compound meaning, often at the expense of memory for details. Study results emanating from this theory have been mixed (Hoy et al., 2004), and even if a fixation on details and a lack of ability to recognize wholes, such as faces (prosopagnosia) in relation to root memory facts, is among the clinical features repeatedly described in the ASDs (e.g. Barton et al., 2004), the poor central coherence model has not been empirically established as a specific or universal feature of the ASDs. Baron-Cohen (2002) has more recently launched an empathizing-systematizing model proposing two opposite ways of rendering the world subjectively understandable and predictable, the one end dominated by empathy and coherence, and the other by details and mechanistic explanations. People diagnosed with ASDs have scored higher than others on self-rating instruments compiled to measure these ways of explanations (Baron-Cohen & Wheelwright, 2004), but again, the overlap with persons perceived as normals and with other mental disorders is very important.

Mental retardation and the ASDs

Some authors (e.g. Chakrabarti & Fombonne, 2001) claim a downward trend in the prevalence of comorbid mental retardation (MR) in the ASD group. However, in the narrowly defined group with AD, earlier approximations that around 75% would have a global IQ in the subnormal range (i.e. <70, e.g. Rutter, 1978) seem to be quite stable (e.g. Yeargin-Allsopp et al., 2003), which could imply that a possible decrease in MR among subjects with autism reflects an increase in the detection of normal-intelligence ASDs.

Complications and outcome

Long term studies of subjects with ASDs are scarce and have often referred to small, or highly selected, clinical samples (e.g. Wing, 1981; Tsatsanis, 2003). Although the ASDs are generally assumed to be life-long, meta-analyses suggest that between 3% and 25% of children diagnosed with ASDs no longer meet diagnostic criteria at follow-up (Helt et al., 2008). Further, data suggest that the actual reductions in social functioning associated with the ASDs vary to a large extent, with a substantially better outcome in AS than in AD and in cases with normal or high general intelligence as compared to persons with a comorbid intellectual impairment (Billstedt et al., 2005; Cederlund et al., 2008).

For many years, research on the ASDs was devoted to exploring its biological roots, epidemiology, and its cognitive correlates. No systematic, population-based studies of psychiatric comorbidity in the ASDs or its longitudinal development have yet been conducted, but clinical studies suggest that 50-70% of children with autism meet criteria for other psychiatric disorders (Ghaziuddin, 1998), and these figures are likely to be similar also in adulthood (Ghaziuddin, 2008). The question of comorbidity between AD/HD and ASDs has caused some controversy (Ghaziuddin et al., 1992; Loveland & Tunaly-Kotoski, 2005) in response to the question whether AD/HD symptoms represent “true” AD/HD or are simply epiphenomena to the ASDs (Gadow et al., 2006). The DSM-IV wording that symptoms of AD/HD should not exclusively occur “during the course of” a PDD (American Psychiatric Association, 2000) has been interpreted as indicating that a PDD is an exclusionary criterion for AD/HD.

However, AD/HD is today recognized as a common complication to ASDs (Ehlers & Gillberg, 1993; Gadow et al., 2005), while studies addressing the co-occurrence of AD/HD and ASDs in adults are few (Stahlberg et al., 2004; Rydén & Bejerot, 2008).

The question whether children and adults with ASDs are at higher risk of developing aggressive and/or antisocial behaviours is intriguing. Deficits in social cognition affect the individual's ability to recognize and infer mental states (e.g. intentions, beliefs, desires) in oneself and others, and to understand that others have beliefs, desires, and intentions that are different from one's own (e.g. Loth et al., 2008). This is a likely ground for aggression, particularly when paired with language difficulties (e.g. Werner et al., 2006). A recent study of different clinical groups with neurodevelopmental disorders indicated, however, that deficits in social cognition act "protectively" for some kinds of aggressive behaviours (e.g. "deliberately annoying others" or "blaming others for own mistakes") while, when comorbid with AD/HD, an ASD might worsen the expression of temper tantrums, defiance, and touchiness (Guttmann-Steinmetz et al., 2009)

Personality

Clinical disorders and personality disorders have traditionally been conceived as discrete constructs within psychiatry (Clark, 2005). In the DSM-IV, personality traits are defined as "enduring patterns of perceiving, relating to, and thinking about the environment and oneself" (DSM-IV-TR, p 686, American Psychiatric Association, 2000). When they are inflexible, maladaptive, and cause significant functional impairment or subjective distress, they constitute personality disorders (PDs), according to the DSM-IV. The current version of DSM elaborates with 11 personality disorders (plus two provided for further studies) coded on axis II.

An intense debate on the most useful and appropriate classification of PDs is currently taking place. Limitations referred to in the present system include the high comorbidity across the PDs, the extreme heterogeneity among patients receiving the same diagnoses, the arbitrary diagnostic thresholds for the boundaries between pathological and "normal" personality functioning, and the inadequate coverage of personality psychopathology leading to the diagnosis of personality disorder not otherwise specified (PD NOS) actually being the most common PD (Skodol & Bender, 2009).

Although it is theoretically allowed to record PDs on the axis II of the DSM-IV at all ages (with the exception of antisocial personality disorder), these disorders are rarely diagnosed before young adulthood. Younger populations have historically been described in terms of temperamental traits, typically more closely linked to biological correlates, while adult populations are described in terms of personality traits, often thought to stand under the influences of learning (Nigg, 2006). The child and adult literatures have largely proceeded in parallel (Tackett et al., 2009), with few translational efforts.

The application of personality models in descriptions of neurodevelopmental disorders is relatively new. However, early observed childhood temperaments that have been followed longitudinally displayed significant overlaps with behavioural disorders as defined in psychiatric classifications (Moffitt, 1990). In addition, several studies have demonstrated the possibility of tracing adult PDs to early-onset emotional and behavioural problems corresponding to the ASDs (e.g. Lewinsohn et al., 1997; Helgeland et al., 2005). Anckarsäter and

colleagues (2006) presented specific temperament configurations in adults with AD/HD vs. ASDs and, in both cases, general deficits in character maturation equivalent to PDs. These findings confirmed the possibility of mapping neurodevelopmental disorders onto personality descriptors.

Theories of personality are too numerous and complex to catalogue fully here. Data on personality in this thesis are derived from instruments based on Cloninger´s theory of personality (Cloninger et al., 1993), for which reason this model will be briefly summarized.

Cloninger´s biopsychosocial model

This theory integrates concepts and research findings from neuroanatomy, neurophysiology, and psychology (Brändström, 2009). First, it postulates a system of four independent temperaments, believed to be genetically homogenous and independently inherited, reflecting individual differences in emotional responses: Novelty Seeking (NS) involves a bias in the activation of behaviour in response to novel stimuli and signals of reward or absence of punishment; Harm Avoidance (HA) is defined as a tendency of behavioural inhibition in response to signals of punishment or non-reward; Reward Dependence (RD) originally depicted the tendency to maintain a previously rewarded behaviour without continued reinforcement but was later reverted to a sociability dimension describing dependence of affiliative reward, and Persistence (P) was finally included to incorporate behavioural maintenance aspects. Second, these temperaments interact with individual differences in the maturation of mental self-government, a faculty based on semantic learning and denoted in three character dimensions: Self-Directedness (SD) refers to a person´s concept of him-/her-self as an autonomous individual; Cooperativeness (CO) represents capacity for identification with and acceptance of other people, and Self-Transcendence (ST) is defined as the tendency to feel as an integral part of the universe as a whole.

Neuropsychology

Neurodevelopmental disorders are currently, like all clinical disorders, defined at a behavioural level. Still, symptoms across the various categorical definitions may be analysed at "deeper" levels. Pennington (2002) suggested a neuropsychological level, where variations in behaviour can be reduced to variation in a smaller number of processes.

The neuropsychological models of neurodevelopmental disorders are so far all modular, based on single-deficit hypotheses and linked to specific functional brain regions. The deficits these models emphasize are non-specific to the disorders they want to explain (e.g. Ozonoff & Pennington, 1996). Most probably, these models will turn out to be only partial models, explaining some, but not all, symptoms of the clinical disorders, increasingly emphasizing the need for integrative accounts that address multiple neural systems (e.g. Nigg et al., 2005). Contemporary neuropsychological models of these disorders still lack a broad enough list of domains to account for complex psychopathological processes reflecting interactions between emotion and cognition, e.g. motivation, emotion regulation, and social cognition. In addition, single-cause models have difficulty accounting for the heterogeneity which is being increasingly recognized as a key factor in the disentangling of both the common and specific causes behind AD/HD and ASDs (Sonuga-Barke, 2002; Happé et al., 2006).

Intelligence

Most approaches to cognition and individual differences in these abilities do not consider the term cognition to be a synonym for intelligence. There are several definitions of intelligence, but the term Intelligence Quotient (IQ) generally includes the following elements: basic mental processes such as attention and perception, higher-order thinking such as problem-solving and reasoning, and adaptation to the environment (Carter et al., 2006). IQ represents the summary score on a standardized "intelligence" test derived from a combination of scales. In clinical practice, it often forms a part of a broader assessment, where multiple and overlapping measures of cognitive functioning are used, and the clinician can look for consistencies and inconsistencies in the pattern of findings and generate more robust interpretations.

Intellectual disability or mental retardation (MR) refers to a significantly subnormal intellectual functioning as defined by an IQ of approximately 70 or below on an IQ test, i.e. below two standard deviations from the average. In order to diagnose a MR, there should also be limitations in adaptive behaviours, affecting at least two skill areas from everyday social and practical life. Finally, the disability should have originated before the age of 18 (American Psychiatric Association, 2000), although the developmental delays are most often obvious much earlier than so.

Sex aspects

Sex differences in the prevalences of AD/HD and ASDs are pronounced, approaching three males to every female for both conditions in population-based studies (Szatmari et al., 1989; Fombonne, 2003), and even greater in clinical samples (Gillberg, 1989; Gaub & Carlson, 1997b). These differences are so central that they are included as a defining feature for the neurodevelopmental disorders (Rutter et al., 2006). The reason for the highly skewed sex ratios is not clear, but several hypotheses have been proposed.

Potentially, the differences could be artefactual or related to methodological issues. For example, Zoccolillo and colleagues (1996) have suggested that conduct disorders in girls are much more frequent than usually appreciated, but that the diagnostic threshold for a number of symptoms needs to be different for girls than for boys. Likewise, Crick (1996) has argued that much aggression in girls has been overlooked because it is of a different form from that in boys. This relates to the criticism of the sampling procedures of diagnostic criteria, and the fact that male subjects traditionally have been used as referents for many of these disorders (Nadeau & Quinn, 2002). In girls with anorexia nervosa (AN), a rigid social cognitive style and obsessive-compulsive traits in childhood have long been described as risk factors for later development of the disorder, but the relation of these signs to possible ASDs have seldom been put forward (e.g. Anderluh et al., 2003).

Naturally, biological and genetic factors contribute to sex differences in the emergence and development of psychopathology. The X chromosome is of special interest here, as it contains several susceptibility genes for neurodevelopmental disorders (such as the MAOA gene, Caspi et al., 2002; the neuroligin genes, Jamain et al., 2003; and the fragile X site, Kaufmann et al., 2004). Sex hormones also exert different effects in the prenatal phase, when both the foetus' own hormones and those of the mother may exert effects, and postnatally. Boys and girls also

experience different socialization, interpersonal relationships, adverse events, and cultural norms that can create different adaptive and maladaptive patterns (Zahn-Waxler et al., 2006)

In spite of increasing interest in and focus on hypotheses about sex and clinical phenotypes in psychiatry, there is still an obvious scarcity of studies on female subjects with ASDs (Kopp et al., 2009). However, some authors have argued that the overlap between the sexes is larger than the differences (MacLennan et al., 1993). In AD/HD, comparative studies of sex differences have revealed similar core symptoms, cognitive and functional impairments, and similar comorbid psychopathology (Biederman et al., 2002; Graetz et al., 2005). Notwithstanding, boys are disproportionately more often referred for assessment and treatment as compared to girls (Bussing et al., 2003). This fact could partly be explained by boys' more overt acting-out behaviour in public, which leads to their being referred for assessment of AD/HD (Gaub & Carlson, 1997b).

In the future, models that allow for different parameters to be recorded in males and females when studying factors implicated in the development of childhood-onset psychopathology will help reveal similarities and dissimilarities between the sexes. In addition, increased efforts in mapping the childhood antecedents of adolescence-onset disorders like anxiety and depression, i.e. disorders with a female preponderance (Heller, 1993), will hopefully inform the whole field of developmental psychopathology.

Aims of the present thesis

General aims:

The overall and general aim of the thesis was to describe the adult outcome of two childhood-onset neurodevelopmental disorders, attention deficit/hyperactivity disorder (AD/HD) and autism spectrum disorders (ASDs).

Specific aims:

(1) Review prospective, longitudinal studies of the adult outcome of childhood hyperactivity, equivalent to AD/HD, with special regard to antisocial personality disorder.

(2) Investigate the relationship between AD/HD, ASDs, and aggression.

(3) Describe the clinical presentation, including personality development and psychosocial outcome, in normal-intelligence adult subjects with ASDs.

Methods

Subjects

This thesis is based on two types of data. First, data from a systematic review of the existing literature on prospective, longitudinal studies following hyperactive children into adulthood were used in a meta-analysis of outcome in terms of conduct disorder, antisocial personality disorder, and early, violent death. Second, clinical data collected with highly similar protocols from participants in either of four related projects, the Gothenburg Neuro-Psychiatry Genetics project (NPG), the Paris Autism Research International Sibpair study (P.A.R.I.S.), the Gothenburg Forensic Neuropsychiatry Project (FNP), and the longitudinal Gothenburg Anorexia Nervosa project (AN), were used for analyses of diagnostic overlaps and correlations with behavioural, neurocognitive, and personality traits. These projects contained very similar clinical diagnostic schemes applied by a comparatively small group of clinicians.

Review data (Paper I)

The studies assembled in the meta-analyses of the longitudinal outcome of childhood hyperactivity (*Paper I*) were identified using systematic PubMed searches in October-November 2007 by specific search terms. Inclusion of each study in the analysis was made on the basis of specified criteria. Hand-searches according to the reference lists of the most important textbooks on the field were also performed to identify studies published in non-indexed sources. Twelve studies were included in this meta-analysis, six studies on clinic-referred children and six population-based studies. Included at baseline were 5674 hyperactive (equivalent to AD/HD-C or AD/HD-HI, according to the DSM, or HKD, according to the ICD) children (78% boys and 22% girls) and 723 children (90% boys and 10% girls) defined as controls according to behavioural criteria.

NPG study group: adult psychiatric outpatients (Papers II and III)

The NPG study group was recruited from adult outpatients included at the Gothenburg Child Neuropsychiatric Clinic (CNC). This clinic was at the time of the data collection the only diagnostic centre specifically focused on neuropsychiatric assessments of childhood-onset disorders (such as AD/HD, ASD, tic disorders, and various kinds of learning disorders) in the city of Gothenburg. The present study cohort consisted of all adults included in the NPG project during the first years (between January 2001 and April 2003) after the launching of an "adult" development project at the clinic. Subjects with ASDs from the NPG cohort were also included in the molecular genetic work performed in the P.A.R.I.S study.

The patients included were either self-referred or referred by general practitioners or specialists in adult psychiatry, and the consecutive cohort constitutes a large (n=273), well-characterized, clinical case series (previously described in e.g. Stahlberg et al., 2004 and Anckarsäter et al., 2006). *Paper II* presents data from 178 subjects (98 men, 80 women, median age 32, range 19-59) who had been assessed with the Life History of Aggression scales. In *Paper III*, data are analyzed from the 83 subjects (53 men, 30 women, median age 30, range 19-60) who had been assigned an ASD diagnosis and had a global intelligence within the normal range as measured by the Wechsler scales.

P.A.R.I.S. study group (Paper III)

In order to extend the data collected on adults with ASDs and other childhood-onset neuropsychiatric disorders, a clinical assessment scheme that included all types of data collected for the NPG study as well as additional instruments was implemented at the Henri Mondor-Albert Chenevier hospital in Paris and at the Psychiatric Outpatient Clinic in Malmö. The aim was to provide data and biomaterial to the P.A.R.I.S molecular genetic study and clinical data to the Swedish Early-onset behaviour DISorders across diagnostic CATegories (DIS-CAT) study. The first 39 adult patients with a diagnosis of an ASD and normal intelligence from Paris and Malmö (29 men, 10 women, median age 25, range 16-47) are included in the analyses reported in *Paper III*.

FNP study group: pre-trial forensic psychiatric investigees (Paper II)

The Gothenburg Forensic Neuropsychiatry Project (the FNP project) consists of all 100 consenting subjects referred by criminal courts for inpatient forensic psychiatric investigations at the Department of Forensic Psychiatry in Gothenburg during a defined period of time. Inclusion required the subjects to be charged with a severe violent crime according to a predefined set of judicial definitions (homicide, attempted homicide, aggravated assault, arson, rape, or sexual violation of minors) and to have had their basic education in Sweden (92 men and 8 women, median age 30, range 17-76). The FNP study has been used for analyses of mental health problems and neurobiological aberrations among violent offenders (e.g. Soderstrom et al., 2004). In *Paper II*, the FNP study group was used together with the NPG group to analyze levels of aggression and their clinical correlates.

AN study group: research subjects with anorexia and comorbid ASDs (Paper IV)

The Gothenburg Anorexia Nervosa (AN) study is a longitudinal follow-up in four phases of a population-based cohort of teenage-onset AN and matched controls. In *Paper IV*, data are analyzed on the 16 (out of 51) original cases who had been assigned an ASD diagnosis at some phase of the project (1 man and 15 women, median age 32, range 26-34). In another AN case, empathy problems had been noted earlier, but after suffering a severe traumatic brain injury at about 20 years of age, she repeatedly displayed social interaction problems considered to correspond to an ASD. This subject was omitted since her social interaction problems had clear adult-age exogenous causes (even if these, of course, may have acted on an underlying susceptibility).

In this thesis, these 16 subjects are lumped with the other clinical groups of adults diagnosed with an ASD and stand out as a group with a female preponderance and a different pattern of comorbidity from that found in the other clinical groups. In the *Paper IV*, data on these subjects are analyzed in comparison to the AN subjects who had never been diagnosed with an ASD (2 men, 32 women, median age 33, range 29-34) and a control group of 51 subjects from the general population matched for age, socio-economic status (SES), and sex.

Table 6. Study group characteristics

	NPG (n=273)	P.A.R.I.S. (n=39)	FNP (n=100)	AN (n=16)
Males (n, %)	152 (56%)	29 (74%)	92 (92%)	1 (6%)
Females (n, %)	121 (44%)	10 (26%)	8 (8%)	15 (94%)
Age (years)	19-60	16-47	17-76	26-34
	(median 31)	(median 25)	(median 30)	(median 32)
Full scale IQ	42-134	72-139	45-150	73-127
	(median 87)	(median 94)	(median 89)	(median 99)[a]

[a]Assessed at the follow-up phase at a mean age of 21

Measures

In the NPG, P.A.R.I.S., and FNP study groups, individual diagnoses were assigned in consensus by at least two clinicians on the basis of all available information, including previous medical records, collateral interviews with caregivers from childhood (when possible), diagnostic instruments, current clinical status, and assessments by multi-professional teams with psychologists specially trained in test methods. In the AN study group, problems related to the ASDs and personality were evaluated by clinicians blind to previous information, while the remaining diagnostic work-up was performed as in the other study groups. Childhood developmental problems were thus assessed retrospectively in all studies included, using information from the research subjects, records, and, in most cases, also from their parents. The included instruments were not invariably used in all subjects in a study group due to clinical considerations taken in each project or to practical circumstances. In the NPG, P.A.R.I.S., and FNP study groups, several subjects had been assigned psychiatric diagnoses in previous contacts with various mental health services and were now secondary or tertiary referrals from specialists in adult psychiatry for additional diagnostic work-up. Childhood medical records, including previous psychiatric or psychological assessments, were provided by the patients or obtained from child medical centres.

Diagnostic interviews

The research protocols were at the time of their planning, standard assessment methods for clinical psychiatric practice, and the instruments used in these studies are good to excellent in terms of reliability and validity. All patients in the NPG study group had their final diagnoses confirmed in consensus by two clinicians (Maria Råstam and Henrik Anckarsäter), just as in the FNP project (Anders Forsman and Henrik Anckarsäter). In the P.A.R.I.S. study group, either of two clinicians (Marion Leboyer or Henrik Anckarsäter) was responsible for the final assessments of the subjects included. The principal investigator in the AN project (Maria Råstam) was responsible for the diagnostic decisions made in this study group, while the evaluations of ASDs in the latest phase of the project were in most cases made by Henrik Anckarsäter.

The Structured Clinical Interview for DSM IV – Axis I Disorders (SCID-I, First et al., 1997a) was generally used for diagnostic axis I assessments according to categorical DSM-IV diagnoses. In the P.A.R.I.S study, a structured, DSM-IV-based, clinical interview according to a life-time DSM-IV

symptom checklist containing individual criteria or symptom definitions for all relevant axis I disorders, in content corresponding to the SCID. The SCID-I is a semi-structured interview designed for use by trained clinicians for assessing most of the DSM-IV axis I diagnoses (AD/HD and ASDs are not included). It begins with an open-ended background part in which the history and development of the present mental health problems are penetrated, and tentative diagnostic hypotheses are generated. Then, the SCID systematically presents modules that allow for assessment of specific disorders and symptoms. Most disorders are evaluated for two time periods; current (meets criteria for the past month) and life-time (ever met criteria). During administration, each symptom is dichotomously rated as either present or absent, if sufficient information is at hand. In the FNP project, subjects not participating in the SCID-interview were psychotic and considered too unstable to pursue a full interview. For the P.A.R.I.S. project, the SCID-I was not used.

Axis II disorders of personality were assessed by the Structured Clinical Interview for DSM IV – axis II Personality Disorders (SCID-II, First et al., 1997b) in most cases and in the others by a DSM-IV-based clinical interview. The SCID-II closely resembles the SCID-I in its basic design and conventions. It covers the ten standard DSM-IV axis II PDs, as well as the depressive and passive-aggressive PDs, listed as disorders for further study in the DSM-IV appendix.

For all disorders, DSM criteria that limited the possibility of assigning other comorbid psychiatric diagnoses were disregarded to allow a comprehensive recording of the pattern of comorbidity.

Table 7. Methods used in the studies

Instrument	NPG (n=273)	P.A.R.I.S. (n=39)	FNP (n=100)	AN (n=16)	Total (n=428)
SCID-I	201 (74%)	0 (0%)[a]	89 (89%)	15 (94%)	305 (71%)
SCID-II	175 (64%)	39 (100%)	74 (74%)	16 (100%)	304 (71%)
ASDI-patient	226 (83%)	39 (100%)	89 (89%)	16 (100%)	381 (89%)
Collateral interview	181 (66%)	39 (100%)	31 (31%)	16 (100%)	267 (62%)
LHA	178 (65%)	not analyzed	92 (92%)	0 (0%)	270 (69%)
TCI	234 (86%)	not analyzed	78 (78%)	13 (81%)	325 (84%)
GAF	266 (97%)	not analyzed	100 (100%)	16 (100%)	382 (98%)
WAIS (-R or -III)	241 (88%)	31 (79%)	81 (81%)	16 (100%)	369 (86%)

[a]Instead a check-list based on the DSM-IV was used in all these subjects

Developmental history

Assessments of childhood-onset neurodevelopmental disorders were retrospective in all cases and, whenever possible, performed not only by self-report but also by an interview with a relative who had known the index subject as a child. For most subjects, a semi-structured collateral interview including the ASDI was used.

In all studies, diagnoses of AD/HD and ASD were assigned for all patients according to specific checklists including all relevant DSM-IV criteria and also the Gillberg and Gillberg (G & G)

criteria for AS/high-functioning autism (Gillberg & Gillberg, 1989). The patient version of the Asperger Syndrome/high functioning autism Diagnostic Interview (ASDI, Gillberg et al, 2001) was used in all studies, completed with assessments of perceptual hyper- and hypo-sensibilities. The ASDI is a semi-structured diagnostic interview, containing questions to ask the patient as well as observational issues, yielding 20 items that should be assessed by the clinician based on all information in a way similar to the SCID-interviews. These items systematically address the six G & G criteria by defined cut-off levels for each criterion. The collateral version is intended for use with informants with knowledge about the subject's developmental history and present functioning.

In the P.A.R.I.S. study group, the Autism–Tics, AD/HD and Other Comorbidities Inventory (A–TAC, Hansson et al., 2005), was used for collateral interviews in all cases. This is a recently developed Swedish telephone interview designed to cover core domains of ASDs, AD/HD, tics, and other common overlapping conditions. A preliminary validation was published a couple of years ago based on a study group from the CNC, and, recently, a new validation study used a large population-based data-set and a new group of clinical cases (Larsson et al., accepted for publication). These validations have provided screening and diagnostic algorithms with sensitivities and specificities well above 95% for all major neurodevelopmental disorders.

The Wechsler scales

The Wechsler Adult Intelligence Scale- Revised (WAIS-R, Wechsler, 1981) and the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III, Wechsler, 1997) were used in all the studies These scales are the most widely used psychometric instruments in Sweden for the assessment of cognitive functions and intellectual capacity in older adolescents and adults, providing measures of global intelligence (Full Scale Intelligence Quotient (FSIQ), verbal (VIQ) and performance (PIQ) scores). The WAIS-R comprises the following 11 subtests: Information, Comprehension, Arithmetic, Digit Span, Similarities, Vocabulary, Picture Arrangement, Picture Completion, Block Design, Object Assembly, and Digit Symbol. The WAIS-III is basically a development of the WAIS-R and has kept the previous 11 subtests, though with a slightly different content and design. Three subtests have been added: Matrix Reasoning, Letter-Number Sequencing, and Symbol Search. There is a substantial correlation between the WAIS-R and the WAIS-III (.80 and above), though subjects tested with the WAIS-III tend to get slightly lower scores compared to their test results on the WAIS-R (The Psychological Corporation, 1997).

Neuropsychological testing

In the AN study group, attention processes were measured with the Test of Variables of Attention (TOVA, Greenberg et al., 1993). The TOVA is a computerized, standardized visual continuous performance test. It consists of two visual stimuli that are presented for 100 milliseconds at two-second intervals in two 11-minute test conditions. The first half of the task presents the target infrequently, with intent to elicit boredom and thus measure the ability to sustain attention. The second half presents the target frequently and is designed to measure impulsivity. Scores on the following variables are calculated: errors of omission, errors of commission, mean correct response time, standard deviation response time, anticipatory responses (guesses), post-commission mean correct response times (average number of correct responses immediately), and multiple responses (more than one response per stimulus).

The Tower of London (ToL, Shallice, 1982) consists of a series of 12 problems of graded levels of difficulty demanding planning capacities, working memory, response inhibition, and visuospatial memory. The subject is required to move coloured beads between three vertical rods in order to match a goal arrangement. The constraints are that only one bead may be moved at a time, and only a specified number of beads may be left on each rod at a time. The total number of moves on each task, the time used before initiating each solution, the total time used for execution of task, and a total score are calculated in ToL.

The mental and non-mental cartoons test of Francesca Happé (Gallagher et al., 2000) was used to tap social cognitive abilities. This test consists of ten pictures, five of which are considered to reflect theory of mind skills, i.e. an attribution of mental state is needed to understand the cartoon, and the other five pictures are included as a control task. Results on each cartoon are presented on a four-point scale, 0 indicating "complete failure", 1 "being able to describe what's in the cartoon", 2 "being able to describe and understand the gist of the cartoon without giving a detailed account of the underlying theme", and 3 "being able to describe, understand, and provide a detailed account of what is going on in the cartoon".

Measures of aggression

The Life History of Aggression (LHA, Brown et al., 1982) was developed to measure the frequency of the occurrence of 11 distinct aggressive behaviours in research on neurobiological correlates to aggression. The assessment may be based on ratings by collaterals or health professionals in close contact with the subjects, such as ward staff, or by the subject him-/herself. It has been shown to have excellent test-retest stability, inter-rater reliability, and internal consistency reliability (Coccaro et al., 1997) and has been used in many studies of violent behaviour (e.g. Coccaro et al., 1998; Hoptman et al., 2002). It contains 11 items, each reflecting a different form of aggressive behaviour. Coccaro and co-workers (1997) used the items to create three a priori subscales. The Aggression subscale includes temper tantrums, physical fights, verbal aggression, physical assaults on people (or animals), and assaults on property (items 1-5). The Self-directed aggression subscale quantifies self-injurious and suicide attempts (items 6a and 6b). The Consequences/Antisocial behaviour subscale denotes school disciplinary problems, problems with supervisors at work, antisocial behaviour not involving the police, and antisocial behaviour involving the police (items 7-10). Each item is rated on a five-point scale based on the number of occurrences of the behaviour since adolescence, from 0 ("no events") to 5 ("so many events that they cannot be counted"), with possible total scores ranging from 0-55. In the present studies, the LHA was first administered as a self-rating instrument, although subjects who had problems filling-out self-rate questionnaires received help from contact persons or clinicians. Subsequently, patients´ self-reports were reviewed in relation to the extensive clinical interview and all available records and file reports.

Self-report instruments

To provide dimensional measures of personality, the Temperament and Character Inventory (TCI, Cloninger, 1993) was used in all study groups (the TCI results from the NPG study have previously been published by Anckarsäter et al., 2006). The TCI is based on Cloninger's personality theory (Cloninger, 1987), a model encompassing four dimensions of temperament and three dimensions of character. Temperament refers to individual differences in conditioned emotional responses, such as anger, fear, and disgust. The temperaments are dimensionally

distributed traits, namely, Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD), and Persistence (PS). Character refers to individual differences in goals, values, and self-conscious emotions such as shame, guilt, and empathy. The character dimensions are Self-Directedness (SD), Cooperativeness (CO), and Self-Transcendence (ST). The TCI is a 238-item, true-false, self-administered, paper-and-pencil test providing a raw score for each dimension that can be converted to standardized percentiles or t-scores.

The Autism Spectrum Quotient (AQ, Baron-Cohen et al. 2001) is a self-report instrument designed to quantify autistic symptoms in normal-intelligent adults. The AQ consists of 50 statements, reflecting personal beliefs, views, and preferences. The respondent can agree or disagree with each of these statements using a 4 point Likert scale (1 = "definitely agree", 2 = "slightly agree", 3 = "slightly disagree", and 4 = "definitely disagree"). The 50 items were divided by the authors into five theoretical subscales of ten items each: Social skills, Communication, Imagination, Attention to detail, and Attention switching.

Other assessments

Global Assessment of Functioning (GAF, American Psychiatric Association, 1994) was used in all studies. The GAF is a part of the multi-axial diagnostic assessment system in the DSM-IV. The GAF, a numeric scale (0 through 100), is intended to be a tool for the assessment of global (social, occupational, and psychological) functioning, noted on the axis V in the DSM diagnostic system. This supplements existing data on symptoms and diagnoses and helps predicting the allocation and outcome of mental health treatment.

Medical examinations

Somatic status according to structured checklists was assessed in all patients, and three-generation pedigrees were drawn.

Exclusion criteria

No patient was in need of language interpretation for communication. Cases with known medical causes of autism, including genetic syndromes, or injuries of relevance for the mental disorders assessed, were identified by history, physical examination, and in dubious cases by karyotype, Fragile X PCR, southern blot, and FISH analyses (15q11-q13, 22q11 and 22q13 deletion syndromes) and excluded from further analyses in the study groups focused on the ASDs (P.A.R.I.S, NPG, and AN). These subjects generally had FSIQ below the normal range. Subjects with normal intelligence and balanced translocations were kept in the studies. Organic and substance-related psychotic and mood disorders were differentiated and not included in the prevalence figures of these disorders.

Analytical methods

All data used in this thesis were anonymized, coded, and subjected to statistical analyses in the SPSS 15.0 or 17.0. Parametric and non-parametric statistical methods were used depending on the distribution of data.

In the meta-analyses presented in *Paper I*, differences in outcome between hyperactive subjects and controls were analyzed using χ^2-statistics.

Since data in *Papers II*, *III,* and *IV* were not normally distributed, statistical analyses of group differences were non-parametric. Fisher´s exact χ^2-test was used for group comparisons of frequencies of dichotomously fulfilled diagnoses or criteria. When variables were continuous, Mann-Whitney U Tests were used for comparisons between two groups and Kruskal-Wallis Test for comparisons between three groups. The Wilcoxon sign rank test was used to evaluate the median difference in paired data. In these analyzes, all p-values were two-tailed, and significance was considered at the 5% level. In *Papers II* and *IV*, correlations were analyzed with Spearman´s non-parametric correlation coefficients, with level of statistical significance set at 1% ($p \leq 0.01$) considering the number of analyses performed.

In *Paper II*, multiple linear regression analysis models were used to test the association between the clinical and demographical variables and the total score of the LHA. Initially, the full multivariable model included all independent variables that had shown a covariance by a $p<0.30$ in bivariate analysis, after which we excluded one insignificant independent variable at a time, starting with the variable with the highest p-value, until all remaining predictors had a $p<0.10$. However, we did not exclude variables that changed the estimated effect of symptoms of conduct disorder with more than 10%. The adjusted amount of explained variance (R^2) and standardized regression coefficients (β) are presented. The analysis of variance assessed the significance of the explained amount of variance (Adjusted R^2). A *t* statistic assessed the significance of β. P-values were two-tailed in all studies.

In *Paper IV*, Cohen´s kappas were calculated for analyses of diagnostic agreement across assessments.

Response rate

The NPG and P.A.R.I.S. projects were both consecutive studies including all patients referred to the clinics, and as these clinics were highly specialized assessment centres for subjects searching neuropsychiatric assessments, none declined participation in the studies. In the FNP project, 21 subjects who met criteria for inclusion declined to participate. These subjects had a higher incidence of psychosis but were otherwise comparable to those who entered the study. The response rate is detailed in Soderstrom et al., 2004. There were no subjects lost to follow-up in the AN study, but the degree of clinical information obtained varied, as detailed in Råstam et al., 2003 and Wentz et al., 2009.

Power

As these studies were descriptive and did not have any primary or secondary target variables defined pre-hoc, standard deviations and traditional power estimates could not be calculated. However, *Papers II, III,* and *IV* present clinical data from groups of sizes that are virtually unprecedented in earlier studies and report diagnostic overlaps to a greater extent than the existing literature, which supports that they have had power enough to detect the most substantial associations between diagnostic categories and assessments and thus avoid Type II errors (i.e. false negative findings).

Multiple comparisons

In *Papers II* and *IV*, the comparisons between instruments are descriptive and therefore not formally corrected for multiple comparisons in order to avoid Type I errors (i.e. false positive

results). The number of correlations analyzed in *Papers II* and *IV* will, on the 1% level set for significance, produce a negligible number of random significances (for example, the repeated bivariate correlations described in Table 2 of *Paper II* would, if the total group level is considered, have yielded one significant correlation on the 1% level by chance out of the 96 calculated). In fact, the significant correlations described in the paper were generally on the 0.1 % level and present in both groups, which makes it improbable that the main findings would be due to mass significance only.

Ethical aspects

All potential subjects in the projects contributing to this thesis were given written information about the studies and the opportunity to ask questions. All gave informed consent that the data compiled could be used for research. They were, at any given moment, free to interrupt their participation in the study. Clear information was provided about data handling and anonymization. In the FNP study group, subjects underwent a pre-trial forensic psychiatric investigation and were thus deprived of their liberty. Great caution was therefore applied in information and collection of consent. Several subjects in this project – and the other studies included - have kept contact with the researchers involved over the years and expressed their gratitude for the insights provided by participation in the studies. In all cases, subjects were further allowed to participate in some parts of the study but to refrain from others. All subjects were clearly informed that withdrawal from research participation would not affect the quality of their care. Subjects were not monetarily or otherwise rewarded for their participation, with the exception of those in the AN study group (which consisted of non-patients), who were compensated for any loss of income in connection with the last follow-up (AN-IV). All studies in this thesis were approved by relevant research ethics committees.

Results

AD/HD in adulthood

Paper I: Longitudinal studies of hyperactivity

Of all hyperactive children included in the meta-analysis (summarized in Table 8), 32% met criteria for CD at some point during their childhood or adolescence, as compared to 5% of the controls. Among the cases where diagnostic stability was assessed, only 6% of the original group met criteria for AD/HD (combined type) as adults. However, a large proportion of the subjects met criteria for other axis I and II disorders. Violent deaths were more common in the hyperactive group (n=7, 1.3% compared to n=1, 0.3% in the control group), a difference that did not reach statistical significance. Seventeen per cent of the hyperactive children met criteria for ASPD in adulthood. This prevalence was significantly larger ($p<.001$) than that in the control group (3%). However, since all the studies included in this review either included children with a wide age range from start, or did not systematically assess both CD and hyperactivity before the proposed cut-offs at ages 10, 12, or at puberty, none of them could demonstrate that AD/HD alone, in the absence of CD, predicted ASPD. Nor could the review show that attention deficits, in the absence of hyperactivity, played a part in the longitudinal outcome of AD/HD subjects.

Table 8. Summary of follow-up data on hyperactive and control children. The total numbers differed between the outcome measures and therefore only percentages are given in this table.

	Cases	Controls	p
CD childhood/adolescence	32%	5%	p<.001
ASPD in adulthood	17%	3%	p<.001
AD/HD in adulthood	6%	0.3%	p<.001
Violent deaths	1.3%	0.3%	ns

Paper II: AD/HD and aggression in adults

Group comparisons indicated that the psychiatric outpatients with neurodevelopmental problems and the forensic psychiatric group had similar levels of aggression on the composite LHA score (Total) and on the subscores of Aggression and Self-directed aggression. However, there were significantly higher scores on Antisocial behaviour in the forensic group ($p\leq0.001$). The only difference that emerged between men and women was a significantly higher score for men on Antisocial behaviour in the total study group ($p<0.01$). In the forensic group, age was negatively correlated to all LHA scores except that for Self-directed aggression but did not correlate to any LHA score in the outpatient group or in the total group.

Strong positive correlations were seen between all LHA subscales (except the Self-directed aggression subscale) and criteria for attention deficits, hyperactivity, CD symptoms before the age of 15, and alcohol or drug abuse/dependence. The number of SCID-II personality disorder diagnoses, used as a dimensional variable, was also positively correlated with all LHA subscales. Among the TCI measures of temperament, only high Novelty Seeking was correlated to LHA

(except the Self-directed aggression score). All three character variables (low Self-Directedness, low Cooperativeness, and high Self-Transcendence) were significantly related to the LHA scores. IQ and GAF-scores were negatively correlated with the Self-directed aggression subscale. In contrast to all other studied variables, ASD symptoms showed a non-linear relation to LHA across the two groups. Low rate of autistic symptoms was correlated to high LHA scores in the outpatient group, while the opposite was true for the forensic group.

We eventually tried to identify the most important clinical covariates of aggressive behaviour patterns in a linear regression model, using the variables from the correlation analyses. In the total study group, conduct problems before the age of 15 emerged as the single most important predictor, followed by three other significant, independent predictors: hyperactivity, drug abuse/dependence, and low Cooperativeness (Table 9). In this model, the independent variables predicted 49% of variance (adjusted R-square) in the dependent variable ($p<0.001$).

Table 9. Multiple regression analyses with LHA total score as dependent variable and clinical and demographical variables as predictors

Predictor	β	95 % CI	t
Clinical variables			
Hyperactivity symptoms	0.22	0.16-1.64	2.39*
Drug abuse	0.16	0.40-9.04	2.16*
Conduct symptoms	0.31	0.65-1.93	3.97***
TCI dimensions			
Cooperativeness	-0.10	-0.25- -0.04	-2.81**

ASDs and co-occurring problems in adult age

Papers III and IV: Clinical characterization and psychosocial adversities in adults with ASDs

Clinical autistic features

In *Paper III*, virtually all subjects (n=119, 98%) displayed symptoms required for the first DSM-IV and G & G criterion (i.e. social interaction problems, in the DSM-IV also including non-verbal communication deficits). Accordingly, nonverbal communication problems according to the fifth G & G criterion were very common, described in 89% (n=108) of all subjects. The AS and the PDD NOS subjects did not differ significantly in the DSM-IV and G & G areas of social interaction and the DSM-IV area of communication.

A similar pattern of autistic features was found among the ASD subjects in *Paper IV*, including predominantly women. All subjects met criteria for deficits in social interaction and non-verbal communication (the first DSM-IV and the first and fifth G & G criteria). Flexibility problems were found in a subgroup of these ASD cases, while verbal communication problems were present only in a few subjects and did not characterize the ASD group with eating disorders as a whole.

Table 10. Distribution of DSM-IV and Gillberg and Gillberg (G & G) criteria across the diagnostic categories and study groups in *Papers III* and *IV*

	Autistic disorder (n=6)	Asperger´s disorder (n=70)	PDD NOS (n=59)	Total (n=135)
Paper III	5 (4%)	67 (55%)	50 (41%)	122 (100%)
Paper IV[a]	1 (8%)	3 (23%)[b]	9 (69%)[c]	13 (100%)
DSM IV criterion A1: "Qualitative impairment in social interaction"				
Paper III	5 (100%)	67 (100%)	47 (94%)	119 (98%)
Paper IV	1 (100%)	3 (100%)	9[c] (100%)	13 (100%)
DSM-IV criterion A2: "Qualitative impairment in communication"				
Paper III	5 (100%)	34 (51%)	18 (36%)	57 (47%)
Paper IV	1 (100%)	0 (0%)	2 (22%)	3 (23%)
DSM-IV criterion A3: "Restricted, repetitive and stereotyped behavior, interests, and activities"				
Paper III	5 (100%)	65 (97%)	29 (58%)	99 (81%)
Paper IV	1 (100%)	3 (100%)	4 (44%)	8 (62%)
G & G criterion 1: "Social interaction problems"				
Paper III	5 (100%)	67 (100%)	47 (94%)	119 (98%)
Paper IV	1 (100%)	3 (100%)	5 (56%)	9 (69%)
G & G criterion 2: "Narrow interests"				
Paper III	5 (100%)	64 (96%)	33 (66%)	102 (84%)
Paper IV	1 (100%)	3 (100%)	4 (44%)	8 (62%)
G & G criterion 3: "Repetitive routines"				
Paper III	5 (100%)	61 (91%)	25 (50%)	91 (75%)
Paper IV	1 (100%)	3 (100%)	3 (33%)	7 (54%)
G & G criterion 4: "Speech and language"				
Paper III	5 (100%)	56 (84%)	22 (44%)	83 (68%)
Paper IV	1 (100%)	0 (0%)	1 (11%)	2 (15%)
G & G criterion 5: "Non-verbal communication problems"				
Paper III	5 (100%)	66 (99%)	37 (74%)	108 (89%)
Paper IV	1 (100%)	3 (100%)	6 (67%)	10 (77%)
G & G criterion 6: "Motor clumsiness"				
Paper III	5 (100%)	57 (85%)	31 (62%)	93 (76%)
Paper IV	1 (100%)	2 (67%)	0 (0%)	3 (23%)

[a]In the AN group, the most recent ASD diagnosis or, if in remission, the most frequent ASD diagnosis across earlier assessments is reported; [b]Details from three of these six subjects were not available at the time of writing; [c]In two cases the A1 criterion was met atypically

AD/HD comorbidity

A large proportion of all subjects in *Paper III* (n=52, 43%) were diagnosed with AD/HD. Subjects with PDD NOS had significantly more symptoms of inattention (p=0.01) and

hyperactivity/impulsivity (p=0.007) compared to subjects with AS. However, the prevalence of the categorical diagnosis of AD/HD did not differ significantly between the groups. Among the ASD cases in *Paper IV,* none met criteria for AD/HD.

Other axis I disorders

In *Paper III*, all subjects with AS or PDD NOS had at least one comorbid axis I disorder (95% if AD/HD was not included), while among the small number of subjects with AD, 80% (n=4) met criteria for at least one other major axis I disorder. The most common life-time comorbid condition was mood disorder (n=65, 53%) followed by anxiety disorder, affecting 59 subjects (50%). One-third of subjects (n=42, 34%) had been treated with an antidepressant at least once in their lives. Criteria for a bipolar disorder (BP) were met by 10 subjects (8%). No subject with AD met criteria for BP. Only three patients (2 %) had ever been treated with a mood stabilizer. In *Paper IV*, all 16 subjects met criteria for at least one axis I disorder other than anorexia and ASD. All of these ASD subjects met criteria for a mood disorder, either depression or bipolar disorder, at some point in their lives. Almost as many (88%) met criteria for an anxiety disorder. OCD was very common in both groups, affecting 24% in *Paper III* and 44% in *Paper IV*.

A considerable number of patients in *Paper III* (n=15, 12%) met criteria for a psychotic disorder (most often not otherwise specified). Eighteen subjects (15%) had, at least once in their lives, been treated with neuroleptics of any kind. In *Paper IV*, two ASD subjects (13%) met criteria for a psychotic disorder (schizophrenia in one case and schizophreniform disorder in the other). No subject in *Papers III* or *IV* met criteria for schizoaffective disorder.

Sixteen per cent of the subjects in *Paper III* (n=19) met criteria for a substance use disorder (SUD). The PDD NOS group had significantly more SUD-related diagnoses than the AS group (p=0.002). The majority of diagnoses were related to alcohol (n=15, 12%), four subjects met criteria for cannabis use disorder, three for amphetamine use disorder, two had a history of taking non-prescribed opiates or analgesics, and one had used anabolic steroids. Another subject, a 27-year-old man with AD, had a history of inhaling solvents. In *Paper IV*, there were no ASD subjects fulfilling a SUD-diagnosis.

Among patients in *Paper III* affected with impulse control disorders, intermittent explosive disorder was the most common diagnosis (n=7, 6%), followed by kleptomania, pyromania, pathological gambling, trichotillomania, and impulse control disorder NOS, all affecting one patient each. In *Paper IV*, the prevalence of these disorders was not investigated.

Six patients (5%) in *Paper III* had an eating disorder. This condition was twice as common in the PDD NOS group as in the AS group, though this difference did not reach statistical significance.

Overall, there were no significant differences in axis I comorbidity between male and female subjects in *Paper III*, but a tendency was found for major depression, OCD, and eating disorders to be over-represented among the female subjects. The opposite was seen for psychotic disorders, which tended to be more common among men with ASDs in this study.

Table 11. Life time prevalence of axis I disorders in subjects with ASDs

	Paper III (n=122)	Paper IV (n=16)	Total (n=138)
AD/HD	52 (43%)	0 (0%)	52(38%)
Chronic tic disorder	25 (20%)	not analyzed	25 (20%)
Mood disorder	65 (53%)	16 (100%)	81 (59%)
Psychotic disorder	15 (12%)	2 (13%)	17 (12%)
OCD	29 (24%)	7 (44%)	36 (26%)
Anxiety disorder	59 (48%)	14 (88%)	73 (53%)
Eating disorder	6 (5%)	16 (100%)	22 (16%)
Impulse control disorder	11 (9%)	not assessed	11 (9%)

Personality disorders

Rates for personality disorders (PD) according to DSM-IV were high in *Paper III*, with almost two-thirds (n=73) meeting criteria for at least one PD. Obsessive-compulsive PD (OCPD) was significantly more common in the AS group (p=0.04) and ASPD in the PDD NOS group (p=0.04). The overall frequency of PDs did not differ between men and women, with the exception of schizoid PD, which was significantly more common among the female subjects (p=0.02). In *Paper IV*, OCPD was by far the most common PD, affecting 75% (n=12) of the group. Only two subjects did not meet criteria for a PD (i.e. 88% had a PD). Well over half of the group (56%) met criteria for two or more PDs.

Personality dimensions

Self-rated personality traits, as conceptualized by the TCI, in the ASD subjects in the NPG and AN projects differed dramatically from the patterns seen in normal subjects. Means and standard deviations in T-Scores are reported in Table 12. The ASD subjects had a TCI temperament profile of high Harm Avoidance and low Reward Dependence. Very low scores on Self-Directedness and Cooperativeness indicated "character immaturity" and a high prevalence of PDs.

Table 12. TCI dimensions in ASD subjects compared to the norm (T-score 50, with a standard deviation of 10) with One-sample t-test[a]

TCI-dimension	Mean and standard deviation	One-sample t-test
Novelty Seeking	49±12	ns
Harm Avoidance	64±13	<0.001
Reward Dependence	43±11	<0.001
Persistence	52±13	ns
Self-Directedness	34±14	<0.001
Cooperativeness	37±17	<0.001
Self-Transcendence	52±14	ns

[a]Unpublished data

Neuropsychological functioning

A Wilcoxon sign rank test was conducted for the patients from *Paper III* to evaluate the differences between VIQ and PIQ for the different ASD groups (Table 13). The difference was significant in the AS group (Z=-5.192, p=<.001) as well as in the PDD NOS group (Z=-3.175, p=.001) but not in the AD group (Z=0.677, p=.625).

In *Paper IV*, the ASD cases had lower results than normal controls on Working Memory Index (WMI, p<0.05) and on its subtest Arithmetic (p<0.05). On the T.O.V.A., the ASD subjects made significantly fewer impulsive errors (Commissions, p<0.01). Further, the ASD subjects had significantly fewer correct answer on the Happé's cartoons, on those requiring a theory of mind (p<0.01) as well as on those considered not to (p<0.05), compared to normal controls.

Table 13. Differences between ASD groups from the NPG project (n=114) on VIQ minus PIQ[a]

		FSIQ	VIQ	PIQ	Comparison
	n	Mean (SD, range)	Mean (SD, range)	Mean (SD, range)	VIQ-PIQ[b]
					p
Autistic disorder	5	97 (21.7, 79-132)	95 (17.5, 80-121)	100 (23.3, 73-137)	ns
Asperger´s disorder	61	99 (17.6, 71-139)	104 (18.8, 66-155)	93 (16.1, 62-128)	<.001
PDD NOS	48	91 (15.2, 70-134)	96 (15.4, 75-131)	87 (16.8, 56-130)	.001

[a]Unpublished data; [b]Wilcoxon sign rank test, exact method for the AD group

Psychosocial complications

In *Paper III*, a majority of the subjects (n=68, 56%) reported that they had been bullied at school. Such victimization was most common among the women (p=0.02). The educational level was relatively high in the entire study population. Two-thirds (n=77, 65 %) had graduated from upper secondary school, and a quarter (n=29, 24 %) had completed college or university studies. In terms of daily occupation, 43% (n=50) were employed or students at the time of the assessment, with no significant differences between males and females. The others had no organized daily activities, were on sick leave, held a medical pension, or were unemployed. Half of the subjects aged 23 years or more had independent living arrangements, as did some of the younger subjects. Only 19 (16%) had lived in a long-term relationship, but 31% had children. Men and women did not differ in terms of marriage or cohabitation. In *Paper IV*, a considerable number of ASD subjects (n=9, 56%) reported being bullied during their school years. At the latest follow-up, half of the group (n=8, 50%) had a medical pension or were on extended sick leave. The mean GAF score was low, 55 (median=55, sd=18.6, range 30–90). Fifty-six per cent (n=9) had poor psychosocial functioning with GAF scores of 55 or below.

Summary of findings

(1) At least half of hyperactive children develop ODD and about a third CD (i.e. AD/HD+CD or HKCD) before puberty. About half of children with this combined problem constellation develop criminality and/or antisocial personality disorder (ASPD) in adulthood. Notwithstanding occasional claims to the contrary, the existing literature does not allow the conclusion that AD/HD alone (in the absence of intermediary CD), or attention deficits (AD/HD, inattentive subtype without hyperactivity) are risk factors for ASPD in adult life. (*Paper I*)

(2) Adult outpatients with AD/HD and/or ASDs had similar scores on the Life History of Aggression (LHA) instrument as subjects referred for forensic psychiatric investigations for severe violent or sexual crimes. High LHA scores were independently predicted by childhood CD (as the strongest factor in a multivariate analysis), the hyperactivity facet of AD/HD, substance-related disorders, and low development of the character dimension Cooperativeness. Lower IQ and GAF were correlated with Self-directed aggression. Among outpatients, autistic features were inversely correlated with aggression, while the opposite pattern was noted in the forensic group. (*Paper II*).

(3) Social interaction deficits (including restrictions in non-verbal communication) were present in virtually every adult outpatient assigned a diagnosis in the autism spectrum irrespective of diagnostic subgroup (autistic disorder (AD), Asperger´s disorder (AS), or pervasive developmental disorder not otherwise specified (PDD NOS)). Contrary to current DSM criteria, verbal communication deficits were common in all three subgroups. Almost all adult patients with ASDs had at least one additional life-time psychiatric axis I disorder, most notably mood and anxiety disorders, but also AD/HD and psychotic disorders. The frequencies of these diagnoses did not differ between the ASD subgroups or between males and females. AD/HD was common in all ASD subgroups studied, with the notable exception of subjects with ASDs and anorexia nervosa, none of whom had AD/HD. Antisocial personality disorder and substance abuse were more common in the PDD NOS group than in the other categories. Of all adults diagnosed with ASDs, less than half led an independent life and comparatively few had ever had a long-term relationship. Female subjects more often reported having been bullied at school than male subjects (*Papers III* and *IV*).

(4) The majority of adults with ASDs met DSM-IV criteria for one or several personality disorders (PDs), most commonly obsessive-compulsive PD (OCPD). ASPD was significantly more common in the PDD NOS group, compared to the other ASD groups. Self-rated personality also differed significantly from that seen in normal subjects. A temperament profile of anxious and pessimistic (high Harm Avoidance) traits in combination with a hampered development of conceptual interpersonal character (low Cooperativeness) and Self-Directedness was consistent with the high prevalence of PDs (*Papers III* and *IV*).

Discussion

Limitations

This thesis encompasses methodologically different approaches to the study of AD/HD and ASDs in adults, each with specific pros and cons:

(1) In the search process for longitudinal studies of hyperactive children (Paper I), the choice of key words inevitably limited the scope of the studies included. In addition, a number of studies of potential interest to the overall aims of the review were dropped from the list of included studies as they did not match the criteria set up for the review. For example, the IDA-study (Magnusson & Dunér, 1981) was omitted due to the fact that the diagnostic procedures were too far removed from clinical practice. Even if we tried to select the included studies by clear and pre-defined criteria, this process may not have been altogether free from arbitrariness. As systematic reviews have been assigned an increasingly high importance in the scientific literature, the possibility of bias in selection has been acknowledged. There is also the obvious risk that relevant but older studies have been published in books or other non-indexed sources that have escaped our attention.

(2) The meta-analysis (*Paper I*) is not presented with effect sizes as a measure of the strength of the relationship between the hyperactivity and ASPD. We concluded that the studies included were, at base-line, too diverse in terms of diagnostic criteria and overall protocol design to perform such results reliably.

(3) In the cross-sectional study groups (NPG and P.A.R.I.S.), no formal control groups representative for the general population or other types of outpatients were assessed. Instead, in *Paper II*, another cross-sectional group (FNP) was used for comparisons. All these subjects were, however, consecutively recruited, which supports the argument that they were representative for the type of setting and patient groups they were recruited from.

(4) The likelihood that Berkson effects and referral bias have resulted in a disproportionate number of individuals with comorbid disorders in the NPG, P.A.R.I.S., and FNP study groups is obvious. These problems are discussed in reference to the possibility of inflated prevalences of the clinical and psychosocial correlates investigated. We nevertheless think that our results are probably representative for other clinical settings, if not for the general population or for all adults meeting diagnostic criteria for AD/HD and/or ASDs.

(5) Even if most instruments used have previously been subjects of formal assessments of inter-rater and test-retest reliability, the design of the clinic-based study groups reported here did not allow formal tests of these psychometric properties for the actual patient groups and raters.

(6) The extensive use of retrospective, self-reported information in the diagnoses of AD/HD and ASDs is a major problem in non-prospective, adult studies (Mannuzza et al., 2002;

Barkley et al., 2002). When targeting adult groups of patients who most often have not previously been assessed for childhood-onset disorders, the diagnostic processes have to rely on all available information. In most cases, this has meant that self-reports were complemented with collateral interviews and clinical records collected from paediatric, child psychiatric, and school health services. In addition, in the studies presented here, most diagnoses were made in consensus by two experienced clinicians. These measures should somewhat reduce the risk that recall bias has exerted a decisive influence on diagnoses.

(7) As we have stated in *Paper II*, the LHA is an instrument assessing the frequency of different aggressive behaviours. This has far-reaching implications for how the results in this paper can be interpreted. Even though the frequency of aggressive acts did not differ between the two study groups, several of the patients investigated in the pre-trial assessments were subsequently convicted of violent offences with consequences far more detrimental than a large number of every-day life aggressive behaviours.

(8) In *Paper III*, two study groups (NPG and P.A.R.I.S.) were pooled albeit there were significant differences between them in terms of age and diagnostic subgroup adherence. However, these studies had very similar designs regarding recruitment procedures, and the research protocols were attuned. Even if the differences between the groups reduce the value of statistical analyses, it may be argued that they represent two slightly different types of adult outpatients with ASDs, and that their differences thereby add to the overall representativeness of the collapsed study group. Similarly, it may be argued that the small study group of subjects with AN and ASDs add yet another type of subjects to the total picture.

(9) In *Paper III*, our assessments of psychosocial outcome did not involve structured measures. However, as stated by Helt and colleagues (2008, p. 341), variables such as "living independently, working full-time, being married, and having friends" have generally been considered to be good indicators of outcome in the literature, at least for adults. It is not evident that structured scales would have added to this information.

(10) Though largely homogenous, the instruments used in the different study groups vary. These studies are all based in clinical practice, which means that a certain degree of freedom is unavoidable when it comes to choice of methods. Further, the response rate on some of the instruments was below the expected. In the individual meeting with a patient, the clinician is obliged to make a decision as to what instrument to use. In cases where the patient has been psychotic, for example, long, structured interviews have generally not been feasible.

(11) Some instruments used in the FNP study group have been shown to be less adequate for clinical or research purposes (e.g. the Wender Utah Rating Scale, which is not well validated). This is due to the fact that they were still considered to be standard instruments at the time when that project was designed.

Comments to main findings

(1) Studies on the longitudinal development of hyperactivity are quite consistent on some basic figures: the majority of children identified as hyperactive (equivalent to the diagnoses of AD/HD-C, AD/HD-HI, or HKD), will, at least during some period, develop a pattern of social interaction characterized by opposition, which, in at least a third of all hyperactive children, progresses into pre-adult antisocial behaviour. In about a fifth of the original group, this will persist into an ASPD in adulthood. Inattention has not really been studied in relation to risk of adult antisociality, and whether inattention should be described as a co-existing problem to hyperactivity (as in the ICD-10) or as a facet in a common syndrome (as in the DSM-IV) is still unclear. The tentative conclusion from the 1990 review by Lilienfeld and Waldman, that the risk for adult ASPD in hyperactive children is mediated by early-onset antisocial behaviours has still, due to methodological pitfalls of the longitudinal studies conducted, not been refuted. There is reason to believe that attention deficits and hyperactivity also predict later adult ASPD, but such a model would produce a considerable number of false positives. The risk seems to be mediated by the developmental pathway, in which symptoms of hyperactivity increase the risk of conduct problems, thereby leading to ASPD. In clinical settings, AD/HD symptoms appear to be nearly ubiquitous when diagnostic criteria for early-onset CD are met, while late-onset CD often has quite different types of backgrounds. These findings may help us to refine existing models of hyperactivity and childhood-onset aggressive antisociality (Moffitt, 1993; Lynam, 1996; Lahey & Waldman, 2003), conceptualizing a single behavioural progression model from hyperactivity to aggressive antisocial behaviours, known to have a high heritability (Burt, 2009), specifying the age at onset, and subsequently use all types of proposed underlying problems, such as attention deficits, as covariates in empirical studies rather than as parts of theoretically defined "syndromes", such as AD/HD with CD.

(2) In accordance with our clinical experience, outpatients referred for neurodevelopmental assessments had considerable scores on the LHA measure of aggression, actually on the same level as subjects referred for pre-trial forensic examinations because of severe, aggressive crimes. The only difference found was significantly higher scores on antisocial behaviours in the forensic group. Since men had significantly higher antisocial scores, the substantially larger proportion of men in the forensic group (92% vs. 55%, $\chi 2$=38.7, df=1, p<0.001) is one possible explanation to this finding. Another possible explanation would be that during forensic psychiatric investigations, antisocial behaviours are focused from various angles throughout the assessment, which could increase their detection.

The results support an association between increased levels of aggression and hyperactivity, conduct problems, substance abuse, and low scores on the character dimension of Cooperativeness in adults both from a non-correctional and a forensic setting. No other mental disorder category showed the same associations with aggression as these childhood-onset behavioural disorders, substance abuse, and specific immature personality traits in social interaction. This can be due to the selection in the present study groups, and calls for replication in other general psychiatry groups, but we think that it may at least be accepted as a preliminary finding, as our two groups indeed covered a broad variation of psychiatric co-existing conditions, and the findings were consistent across both groups.

Early-onset conduct problems showed the strongest association with the different measures of life-time aggression, including self-injurious behaviours. Our analyses also suggest that the hyperactive dimension of AD/HD (and not the inattentive) is more predictive for high aggression scores in adulthood. Our finding that hyperactivity was independently associated with aggression is seemingly in contradiction with our previous conclusion that this effect was mediated through early-onset CD. It is therefore crucial to remind ourselves again that our earlier standpoint, following Lilienfeld and Waldman, that the risk for later antisociality carried by hyperactivity is mediated through early-onset CD only refers to the current, prospective, longitudinal literature, which has been unable to test the hypothesis that hyperactivity in the absence of early CD still forms an independent risk factor for later criminality.

Further, in our study group, low IQ was significantly related to self-injurious behaviours, but contrary to several other studies (Harris, 1993; Emerson et al., 2001), IQ was not related to other forms of aggressive behaviour or antisociality. The strong relationship between violent criminality and substance abuse has been demonstrated in a variety of settings, in prison surveys (Fazel et al., 2006) as well as in inpatient medical facilities (Steadman et al., 1998). Cloninger (1981) described a hereditary vulnerability model of alcoholism (Type II alcoholism) including early-onset substance abuse and disruptiveness, and a specific personality profile (high Novelty Seeking, low Reward Dependence, and character immaturity). Gustavson and colleagues (2007) replicated the importance of these personality and behavioural correlates in a model predicting violent recidivism. Our study supports these findings in an outpatient as well as a forensic psychiatric context.

(3) ASDs in adulthood may be diagnosed according to criteria reflecting the same socio-communicative deficits as in children. A wide range of symptoms will be found in all subgroups, questioning the current classification. Across all ASD subgroups, deficits in social interaction and non-verbal communication seem to form a coherent clinical entity, the "core autistic deficit", extending the formulation of the first criteria in the DSM-IV to be the basis and characteristic feature of all ASDs. In adults with ASDs, seen in clinical settings, there seems to be a considerable number who do not present with verbal communication deficits, even if they are not uncommon among subjects diagnosed with Asperger's disorder in spite of criteria to the contrary (paradoxically, the Gillberg & Gillberg criteria include verbal abnormalities that would in many cases preclude a diagnosis by the DSM-IV criteria, and it has been argued that not a single of Asperger's original cases would have met the current DSM-IV criteria for the disorder that carries his name, Miller & Ozonoff, 1997). Another subgroup diagnosed with PDD NOS did not meet criteria for restricted, repetitive behaviours and interests. Ronald and coworkers (2005, 2006) presented evidence that the triad of autistic deficits is genetically heterogeneous, with genes influencing social interaction deficits and repetitive behaviours most likely being non-overlapping. Autism and autistic traits seem to lie on a continuum of impairment, and we appear to be far from a professional consensus on the best model for classifying the ASDs.

Patterns of psychopathological comorbidity are insufficiently described in adult patients with ASDs. This study demonstrated the high rates of DSM-IV axis I disorders, especially depression and AD/HD, affecting all patients seen in clinical practice. Earlier studies (Guttmann-Steinmetz et al., 2009) have confirmed the mediating role of comorbid

hyperactivity and oppositional behaviours in young subjects with ASDs in predicting conduct problems. In our study group, the PDD NOS subgroup was more affected by disruptive symptoms in childhood, substance abuse disorder, and adult ASPD compared to the other two ASD subgroups. This is in accordance with a recent review of the literature on ASDs among institutionalized subjects, which showed small over-representations, within the margins of random, for AD and AS, but a very considerable subgroup, between 10 and 15%, meeting criteria for PDD NOS across all forensic and institutionalized groups reported so far (Anckarsäter et al, 2008b). Differences in clinical presentation and outcome between men and women were few. However, AD/HD and substance abuse problems seem to be rare among the predominantly female subjects concomitantly affected with eating disorders. Our results reflect the indistinct demarcations of the adult clinical neurodevelopmental phenotypes, with a very high degree of coexistence with other mental disorders, and, as based on the literature, a fuzzy border towards the normal variation (Constantino & Todd 2003, Anckarsäter et al., 2008a). The importance of the clinician's attention to a wide spectrum of psychiatric symptoms and a patient-focused rather than a disorder-focused approach is obvious. These findings also point to the need of careful re-examination of the exclusion criteria for adult patients with ASDs and other diagnoses, such as schizophrenia or mental retardation, in the next revision of the DSM. Finally, in spite of a normal or high intelligence, most subjects who seek clinical assessments of ASDs have a considerable psychosocial impairment in addition to the subjective suffering created by socio-communicative shortcomings in everyday life and the experience of otherness and marginalization frequently described by our patients.

(4) Personality has long been an ambiguous term referring to heterogeneous aspects of an individual, such as emotions, affects, reality testing, interpersonal behaviour, and ability to control impulses. It has been presumed to be consistent from adolescence or early adulthood into mature adult life. While the association between AD/HD and related constructs in childhood and adult ASPD since long has attracted scientific interest, the literature on AD/HD and PDs outside the field of antisocial behaviours is much more scarce, and in the ASDs, it is virtually non-existent but for publications by Wolff and colleagues on boys/children with what was at the time called "schizoid PD" but later acknowledged to be more or less overlapping with Asperger syndrome (Wolff, 2004). Using the TCI, it has been possible to disentangle the temperament profiles associated with AD/HD (high Novelty Seeking) and ASDs (low Reward Dependence, high Harm Avoidance), and identify a common progression into a disordered character profile (Anckarsäter et al., 2006). In our analyses of aggression among adults, low character development in relation to others was an independent, significant predictor besides drug abuse, hyperactivity, and CD, which highlights interpersonal, social cognitive distortions and empathetic aspects in the background of aggression, in line with the larger literature on psychopathic personalities (Kiehl, 2006). The results presented here provide further support for the temperament aberrations described in ASDs, showing the same profile in a patient group with ASDs and a large female representation. The common adult outcome of childhood neuropsychiatric disorders seems to be a hampered development of character as a conceptual guidance of the own behaviour and in relation to others.

Most subjects with AD/HD and ASDs diagnosed with PDs meet the criteria for more than one disorder in the DSM-IV system, even from several different clusters, which implies that this system is inadequate for describing these patient groups. Finally, the empirical results presented here are in line with the conceptual overlaps between the definitions for PDs and for neuropsychiatric disorders. Instead of arguing which one of these classifications is the most accurate, they can probably be conceived as two different aspects of describing similar function deficits.

Clinical implications and future research directions

In describing the clinical expression of the neurodevelopmental disorders, in addition to the age at onset, the possibility in the current diagnostic system of severity ratings of mild, moderate, and severe is often forgotten. Severity as measured by the behaviour expressions, the psychosocial adverse effects and the subjective health impact could aid clinical assessment schemes in following outcome and make them compatible with scientific endeavours.

Aggression is a central problem constellation for psychiatric investigations and treatment planning, not only in forensic psychiatric settings but also in community-based adult psychiatric services. The use of information about behavioural aberrations, especially conduct problems, in childhood and adolescence should become core ingredients in clinical psychiatric assessments. For the other neurodevelopmental disorders, a tentative conclusion based on the current literature might be that AD/HD is specifically associated with frequent aggressive behaviours, while autism may entail a risk of, especially stress-related, violent acting out.

The detection and description of female subjects within the neurodevelopmental spectrum is still hampered by criteria and instruments designed for males. Indications of similarities in the clinical phenotypes of men and women should, however, call for caution to avoid sex-stereotyping of psychiatric problems.

Finally, childhood-onset neurodevelopmental disorders are highly overlapping conditions, and clinicians must be attentive to a wide spectrum of psychiatric symptoms when seeing these patients. These disorders are most probably waxing and waning in their expression, above and below the current diagnostic cut-off level, and in clinical practice there seems to be good reason to let no single kind of clinical information take precedence and to consider also sub-threshold problems or risk phenotypes. Situational factors rather than the underlying susceptibility may determine the actual symptom expression at a precise moment, which calls for a developmental perspective in assessments.

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Paper I

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Continuity of aggressive antisocial behavior from childhood to adulthood: The question of phenotype definition ☆

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ABSTRACT

Aiming to clarify the adult phenotype of antisocial personality disorder (ASPD), the empirical literature on its childhood background among the disruptive behaviour disorders, such as attention deficit/hyperactivity disorder (AD/HD), oppositional defiant disorder (ODD), conduct disorder (CD), or hyperkinetic conduct disorder (HKCD), was reviewed according to the Robins and Guze criteria for nosological validity. At least half of hyperactive children develop ODD and about a third CD (i.e. AD/HD + CD or HKCD) before puberty. About half of children with this combined problem constellation develop antisocial personality disorder (ASPD) in adulthood. Family and adoption/twin studies indicate that AD/HD and CD share a high heritability and that, in addition, there may be specific environmental effects for criminal behaviours. "Zones of rarity" delineating the disorders from each other, or from the normal variation, have not been identified. Neurophysiology, brain imaging, neurochemistry, neurocognition, or molecular genetics have not provided "external validity" for any of the diagnostic categories used today. Deficient mental functions, such as inattention, poor executive functions, poor verbal learning, and impaired social interaction (empathy), seem to form unspecific susceptibility factors. As none of today's proposed syndromes (e.g. AD/HD or psychopathy) seems to describe a natural category, a dimensional behavioural phenotype reflecting aggressive antisocial behaviours assessed by numbers of behaviours, the severity of their consequences and how early is their age at onset, which will be closely related to childhood hyperactivity, would bring conceptual clarity, and may form the basis for further probing into mental, cognitive, biological and treatment-related co-varying features.

1. Introduction

That problem behaviours in children may herald psychosocial problems in adult life is basically a universal insight and the mainstay of most educational efforts. The association has also been demonstrated in a number of longitudinal studies and forms the nucleus in phenotype definitions of adult impulsive behaviours, physical aggression, violation of societal norms, and deficient emotional reactions, that is antisocial personality disorder (ASPD, American Psychiatric Association (APA), 1994), dissocial personality disorder (ICD-10, World Health Organization, 1993) or psychopathy (Hare, 1980). Nevertheless, the nosological categories proposed to capture specificproblem constellations both overlap and are heterogeneously defined.

Attention-Deficit Hyperactivity Disorder (AD/HD) is an umbrella term by definition consisting of three problem domains, inattention, hyperactivity and impulsivity, listed in two separate sets of criteria that may be met individually or together. Two persons who both have this diagnosis may theoretically not share a single criterion. The International Classification of Diseases, tenth edition (ICD-10, WHO, 1993) has based its corresponding definition on hyperactivity (Hyperkinetic Disorder), noting attention deficits as a common complication. If hyperkinesia is combined with outright antisocial behaviours, the diagnosis of hyperkinetic conduct disorder (HKCD) may be made. In the DSM-IV, Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) are instead treated as two separate disorders.

Other diagnostic categories that have been implicated in the context of childhood aggressive behaviours are the autism spectrum disorders (ASD), describing deficits in social interaction or "empathy", verbal and/or non-verbal communication and flexibility, and "paediatric mania" or bipolar disorder with irritable, elated mood swings. A brief overview of the current diagnostic definitions that may be related to early-onset antisocial behaviours provided by the DSM-IV and the ICD-10 is given in Table 1.

Assessing the validity of diagnostic concepts in psychiatric nosology is a continuous process, where, in the absence of knowledge about specific aetiological factors, definitions have to be regarded as preliminary and subject to revision. A seminal paper by Robins and

☆ This study is based on a lecture by Professor Henrik Anckarsäter given in a symposium on early age at onset of psychiatric disorders, organized by Professor Marion Leboyer at the ECNP annual meeting in Paris, France, September 2006.

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Table 1
Currently used diagnostic definitions for childhood-onset behavioural disorders.

Diagnostic categories	Diagnostic code (DSM-IV and ICD-10)	Age at onset	Problem dimensions	Definitional context (cf. temperament as patterns of reactions to stimuli/percepts)
AD/HD	314.01 F90.0	0 years	Hyperkinesia	Behaviours in face of situations demanding motor activity control
ASD	299.00 F84.0, 5, 9	0 years	Social interaction / Communication	Behaviours, cognitions and emotions in relation to others
AD/HD	314.01 F90.0	4 years	Impulsivity	Behaviours in conversations and queues
ODD	313.81 F91.3	4 years	Opposition	Emotional expressions and behaviours in face of other people
AD/HD	314.00 F90.0	~6 years	Inattention	Behaviours in face of situations demanding attention and executive functions (school work)
Mania	296.0× F30.1	?	Agitation, irritability, elation, grandiosity	Dysregulated behaviours related to unstable mood
CD	312.81 F91.0–2	~4.5–5 years	"Criminality"	Behaviours in contradiction with norms and regulations

Table 2
Criteria for diagnostic validity.

According to Robins and Guze (1970) and Andreasen (1995)
1. Clinical description (including unique symptoms that do not occur in other disorders, sex, age, precipitating factors, response to various forms of treatment).
2. Laboratory studies identifying biological or other so called "markers" for the disorder. In addition, Andreasen proposed "external" validators from molecular genetics, molecular biology, neurochemistry, neuroanatomy, neurophysiology and cognitive neuroscience.
3. Delimitation from other disorders.
4. Follow-up studies showing a homotype progression, i.e. that the disorder remains stable over time.
5. Family studies showing higher familial aggregation as compared with control groups.

Guze (1970) argued that a valid classification should be based on systematic empirical studies rather than on "a priori principles", according to five specific criteria (Table 2). We have reviewed the literature by these criteria in order to

1. assess the validity of current categorical diagnoses and
2. propose more specific clinical descriptions of the development of aggressive antisocial behaviours.

2. Method

The studies assembled for this review were identified using systematic PubMed searches in October–November 2007 by the search terms detailed in Table 3. Hand-searches according to the reference lists of the most important textbooks on the field (Lahey, Moffitt, & Caspi, 2003; Patrick, 2006; Quay & Hogan, 1999; Stoff, Breiling, & Maser, 1997) were also performed to identify studies published in non-indexed sources. Selected references of importance for the research questions were added for a revision of the manuscript in March 2009.

Clinical and population-based prospective studies of the longitudinal development of childhood hyperactivity were selected if they included: 1. a group size of at least a hundred subjects; 2. a longitudinal design with duration of at least four years starting in childhood and assessments performed in adult age; 3. assessments of behavioural disorders equivalent to contemporary diagnostic criteria; 4. descriptions of prevalence of criminality. An exception from the third criterion was made for the outstandingly important Dunedin study, which was initially based on behavioural descriptions that were not equivalent to psychiatric diagnoses. Papers were considered in detail, summarized in Table 4 and used for a meta-analysis of the adult outcome for cases identified with hyperactivity in relation to controls in terms of: 1. diagnostic stability; 2. ASPD; 3. criminality; and 4. death by violence or accidents by Fischer's exact tests. These longitudinal studies also address both the overlap between disorders/problem types (Robins & Guze criterion 3) and homo- vs. heterotype development (criterion 4). We subsequently assessed criterion 1, the specificity of clinical description (in relation to non-disordered states and to other types of disorders); criterion 5, patterns of familial aggregation and associations within and across diagnostic categories by family-adoption and twin studies; and finally, criterion 2, "external" validators with the extension proposed by Andreasen (1995), as detailed in Table 2.

3. Results

3.1. Criteria 3 and 4: Delineation and homotype progression

Six studies on clinic-referred children and six population-based prospective, longitudinal studies following hyperactive children into adulthood were identified (Table 4). All these studies had included children according to behavioural criteria at base-line. Detailed figures for the follow-up of cases and controls in relation to our defined outcome parameters are given in the bottom row of the table with *p*-values for comparisons. Studies included in the meta-analyses are indicated in the table. The studies that were not included in the meta-analyses did not provide precise figures for cases versus controls or did not include certain measures, such as personality disorders, in their follow-ups. Hyperactive children were at significantly increased risk for ASPD, including CD. There were also more violent deaths in this group, but due to small numbers, the difference in risk (1.3% vs 0.3%) did not reach statistical significance. Diagnostic stability was surprisingly low, and only a small minority (6%) of formerly hyperactive children still met full criteria for AD/HD combined or hyperactive subtypes) at follow-up. In contrast, the prevalences of several other mental disorders were higher than that of AD/HD.

Some conclusions may be drawn from the joint studies. ODD is very common in hyperactive children. Almost all children who develop CD have had ODD, while a subgroup of children with ODD

Table 3
Search terms for literature searches in PubMed, in October–November 2007.

"ADHD"	"ADD"	"Hyperactivity"	"Hyperkinetic"	"Attention-deficit disorder"
"Oppositional defiant disorder"	"Conduct disorder"	"Disruptive behavior"	"Antisocial behaviour + children"	"Antisocial behaviour + adolescents"
"Delinquency"	"Criminality + children"	"Criminality + adolescents"	"Aggression + children"	"Aggression + adolescents"
Cross referenced				
"Neuropsychology"	"Neurocognitive"	"Cognitive"	"Executive function"	"Inhibition"
"Motivation"	"Reward"	"State regulation"	"Diagnostic imaging"	"Diagnostic techniques"
"MRI"	"fMRI"	"PET"	"EEG"	"HPA"
"Hormones"	"Endocrine"	"Neurotransmitter"	"Gene"	"Genetic"

In addition, the reference list of each paper was reviewed for additional studies. Papers for the analyses were chosen according to relevance for the validity criteria, mainly among publications dating from 2000 or after, following cited publications into earlier decades.

Table 4
Outcomes in the reviewed prospective longitudinal, clinical and population based, studies.

Main reference	Cases[a]	Controls	Follow-up[b]	Adult persistence of AD/HD	Conduct disorder identified at follow-up	Antisocial personality disorder and criminality	Violent deaths
Montreal Hechtman and Weiss (1986)	104 (95 boys and 9 girls) hyperactive children (aged 6–12), 24 had psychopharm treatment	45 matched 'hypernormal' school-mate controls	61/104 (59%) followed up at ages 21–33 by clinical assessments and court records	22/61 (36%) vs. 1/41 (2%) had "at least one moderately or severely disabling symptom"	About 10% "antisocial disturbed" among cases	ASPD 14/60 (23%) vs. 1/41 (2%)[a] Court appearances: 11/60 (18%) vs. 2/41 (5%)	2 MC accidents + 1 suicide vs. 0[a]
New York Group 1 Mannuzza, Klein, Bessler, Malloy and LaPadula (1993)	103 (Group 1) and 104 (Group 2) hyperactive boys (aged 6–12), all had "medication and/or behavior therapy"	100 + 78 matched 'hypernormal' non-psychiatric male outpatient controls	91/103 (88%) and 85/104 (82%) followed up at mean ages 26 and 24 by structured assessments and, for the first group, by official files	7/91 (8%) vs. 1/95 (1%) (Group 1)[a]	27/100 (27%) vs. 8/100 (8%) (Group 1)[a]	ASPD 16/91 (18%) vs. 2/95 (2%)[a] incarcerations 5/91 (5%) vs. 0/95 (0%) (Group 1)	1 accident, 1 stab wound, 1 possible suicide vs. 0 (Group 1) [a]
Group 2 Mannuzza, Klein, Bessler, Malloy and LaPadula (1998)				3/85 (4%) vs. 0/73 (0%) (Group 2)[a]	30/94 (32%) vs. 6/78 (8%) (Group 2)[a]	ASPD 10/85 (12%) vs. 2/73 (3%)[a] criminality not reported (Group 2)	0 (1 death "before adolescence") vs. 0 (Group 2)[a]
Boston Biederman, Faraone, Milberger, Guite, et al. (1996)	140 referred or recruited boys with ADHD (aged 6–17), 89% had stimulants	120 unmatched control boys from out-patient services or recruited by advertisements	112/140 (80%) were followed-up at ages 16–27 by new assessments	ADHD: 63/112 (58%) had "full or subthreshold ADHD" vs. 6/105 (6%)	26/112 (23%) vs. 3/105 (3%)[a]	ASPD 12/94 (13%) vs. 2/96 (2%)[a] Criminality not reported	Not reported
Los Angeles Satterfield, Hoppe and Schell (1982)	110 hyperactive boys (aged 6–12), "most" or "all" had stimulants	75 matched, paid, public school controls, 13 non-ADHD brothers of cases	81% were followed up until age 25 through official records	Not assessed	73/89 (82%) vs. not reported	ASPD not assessed Felony arrests 21% vs. 1%.	Not reported
Wisconsin Barkley, Fischer, Smallish and Fletcher (2004)	158 hyperactive children (144 boys, 14 girls, aged 4–12), 22% had stimulants	81 matched non-hyperactive controls recruited among the subjects' friends	147/158 (93%) were followed up at ages 19–25 through structured interviews and official records	8/147 (5%) vs. 0/73 (0%)[a]	53/123 (43%) vs. 1/66 (2%) had developed CD at 8 year follow-up[a]	ASPD 31/147 (21%) vs. 3/73 (4%)[a] Arrested ≥ 2 times 58/147 (39%) vs. 9/73 (12%)	1 suicide vs. 1 car crash and 1 non-violent death (sudden heart arrest)[a]
Developmental Trends Study Loeber, Green, Lahey, Frick and McBurnett (2000)	177 outpatient boys (aged 7-12), 111/177 (63%) AD/HD, 71/177 (40%) ODD, 68/177 (38%) CD, medication "discontinued prior to assessment"	No group defined as controls	On average 92% followed-up until age 19	Not assessed	94/158 (59%)	ASPD in 60/158 (38%) of AD/HD-probands 54% of CD-probands met ASPD criteria.	Not reported

Gothenburg Rasmussen and Gillberg (2000)	61 population based cases (47 boys, 14 girls, aged 7) 90% ADD, 10% DCD, no stimulants	51 population-based controls (27 boys, 24 girls) matched for SES and age	55/61 (90%) followed up with structured assessments and official files at age 22	Severe hyperactivity impulsivity 8/55 (15%) vs. 1/46 (2%) severe inattention 24/55 (44%) vs. 3/46 (7%). combination of both 5/55 (9%) vs. 0/46 (0%)[a]	Not assessed	ASPD 10/55 (18%) vs. 1/46 (2%)[a] Criminal offences 8/55 (15%) vs. 0/46 (0%)	No deaths[a]
Pittsburgh Loeber et al. (2001)	Population-based sample, 1517 boys, aged 7–13, enriched for disruptive behaviors, no info on medication	No group defined as controls	>83% followed-up until ages 19–25 years with interviews	Prevalence of AD/HD decreased from 15% to 8% from youngest to oldest sample	In the youngest and oldest sample groups AD/HD was not a risk factor for persistent serious delinquency	ASPD not assessed	Not reported
Cambridge Farrington (1995)	Population-based sample from "working class area", 411 boys, aged 8–9. 34/411 (8%) had only HIA, 59/411 (14%) had HIA and "conduct problems", no info on medication	No group defined as controls	93% followed up by interviews until age 48	Not assessed	At ages 8–10 40/411 (10) had conduct problems. HIA and conduct problems at 8–10 independently predicted juvenile convictions at ages 10–16	6% "chronic offenders" at age 32. Subgroup figures not reported	17 deaths at age 48, causes not specified
Dunedin Moffitt (2006)	1037 children, from birth cohort (52% boys, 48% girls), aged 3–, 53 /925 (6%) had ADD at ages 11 (45 boys and 8 girls), 85% of these were also hyperactive, no info on medication	No group defined as controls	93% average participation, followed-up until age 32	Not reported	226/1012 (22%) 41/226 (18%) in this group had ADHD	ASPD 40/973 (4%) at age 26	22 deaths at age 32 no info on causes
San Francisco Babinski, Hartsough and Lambert (1999)	Population based sample of 332 hyperactive children (78% boys, 22% girls), aged 5–12, no info on medication	160 populations based, gender matched controls	81% were followed up at age 23–30 through self reports and official arrest records	Not assessed	Not reported	Hyperactivity/impulsivity and early CPs, but not inattention, predicted arrest records. CP only predicted "crimes against people"	Not reported
Great Smoky Mountain Costello et al., 1996	Population-based sample of 1420 children, aged 9–13, enriched for disruptive behaviors. Of children aged 9–10 ADHD 21/936 (2%), ODD 20/936 (2%) and CD 25/936 (3%), no info on medication	No group defined as controls	83% average participation, followed-up until ages 16–21	4.1% life time prevalence of AD/HD at age 16	9% life time prevalence of CD at age 16	ASPD not assessed CD in combination with anxiety or depression, but not ADHD, predicted arrests for severe/violent offences	Not reported
Metaanalyses of cases vs. controls				23/378 (6.1%) vs. 1/287 (0.3%) $p<.001$[b]	136/429 (31.7%) vs. 18/349 (5.2%) $p<.001$[b]	93/532 (17.5%) vs. 11/424 (2.6%) $p<.001$[b]	7/530 (1.3%) vs. 1/353 (0.3%) $p<.154$[b]

All percentage units from the studies were rounded. Figures in metaanalyses are given with one decimal.

[a] Used in metaanalysis.

[b] Fischer's exact test.

develop CD. A central question is whether hyperactivity in itself, without early-onset CD, increases the risk for ASPD and criminality. To study this association would require studies that systematically identified all cases with pre-pubertal CD within their study groups. We did not find any such study. Often CD was not clearly assessed at inclusion, and children varying broadly in age were included. A seven-year old with hyperactivity but not CD will be at risk during the rest of his childhood to develop the combination. It is therefore not possible by today's literature to pin a risk increase for ASPD and criminality in adulthood on hyperactivity without early-onset CD, even if such an association may exist in real life.

3.2. Clinical description

Diagnostic criteria describe behaviours in relation to specific situations (e.g. "home", "school") or to different challenges (e.g. "remaining seated when expected", "to comply with adults' requests") (Table 1). At first glance, there seems to be no direct content overlaps. Yet, as items across the categorical definitions are worded in relation to heterogeneous contexts, they may still refer to common, more "molar" or general deficits. For example, deficits in behavioural and emotional inhibition are central to AD/HD, ODD, and CD, and can also play a role in some autism spectrum disorder (ASD) criteria (such as problems in sustaining a mutual conversation with others) or symptoms of mania (disinhibited behaviours with negative consequences). Similarly, criteria referring to social interaction problems are found across all diagnostic categories (e.g. the AD/HD criterion; "often interrupts or intrudes on others", or the HCD criterion; "socially disinhibited", just as the at least four ODD and seven CD criteria that refer to interpersonal interaction, and the first group of ASD symptom criteria (DSM-IV)).

3.3. Age at onset

Diagnostic criteria are worded in relation to developmental phases, and all definitions of 'disorder' or 'deficit' have to relate to an idea about 'normal' development. Hence, the pattern of overlap between problems depends on the age at which the cross-section is made. Assessment methods (e.g. questionnaires, symptom lists, standardized observational schemes, and neuropsychological tests) for the preschool period have become more available, which has started to bear fruit in birth cohort studies (Angold & Egger, 2007).

Problems manifested early in development, already in the first years of life and at least well before puberty, may be more pivotal to the phenotype definitions, as studies across diagnostic categories have shown higher heritability and persistence over time for early-onset problems (Kim-Cohen et al., 2005; Moffitt, 1993). The DSM-IV defines early-onset CD as onset before 10 years. Among children with AD/HD, studies have indicated that virtually *all* cases of CD develop before the age of 12 (Biederman, Faraone, Milberger, Jetton, et al., 1996). Conversely, most cases of early-onset CD have been shown to arise in children with hyperactive, "undercontrolled temperaments" (Lahey & Loeber, 1997; Moffitt, 1990). Adolescent onset CD differs by being more related to peer groups, less hereditary and less persistent (Moffitt & Henry, 1991).

3.4. Treatment response

Response to treatment merits a review on its own, but let us here merely consider that at least four different types of pharmacological treatments have been studied and used to treat aspects of aggressive antisocial behaviours in children, adolescents, and adults, and that these may target specific neurobiological systems and problem types, which would make them candidates for phenotype markers. Psychostimulants are effective for hyperactivity (Biederman & Faraone, 2005), neuroleptics for aggression (Turgay, 2005), mood stabilizers for negative emotions in mood swings (Smith, Cornelius, Warnock, Bell, & Young, 2007), and, possibly, anti-depressants for impulsivity (Popper, 1997). Psychotherapeutic and educative efforts may target behaviour patterns, deficient cognitive abilities and/or hampered personality maturation.

3.5. Familial aggregation

A unanimous literature describes a high familial aggregation of hyperactivity and AD/HD (e.g. Faraone, 2004). Twin studies have yielded a mean estimate of 76% for the share of variance attributable to genetic factors (Faraone et al., 2005), which is in line with findings from adoption studies (Sprich, Biederman, Crawford, Mundy, & Faraone, 2000). A substantial genetic overlap has been shown between AD/HD and ODD/CD (Nadder, Rutter, Silberg, Maes, & Eaves, 2002), and a recent twin study was interpreted as rejecting the hypothesis that they are three "independent" conditions (Rhee, Willcutt, Hartman, Pennington, & DeFries, 2008). Family studies, however, indicate that AD/HD *with* CD, just as CD on its own, carries an increased prevalence of CD and ASPD in relatives, while relatives to probands with AD/HD in the absence of CD (regardless of whether it is combined with ODD or not) do not have increased risk for criminality (Faraone, Biederman, Jetton, & Tsuang, 1997; Faraone et al., 2000). It therefore seems probable that there is a basic susceptibility for hyperactivity, to which specific genetic and environmental susceptibility factors for the progression into CD or criminal behaviours may be added (Maes, Silberg, Neale, & Eaves, 2007). Furthermore, there is increasing evidence that aggressive and non-aggressive antisocial behaviours can be etiologically differentiated, with the former being highly heritable (accounting for 65% of the variance, Burt, 2009). Genetic factors indeed seems to mediate the progression from early onset, persistent aggression and delinquency to a self-rated psychopathic personality in adolescence, while shared environmental factors are involved in the association to more general antisocial behaviour (Forsman, Larsson, Andershed, & Lichtenstein, 2007). Among the facets of psychopathic personality, unique genetic effects were identified for the lack of emotional reactions and the antisocial behaviour, while the interpersonal dominance seeking was associated with both genetic and shared environmental factors (Larsson, Andershed, & Lichtenstein, 2006).

3.6. "External" validators

3.6.1. Neurophysiology

Gray's (1987) motivational theory suggests three interdependent brain systems, two linked to the balance between activation and inhibition (the behavioral activation system (BAS) and the behavioral inhibition system (BIS)), and the fight-flight-freezing system. Disinhibition purportedly results from an imbalance in BAS and BIS functioning, favouring behavioural activation. BIS activity has been measured by electrodermal responding, i.e. changes in the conductivity of the skin, which is increased by the sweating resulting from activation of the sympathetic autonomous nervous system (Fowles, 1988). A few studies in AD/HD have demonstrated attenuated electrodermal responses to stress (Iaboni, Douglas, & Ditto, 1997), while studies of antisocial subjects have more consistently shown reduced responses as compared to controls (Gatzke-Kopp, Raine, Loeber, Stouthamer-Loeber, & Steinhauer, 2002). Inhibition has also been assessed through neuroendocrine markers in response to stressors. Lower activity in the hypothalamic-pituitary-adrenal (HPA) axis in relation to stress has been reported both from groups with AD/HD and ODD/CD (e.g. Randazzo, Dockray, & Susman, 2008; van Goozen, Fairchild, Snoek, & Harold, 2007). Beauchaine (2001) has suggested an additional emotion regulation deficit in aggressive CD, adding to the BIS and BAS model, and possibly expressed as an inadequate vagal modulation of cardiac output (Beauchaine, Gatzke-Kopp, & Mead, 2007).

A large number of EEG studies have found subjects with AD/HD to be characterized by an overall "theta excess" and "alpha slowing" (Barry, Johnstone, & Clarke, 2003), but similar changes have been described in a very vast range of mental or neurological disorders (Hughes & John, 1999). In criminality, Raine (1997) summarized that there "have probably been hundreds of studies assessing EEGs in criminals, delinquents, psychopaths, and violent offenders" showing these kinds of unspecific patterns.

A reduced amplitude of the event-related P3 (third positive) component potential (ERP), i.e. the wave of brain electrical activity emerging approximately 300 ms following a rare stimulus, has also been unspecifically implicated across a spectrum of disorders, such as alcohol dependence, illicit drug dependence, nicotine dependence, AD/HD, ODD, CD and ASPD (Iacono, Carlson, Malone, & McGue, 2002).

3.6.2. Brain imaging

Brain imaging studies are structural, functional or both. Structural imaging is quantified for research purposes by measuring volumes, while functional imaging is measured by general (such as the blood flow or glucose metabolism) or specific (ligands for receptors or transmitter precursors) indicators of activity in specific regions of interest (ROIs).

A quantitative review of structural studies on AD/HD (Valera, Faraone, Murray, & Seidman, 2007) based on more than 500 index children and young adolescents, and as many controls, showed significant volume reductions in the cerebellum, the callosal body, and the right caudate nucleus, and also for the total and right cerebral volume. A similar picture emerged in an MRI study of 24 adults with AD/HD (Seidman et al., 2006). Cortical reductions have also been longitudinally associated with persistence of AD/HD symptoms and poorer out-come (Shaw et al., 2006). Decreased or aberrant global and regional metabolism, especially in the striatum, has been a fairly consistent finding in studies of regional brain activity in AD/HD, while findings of changed activity in the prefrontal cortex have been less consistent (as reviewed in Bush, Valera, & Seidman, 2005).

In spite of an extensive literature on the structural neural underpinnings of aggression in children (van Goozen et al., 2007), few studies have actually investigated children and adolescents defined as fulfilling criteria for CD. In Bussing, Grudnik, Mason, Wasiak, and Leonard (2002), a small community sample of children with AD/HD in the presence or absence of CD were assessed by MRI and compared to controls, but no significant differences were detected. One study of early-onset CD in combination with AD/HD, however, found significantly reduced right temporal lobe volumes and a tendency to reductions in the prefrontal areas, as compared to healthy controls (Kruesi, Casanova, Mannheim, & Johnson-Bilder, 2004). Another study of early-onset CD reported significantly reduced grey matter volumes in the bilateral anterior insular cortex and the left amygdala, which also correlated with dimensional measures of aggression and even more strongly with attention problems (Sterzer, Stadler, Poustka, & Kleinschmidt, 2007).

In adults with different forms of antisocial behavior, the prefrontal cortex has been in focus for imaging studies ever since Damasio's re-rendering of the Phineas Gage case (Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994). However, Harlow's original case report rather presents a case of progressive bacterial encephalitis with recurrent fits (including epileptic states) than a specific status post the injury so elegantly depicted in the computer simulated imagery from Damasio's paper. Significant prefrontal cortical volume loss was indeed demonstrated in 21 community-recruited adults with ASPD (Raine, Lencz, Bihrle, LaCasse, & Colletti, 2000), while Dolan, Deakin, Roberts, and Anderson (2002) found no significant frontal or temporal structural differences between a group of patients with high psychopathy scores and controls.

Functional or structural changes in brain regions involved in the regulation of emotional behavior, such as the temporal lobes and the limbic system, have been recurrent in imaging studies of adults with antisocial behaviour disorders (Anckarsater, 2006). In adolescents with CD and AD/HD, aberrant functional reactions in the anterior cingulate cortex and the amygdala when processing negative affective stimuli, have also been observed (Stadler et al., 2007; Sterzer, Stadler, Krebs, Kleinschmidt, & Poustka, 2005).

Specific methodological problems for imaging studies include heterogeneous assessment procedures and image evaluation techniques. Just for AD/HD, Valera et al. (2007) emphasized the tremendous variability in the placement of ROIs, with differences in size and definition across studies that make quantitative meta-analyses virtually impossible. Measures of activity are expressed as relative regional signals in comparison to other brain structures, such as the contralateral hemisphere, occipital cortex, or the cerebellum. This may have influenced results since, for example, the cerebellum is also involved across social and emotional reactions, and we therefore do not know whether reduced regional/cerebellar ratios are due to cerebellar *hyper*activity rather than hypoactivity in the studied region (Anckarsater, 2006). In common with other studies comparing possible external markers between cases with antisocial life histories and controls, confounding factors are virtually impossible to control for in imaging studies, as are the effects of publishing biases.

3.6.3. Neurocognition

Clinical as well as community studies have found lower scores on intelligence tests in individuals with AD/HD as compared to control groups, particularly in verbal intelligence (e.g. Mariani & Barkley, 1997; Peterson, Pine, Cohen, & Brook, 2001), and a community twin study found common genetic influences behind inattention and reading difficulties, but not hyperactivity (Willcutt, Pennington, Olson, & DeFries, 2007). The difference typically equals between a half and one standard deviation in intelligence quotients on the group level. Children and adolescents with ODD/CD have similar reductions in comparison to normal controls (Pennington, 2002), even after controlling for socio-economic and ethnic confounders (Moffitt, 2006). It is notably difficult to compare results on intelligence tests across populations, but it may be concluded that specific deficits or uneven profiles form more relevant models than general learning disabilities in the background to hyperactivity or antisocial behaviours.

The central deficit behind the AD/HD symptom complex has been described as executive dysfunction, a broad construct referring to complex organizing of behaviour and various functions involved in the maintenance of behaviour on a goal set over time independently from external saliencies (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). Among these functions, executive motor disinhibition (especially notable in the Stop task) has been most consistently associated with AD/HD (Lijffijt, Kenemans, Verbaten, & van Engeland, 2005), as children with AD/HD have significantly longer reaction times to an inhibition signal than controls. Even if numerous studies have reported on abnormal results for tests of executive functions in AD/HD, negative reports have not been uncommon (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Other functions, such as reaction time to response signals, have been even more deviant in AD/HD, and executive functions have been as deficient in other diagnostic categories, such as autism (Pennington & Ozonoff, 1996) and CD (Oosterlaan, Logan, & Sergeant, 1998). By simply reading the diagnostic criteria, it is, however, obvious that several AD/HD criteria describe what has been defined as executive functions (and the tests are designed to measure), i.e. a lack of focus, direction and consideration of consequences. Coghill, Nigg, Rothenberger, Sonuga-Barke, and Tannock (2005) suggested that inattention, but not hyperactivity/impulsivity, is associated with deficient executive functions and poor academic achievement, referring to clinical as well as community samples (e.g. Chhabildas, Pennington, & Willcutt, 2001), and that hyperactivity/impulsivity is more closely related to

dysfunctions of reward mechanisms (e.g. Sonuga-Barke, Dalen, & Remington, 2003).

Castellanos et al. (2006) reviewed the model presented by Zelazo and Mueller (2003) on the functional differentiations within frontal cortices. They distinguished between more purely cognitive, "cool" aspects of executive functions associated with the dorsolateral frontal cortex and "hot", or affective, aspects, associated with the orbital and medial prefrontal cortex. In this model, 'cool' executive functions are elicited by relatively abstract, decontextualized problems, such as most of the tasks tested so far in AD/HD (e.g. working memory and tests requiring sustained attention and inhibitory activity). 'Hot' executive functions are required for problems that are characterized by high affective involvement or demand flexible or appropriate appraisals of the emotional significance of stimuli. For example, risky decision-making in the Iowa Gambling Task could be a 'hot' executive function (Kerr & Zelazo, 2004). Deficits on this test have also been associated with hyperactivity/impulsivity (Toplak, Jain, & Tannock, 2005) and with symptoms of opposition and conduct problems (Ernst et al., 2003), but not with symptoms of inattention. Children with AD/HD have also exhibited marked difficulties in decoding affective facial expressions, with a specific deficit in identifying anger and sadness (e.g. Pelc, Kornreich, Foisy, & Dan, 2006).

The 'hot' executive functions thus resemble the functions ascribed to the limbic system, processing social stimuli by memories and emotions. Interestingly, clinical states associated with damage in the limbic system, in the non-dominant hemisphere or with reduced interhemispheric communication have shown common clinical features. Thus, problems with 'hot' executive functions, recognition of affects and visuospatial deficits may be found together (Raine et al., 2005). "Callous-unemotional" traits describe reduced emotional reactivity and are associated with antisocial behaviours (such as in the ASPD or psychopathy constructs) (Frick & Stuart, 2008; Loney, Frick, Ellis, & McCoy, 1998). Reductions of these functions also recur in the non-verbal learning disability (NVLD) syndrome described by Rourke (1987), which also includes a risk for aggressive behaviours. The specificity of these problems in relation to the verbal executive functions has been disputed (Moffitt et al., 2008), and, conceptually, these definitions also overlap with core dysfunctions in the autism spectrum, such as deficits in social interaction and non-verbal communication. Inter-hemispheric transfer is targeted in research on brain processes relevant for autism (Nydén, Carlsson, Carlsson, & Gillberg, 2004). Details of these parallels are, however, insufficiently known (Rogers, Viding, Blair, Frith, & Happé, 2006), and clinical experience describe autistic social difficulties as qualitatively distinct.

In sum, two large aspects of neurocognition are often implicated as susceptibility factors for aggressive antisocial behaviour. One is related to problems with language, especially abstractions, deficient strategies, and the prefrontal cortex, the other to shallow affects, visuospatial problems, reduced emotional integration and non-verbal communication and the limbic circuitry, inter-hemispheric transfer and/or the non-dominant hemisphere. These broad domains recur across scientific models in relation to aggressive behaviours. Traditionally, verbal deficits have been proposed to be specific for CD (e.g. Caspi & Moffitt, 1995), but as spatial impairments have increasingly been brought in focus (e.g., Raine et al., 2005; Speltz, DeKlyen, Calderon, Greenberg, & Fisher, 1999), it seems more reasonable to describe these as two large domains of mental functional deficits, whose relations to each other remain insufficiently known.

3.6.4. Neurochemistry

Low serotonergic neurotransmission has been associated with emotionally driven, impulsive, destructive acts (e.g. Asberg, Traskman, & Thoren, 1976; Brown et al., 1982; Virkkunen, Nuutila, Goodwin, & Linnoila, 1987) but not with instrumental violence (Gardner, Lucas, & Cowdry, 1990; Lidberg, Tuck, Asberg, Scalia-Tomba, & Bertilsson, 1985). Kruesi, Swedo, Leonard, Rubinow, and Rapoport (1990) found that children with ODD/CD and/or AD/HD had lower concentrations of serotonin metabolites in the cerebrospinal fluid than children suffering from obsessive–compulsive disorder, and that these concentrations were inversely correlated with ratings of aggressive behaviours. At a two-year follow-up, the metabolite concentrations also predicted the severity of physical, aggressive behaviour and poor outcome (Kruesi et al., 1992). In contrast, Castellanos et al. (1994) found that the same metabolite concentrations were positively correlated with measures of aggression and impulsivity in a study of boys with AD/HD. Since this group was more hyperactive and less aggressive than the previous one, the authors speculated that serotonin measures may correlate with aggression only in groups of children with a core aggression problem.

Lower cerebrospinal fluid concentrations of serotonin metabolites have also been reported in several studies of aggressive antisocial adults and youths with CD (Berman, Kavoussi, & Coccaro, 1997). The ratio between the dopamine and serotonin metabolites in the CSF, which reflects the serotonergic regulation of dopaminergic activity, was positively associated with aggression, AD/HD and CD in two separate studies of adult offenders (Soderstrom, Blennow, Sjodin, & Forsman, 2003). The dopamine systems play a central role in the regulation of attentional processes, psychomotor activity and reward-seeking behavior (e.g. Krause, Dresel, Krause, Kung, & Tatsch, 2000; Spencer, Biedermann, Wilens, & Faraone, 2002). Stimulants, such as methylphenidate, probably reduce AD/HD symptoms by increasing the release of dopamine and norepinephrine (Biederman, 2005).

In addition to neurotransmitters, hormones have been studied as covariates to antisocial behaviours. Activated thyroid hormones (in relation to precursors) have been associated with AD/HD symptoms in clinical (Stein & Weiss, 2003) as well as community study groups (Alvarez-Pedrerol et al., 2007), and have been predictive of criminal recidivism in studies among both young lawbreakers (Levander, Mattsson, Schalling, & Dalteg, 1987) and adult criminals (Stalenheim, 2004). As depression has been associated with the inverse pattern, this may, however, not express a direct link but a lack of depressive reactivity among the more cold-hearted and thereby recidivism-prone subjects (Soderstrom & Forsman, 2004).

Testosterone increases aggressive behaviours (Archer, 1991) and the mere prevalence of violence and criminality in young men as compared to elder men and women, and the increased aggression noticed in females in the prementrual phase (Dougherty, Bjork, Huang, & Moeller, 1997), makes testosterone a prime suspect in the quest for biological background factors to aggression. Testosterone has been related to delinquency, alcoholism and drug use among adults, as well as to conduct problems in childhood (e.g. Dabbs, Carr, Frady, & Riad, 1995). Effect sizes for these relations are typically small, but tend to be larger for males from lower socioeconomic backgrounds. Some studies also have failed to find any relationship between aggression and testosterone (e.g. van Bokhoven et al., 2006).

3.6.5. Molecular genetics

In a comprehensive review of the search for molecular genetic markers for AD/HD, Bobb, Castellanos, Addington, and Rapoport (2005) concluded that of all publications on associations between AD/HD and specific gene variants, 36% were positive, 17% showed trends and 47% were negative. This was uncorrelated with sample size, but studies using dimensional measures, or case-control models, tended to report more positive findings than categorical or family based studies. It was also a clear trend that positive, dimensional, and case-control studies were published earlier than more recent negative replications using family-based models. Again, the publication bias is described as a major obstacle to understand and interpret the results, while underpowered samples and selected populations add to the weakness of possible interpretations.

Linkage studies of AD/HD have identified specific chromosome regions that have also been implicated in aggressive behaviours (e.g.

Kendler et al., 2006), leading to the possible conclusion that "AD/HD co-segregates with disruptive behaviours as a unique, phenotypically variable trait as evidenced by highly significant pair-wise linkages" (Jain et al., 2007). Findings for various definitions of CD or aggression have been inconsistent, but these studies have generally been based on study cohorts originally assembled to study other problem definitions, such as substance abuse (e.g. Stallings et al., 2005).

In association studies, the most thoroughly investigated genes are those implicated in serotonergic and dopaminergic neurotransmission. Repeat polymorphisms, some of which have been shown to be functional, have been studied in relation to aggressive behaviours in the genes for the dopamine receptor 4, the dopamine transporter, the serotonin transporter, and the monoamine oxidase type A. The latter is especially interesting for disorders with a skewed sex ratio as it is located on the X chromosome. The gene for the serotonin receptor 2A contains several single nucleotide polymorphisms that have been studied in relation to psychiatry. Other genes that have been studied in relation to behavioural disorder include those coding for other enzymes and receptors involved in monoaminergic neurotransmission, sexual hormone metabolism, and a vast array of proteins involved in brain development.

So far, no study has indicated any polymorphism or gene locus that may effect the variance in the phenotypical definitions described above by more than a minute effect (typically with odds ratios well below 2 or effect sizes maximally at a couple of percents, Kendler, 2005).

During recent years, intense interest has been focused on interactions between specific genotypes and environmental factors as a possible key to disentangle the inconsistent findings from univariate association studies. The first paper to identify such effects was published in 2002 by Caspi and co-workers, who could show that maltreated boys with the high-activity polymorphism in the MAO-A gene were less likely to develop antisocial behaviours than maltreated boys with the low-activity polymorphism, while the polymorphism did not have any effect on the variation of antisocial behaviours in the population at large. This finding has been replicated in several independent studies (e.g. Foley et al., 2004; Kim-Cohen et al., 2006), while others have been negative (e.g. Widom & Brzustowicz, 2006; Young et al., 2006). A range of similar interactions have been proposed, e.g. that "maternal insensitivity" may lead to aggressive behaviours, specifically in the presence of the DRD4 seven repeat polymorphism (Bakermans-Kranenburg & van Ijzendoorn, 2006). The initial enthusiasm evoked by this line of reports of complex models has faltered as replications have proved as inconsistent as for univariate associations. Simulated analyses by categorical phenotypes and logistic regressions also repeatedly yield models with significant main effect of the environment, no significant main effect of the genotype, and significant G×E interactions, regardless of whether meaningful or nonsense data are used (Eaves, 2006).

In the last few years, new approaches to psychiatric molecular genetics have been called for, focusing on molecular rearrangements and other modifications thought to influence the translation of the genes and thereby the functional activity of its enzymatic end product. Besides some studies of parental imprinting (Kent et al., 2008), convincing associations with behavioural features have not yet been presented for such "epigenetic" models.

4. Summary and proposition

The literature on longitudinal development of hyperactivity is quite consistent on some basic figures: the majority of children identified as hyperactive, at least during some period, develop a pattern of social interaction characterized by opposition, which, in at least a third, progresses into pre-adult aggressive antisocial behaviour. In about a fifth of the original group, this will persist into an ASPD in adulthood. This behaviour progression corresponds to the HKCD and ASPD or dissocial PD in the ICD-10 or in the DSM-system to HD in AD/HD, ODD, CD and ASPD. In AD/HD with CD, ODD at some stage is so common that it is not predictive for later CD development (Biederman, Faraone, Milberger, Guite, et al., 1996; Biederman, Mick, Faraone, & Burback, 2001). Childhood-onset CD, when the full picture is developed at least before puberty, is a very different condition from adolescent CD in terms of prognosis, patterns of comorbidity, and background factors. While adolescent CD has been shown to be mainly a social phenomenon (Moffitt, 1993), the early-onset form is almost always developed from hyperactivity. A dimensional behavioural phenotype of life-time aggressive antisocial behaviours, in which early-onset is one marker of severity, seems far more consistent with the empirical literature as reviewed in this paper than a categorical model of diagnoses. The longitudinal studies give at hand that a young age at onset of aggressive antisocial behaviours will reflect the presence of childhood hyperactivity, and thereby identify it as a promising candidate for assessments of the severity of the antisocial behaviour, even if we are far from understanding the mathematics of this association. In addition to the age at onset, the severity may be measured by the behaviour expressions (for example the number of aggressive behaviour incidents sorted by the types of behaviours), and by the psychosocial adverse effects. To merely count the number of diagnostic items that are met, as in most assessment schemes in use today, seems a poor choice for scientific quantification.

Since no demarcation or "zone of rarity" between subjects with antisocial behaviours and the normal variation has been demonstrated, all categorizations rely on arbitrarily defined "cut-offs". All these behaviours are probably waxing and waning in their expression. Conduct problems have been shown to fluctuate above and below the current diagnostic cut-off level (Biederman et al., 2001), and there seems to be good reason to consider also sub-threshold problems. Situational factors rather than the underlying susceptibility may determine the actual symptom expression at a precise moment, which calls for a developmental perspective in phenotype assessments, especially in studies trying to establish underlying mechanisms to problems.

This persistent pattern of early-onset aggressive antisocial behaviours is the back-bone of all phenotype definitions related to interpersonal violence and criminality, i.e. hyperactivity, CD, ASPD, dissocial PD and psychopathy. Open research questions are whether inattention should be noted as a co-existing problem to hyperactivity (as in the ICD-10) or as a facet in a common syndrome (as in the DSM-IV), whether hyperactivity in itself, without CD, predicts adulthood ASPD (Lilienfeld & Waldman, 1990), and whether ASPD or psychopathy in adulthood should include one, two or three "facets" of mental problems in addition to the aggressive antisocial behaviours (such as childhood-onset disinhibited behaviours, lack of emotional reactions and dominance-seeking interpersonal attitudes (Cooke, Michie, & Skeem, 2007; Vitacco, 2007). A childhood-onset, developmental, dimensional phenotype definition of aggressive antisocial behaviours, in relation to which all other forms of mental and/or psychosocial co-varying problems may be independently studied, resolves all these problems.

As for the first of these research questions, inattention is a vague definition that has not really been studied in relation to adult outcomes. In the heterogeneous AD/HD construct, inattention may, just as hyperactivity, be regarded as a result of impulsivity, or the behaviour manifestations could be regarded as results of inattention. As a result of these definitional ambiguities, we do not know if psychostimulants treat inattention, hyperactivity or some more underlying phenomenon. Both inattention and impulsivity merit clear definitions, through clinical signs and psychometric tests, and to be studied in their own rights.

To the next question, whether childhood hyperactivity carries a risk for adult ASPD or criminality in the absence of early CD, we have not found any new evidence to contradict Lilienfeld and Waldmans

conclusion from 1990 that the risk for adult negative outcomes is mediated by early onset antisocial behaviours. Most research projects presented to this date may not answer this issue, as they have included a wide age range from start or have not systematically assessed both CD and hyperactivity before the proposed cut-offs at ages 10, 12 or at puberty. Again, a dimensional description of aggressive antisocial behaviours, where early-onset hyperactivity and aggressive behaviours are markers of severity, fits the data presented.

Third, there is the issue of various definitions of personality disorder, including "psychopathy". Epidemiological data were collected for the DSM-IV (Widiger et al., 1996), but assessed the overlap with different mental problem types to a limited extent. The nosology of the proposed "psychopathy" construct has been addressed by psychometric analyses of samples gathered from the penal system, which are inadequate to answer whether these problem types belong in a common syndrome. The "facet" proposed to capture the specific interpersonal manipulative dominance-seeking of "psychopathy" rather reflects what is usually called "wickedness" in social relationships, and it merits further research to validate its status as a mental disorder.

A vast array of studies on "external validators" have demonstrated statistical group differences between subjects with behaviour disorders and controls, and sometimes even a statistical covariation between a laboratory measure and clinical ratings of severity. Overall, no specific "marker" has been identified for any of the diagnostic categories proposed and used today, and the two most salient features in this literature are the consistency of differences between cases and controls, for which the publication bias plays an unknown role, and the lack of specificity in relation to diagnostic definitions.

Being clear about what is spoken of is essential for research into mental phenomena. As long as we do not have access to data that permits factor or cluster analyses across the whole spectrum of mental problems, it seems useless to pursue controversies about how to join problems defined on heterogeneous levels such as behaviours, emotions or cognitive abilities into syndromes. Instead, a clearly defined behavioural phenotype of aggressive antisocial behaviours with an early-onset (which will most often be linked to hyperactivity) as a marker of severity may both fit the current literature and form the starting point for the study of all possible susceptibility factors.

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Paper II

Trait aggression in adult psychiatry is predicted by childhood hyperactivity, conduct disorder, adult substance abuse, and low cooperativeness

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ABSTRACT

Background: The prevention of aggressive behaviours is a core priority for psychiatric clinical work, but the association between the diagnostic concepts used in psychiatry and aggression remains largely unknown. **Subjects:** 178 adults referred for psychiatric evaluations of childhood-onset neuropsychiatric disorders (outpatients) and 92 perpetrators of violent crimes referred to pre-trial forensic psychiatric investigations had comprehensive, instrument-based, psychiatric assessments, including the Life History of Aggression (LHA) scales. **Methods:** Total and subscale LHA scores were compared to the categorical and dimensional diagnoses of childhood and adult DSM-IV axis I and II mental disorders, general intelligence, GAF, and personality traits according to Cloninger's biopsychosocial model. **Results:** The two groups had similar LHA scores (despite higher scores on the Antisocial scale in the offender group). Higher total LHA scores were specifically and independently associated with the hyperactivity facet of attention-deficit/hyperactivity disorder (AD/HD), childhood conduct disorder, substance-related disorders, and low scores on the Cooperativeness character dimension according to the Temperament and Character Inventory. IQ and GAF-scores were negatively correlated with the LHA subscale Self-directed aggression. Autistic traits were inversely correlated with aggression among outpatients, while the opposite pattern was noted in the forensic group. **Conclusion:** In these study groups, aggression was predicted by childhood behaviour aberrations, adult substance-related problems, and character immaturity rather than by symptoms associated with the major mental disorders. AD/HD in combined or hyperactive, but not inattentive, forms, was associated with high scores on aggressive behaviours.

Keywords: Aggression; Psychiatry; AD/HD; Conduct Disorder; Personality; Adult

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Introduction

The prevention of aggressive behaviours is often referred to as an important target for psychiatric treatment, but there is little systematic knowledge about which psychiatric problems that may herald violence. The most detailed literature deals with the association between childhood-onset disorders, such as hyperactivity and conduct disorder (CD), and progression towards antisocial personality disorder (ASPD) in adulthood (Hofvander et al., 2009). A core theoretical problem is that both CD and ASPD are defined through antisocial behaviours, which short-circuits models in which these psychiatric factors are supposed to "explain" or "predict" such behaviours. Systematic studies assessing the role of other childhood neurodevelopmental problem constellations, such as attention deficit disorder (AD/HD, inattentive subtype), autism spectrum disorders (ASDs), learning disorders (LDs) and tics, general adult mental disorders on axis I in the DSM system, personality, and cognitive functioning in the aetiology of aggressive antisocial behaviours would therefore seem to be a priority.

Hyperactivity and CD in childhood (AD/HD and CD in the DSM-IV, jointly referred to as hyperkinetic conduct disorder in the ICD) have long been identified as the main psychiatric risk factor for the development of ASPD (Robins, 1966, Hofvander et al., 2009), but a broader range of childhood-onset cognitive and social disorders, such as the ASDs and LDs, have also been implicated in the background to aggressive behaviours across all ages in case reports (Mawson et al., 1985; Wolff and Cull, 1986; Baron-Cohen, 1988; Kohn et al., 1998; Kristiansson and Sörman, 2008), in clinical surveys of correctional/forensic groups (Dalteg and Levander, 1989; Scragg and Shah, 1994; Rasmussen et al., 2001; Siponmaa et al., 2001; Kroll et al., 2002; Soderstrom et al., 2004), and epidemiological research (Farrington, 1987; Hodgins, 1992; Rasmussen and Gillberg, 2000; Moffitt and Caspi, 2001). These childhood-onset neurodevelopmental disorders are more frequent than previously assumed (Landgren et al., 1996; Kadesjo and Gillberg, 1998; Kadesjo et al., 1999; Baird et al., 2006), with severe variants affecting at least 5 % of all children. They are also linked to milder phenotypical expressions in relatives (Epstein et al., 2000; Happe et al., 2001; Dawson et al., 2002; Baron-Cohen, 2003; Briskman et al., 2001), and persist in many cases in similar or modified forms in adulthood (Rasmussen and Gillberg, 2000; Moffitt and Caspi, 2001; Beadle-Brown et al., 2002; Willoughby, 2003), playing a role in the development of personality and its disorders that is probably significant in view of the prevalence figures reported (Anckarsäter et al., 2006, Nigg, 2006).

Several important questions concerning the relation between childhood neuropsychiatric disorders and aggression remain to be disentangled by systematic studies. It is an open question whether childhood attention deficits and hyperactivity in the absence of CD also carry an increased risk for violent acts in adulthood (Lilienfeld and Waldman, 1990), and if the ASDs in the absence of hyperactivity could lead to an increased risk of aggressive behaviours. Using the Temperament and Character Inventory (TCI, Cloninger et al., 1993), Anckarsäter and co-workers (2006) showed a specific temperament configuration in ASDs, with low Novelty Seeking, low Reward Dependence, and high Harm Avoidance, while subjects with AD/HD reported high Novelty Seeking and high Harm Avoidance. Character scores, defined as conceptual tools for handling oneself and others (Self-Directedness and Cooperativeness), were extremely low in both groups, and personality disorders (PDs) according to the DSM-IV were very common. These results have recently been replicated for subjects with AD/HD (Faraone et al., 2009). Low scores in Self-Directedness, Cooperativeness, and Self-Transcendence have also been related to feelings of distrust or anger and to direct aggressive expressions both in clinical groups (Fassino et al., 2001) and in

community-based samples (Yoo et al., 2006), together with specific associations between low character scores and self-injurious behaviours (Evren and Evren, 2006; Favaro et al., 2008).

In the present paper, we have analysed scores from the Life History of Aggression (LHA, Brown et al., 1982) in relation to clinical assessments, including dimensional ratings of symptoms of AD/HD, ASD, tics, and axis I and II adult mental disorders (assessed by structured instruments), IQ (according to the Wechsler scales, 1981), dimensions of personality according to the TCI, and the Global Assessment of Functioning (GAF, American Psychiatric Association, 1995). Two groups of subjects were assessed by similar protocols and together provided a broad coverage of relevant mental disorders for the study of correlates to aggression: outpatients referred for investigations of childhood-onset neuropsychiatric disorders, and violent offenders referred for pre-trial forensic psychiatric investigations. In the latter group, childhood-onset neuropsychiatric disorders were previously analysed in relation to adult psychopathic personality traits, overall aggression scores, and recidivistic crimes (Soderstrom et al., 2005). The results were used to formulate the hypotheses for the present paper, which includes subscale analyses of aggression and a much larger group of subjects with childhood-onset neuropsychiatric disorders from the outpatient group.

We have now aimed to describe aggression according to the subscales formed in the LHA in relation to life-time psychiatric diagnoses and to test the following hypotheses:

1. That outpatients would have high LHA scores, even in comparison to violent offenders.
2. That high LHA scores would be specifically associated with symptoms of hyperactivity, CD, and substance abuse.
3. That high LHA scores would be associated with disordered personality profiles with explosive temperaments and low character scores.

Methods

Procedures

This paper is based on two independent study groups, both assessed for childhood-onset neuropsychiatric disorders and aggression by basically the same research protocol. The Gothenburg Child Neuropsychiatric Clinic (CNC) had at the time, the nation-wide responsibility for assessments of autism and related disorders in Sweden and was the only diagnostic centre specifically focused on neuropsychiatric assessments of childhood-onset disorders in the city of Gothenburg. An adult project carried out at the CNC included specialized evaluations of possible childhood-onset neuropsychiatric disorders (AD/HD, ASD, tic disorders, and various kinds of learning disorders) in outpatients referred by themselves, by general practitioners, or by other specialists in adult psychiatry, forming a consecutive large, well-characterized, clinical case cohorts for the Gothenburg Neuropsychiatric Genetic Study (NPG). The Gothenburg Forensic Neuropsychiatry Project (the FNP project) consists of all consenting subjects referred for inpatient forensic psychiatric investigations in Gothenburg during a defined period who were charged with a severe violent crime (homicide, attempted homicide, aggravated assault, arson, rape, or sexual violation of minors) and had received their basic education in Sweden.

In both projects, DSM-IV diagnoses were assigned by two senior psychiatrists in consensus (in the NPG project by MR and HA, in the FNP project by AF and HA), based on longitudinal, all-data considerations of available information, including clinical status, the Structured Clinical Interview for Diagnosis according to the DSM (SCID-I, First, 1997a, and

SCID-II, First, 1997b), the Asperger Syndrome and high-functioning autism Screening Questionnaire (ASSQ, Ehlers et al., 1999), the Asperger Syndrome Diagnostic Interview (ASDI, Gillberg et al., 2001), and the DSM-IV criteria check-lists for other disorders not included in any of the cited instruments, currently and retrospectively. Reliability and validity for all these scales are good to excellent. When possible, a semi-structured collateral interview was performed (n=123, 69 % in the NPG-project and n=29, 32 % in the FNP-project) with a relative who had known the index subject as a child. Clinical records were collected from paediatric and child psychiatric services and from school health services.

For all disorders, criteria limiting the possibility of assigning other comorbid psychiatric diagnoses were disregarded to allow comprehensive recording of the pattern of comorbidity. The numbers of fulfilled DSM-IV AD/HD and Gillberg & Gillberg criteria for Asperger syndrome/high-functioning autism in childhood were used as dimensional assessments of AD/HD and autism spectrum traits. Full-scale IQ and the subscores for verbal and performance IQ were calculated on the Wechsler Adult Intelligence Scale-Revised (WAIS-R, Wechsler, 1981).

Different aspects of aggression, and the frequency of its occurrence, were measured dimensionally using the LHA. The LHA has been shown to have excellent test-retest stability, inter-rater reliability, and internal consistency reliability (Coccaro et al., 1997). It has been used in many studies of violent behaviour (e.g. Coccaro et al., 1998; Hoptman et al., 2002). The 11-item scale was developed to assess trait aggressive behaviour, with each item reflecting a different form of aggressive behaviour. Coccaro and co-workers (1997) used the items to create three a priori subscales. The Aggression subscale includes temper tantrums, physical fights, verbal aggression, physical assaults on people (or animals), and assaults on property (items 1-5). The Self-directed aggression subscale quantifies self-injurious and suicide attempts (items 6a and 6b). The Consequences/Antisocial behaviour subscale denotes school disciplinary problems, problems with supervisors at work, antisocial behaviour not involving the police, and antisocial behaviour involving the police (items 7-10). Each item is rated on a five-point scale based on the number of occurrences of the behaviour since adolescence, from 0 (“no event”) to 5 (“so many events that they cannot be counted”), with possible total scores ranging from 0-55. In these studies, the LHA was used as an initial self-rating instrument, where subjects who had problems filling-out self-rate formulas received help from contact persons or clinicians. Subsequently, patients´ self-reports were supplemented by extensive clinical interviews and review of all available records and file reports.

Subjects

From the NPG study, among the 273 consecutive subjects (149 men, 124 women, median age 31.0, range 18-61) who gave informed consent, 178 subjects (98 men, 80 women, median age 31.5, range 19-59) completed the LHA, and this group constitutes the outpatient study group. There were no statistically significant differences between those who were rated with the LHA and those who were not in terms of age, sex, intelligence, tics, depression, bipolar disorder, psychotic disorder, and ASDs. A diagnosis of AD/HD was, however, significantly less common (48 % vs. 65 %, $p<0.01$) among those not assessed by the LHA. Among the included subjects, 161 (90 %) had a childhood-onset neurodevelopmental disorder (AD/HD and/or ASD), 81 subjects (46 men, 35 women, median age 28, range 19-57) had ASD (5 autism, 32 Asperger syndrome, and 44 atypical autism), and 116 (61 men, 55 women, median age 33, range 19-55) had AD/HD (35 predominately AD, 12 predominately HD, 58 combined form, and 11 AD/HD in remission). Thirty-six of these subjects had both AD/HD and ASD,

and thus 31 % of subjects with AD/HD also met criteria for ASD, and 44 % of those with ASD also met criteria for AD/HD. Among the 178 subjects, 117 had a mood disorder (i.e. a life-time diagnosis of major depressive or bipolar disorder), 12 met criteria for a psychotic disorder, 41 had an alcohol abuse disorder, 37 had a substance abuse disorder, and 91 subjects met criteria for a personality disorder (PD).

For the FNP project, a total of 121 subjects met the inclusion criteria, and 100 consented to participate (92 men, 8 women, median age 30.0, range 17-76) in some or all parts of the study. In 92 subjects (85 men, 7 women, median age 30.0, range 17-76), the LHA was completed. This group is referred to as the forensic study group. In the forensic group, 46 subjects (50 %) had a childhood-onset neurodevelopmental disorder (AD/HD and/or ASD), 17 subjects met criteria for an ASD (4 autism, 3 Asperger syndrome, and 10 atypical autism), 38 subjects had AD/HD (6 predominately AD, 6 predominately HD, and 26 in combined form), 42 subjects had a mood disorder, 16 met criteria for a psychotic disorder, 49 had an alcohol abuse disorder, 29 had a substance abuse disorder, and 38 subjects had a PD. For more specific information on diagnostic procedures and prevalence figures readers are referred to Soderstrom and co-workers (2005).

Statistical methods

Statistical analyses included Mann-Whitney U Test for group comparisons of continuous variables. All correlations were analyzed with Spearman´s non-parametric correlation coefficients, with the level of statistical significance set at 1% ($p \leq 0.01$) in order to reduce the risk for Type I errors considering the large number of analyses performed. As most tests assessed previously established hypotheses, further corrections for multiple comparisons were not deemed necessary in view of the descriptive nature of the study. In contrast, even if we have used two established consecutive clinical study groups, no pre-hoc power analyses were performed, which implies that negative results have to be interpreted with caution in view of the possibility of Type II errors. Multiple linear regression analysis models were used to test the association between the clinical and demographical variables on the total score of the LHA. Initially using the full multivariable model including all independent variables that had $p<0.30$ in bivariate analyses, we excluded one insignificant independent variable at a time, starting with the variable with the highest p-value, until all predictors remaining had $p<0.10$. However, we did not exclude variables that changed the estimated effect of symptoms of CD with more than 10 %. The adjusted amount of explained variance (R^2) and standardized regression coefficients (β) are presented. Analysis of variance assessed the significance of the explained amount of variance (R^2). A *t* statistic assessed the significance of β. All statistics were calculated, using anonymized data, with the SPSS 17.0 software, using two-tailed p-values.

Ethics

The NPG project and the Gothenburg Forensic Neuropsychiatry Project were approved by the Research Ethics Committee of Gothenburg University. All participants gave informed consent.

Results

The outpatient and the forensic group did not differ in terms of age or full scale IQ, but there were significantly more men in the forensic group (55 % vs. 92 %, $\chi 2$=38.7, df=1, $p<0.001$).

Table 1. Comparison between the study groups on demographic variables and LHA subscales

	Outpatient group (n=178)	Forensic group (n=92)	Group comparison	
			χ^2	p
Males (n, %)	98 (55%)	85 (92%)	38.7	<0.001
Females (n, %)	80 (45%)	7 (8%)		
	Mean and standard deviation	Mean and standard deviation	p[a]	
Age	32.5±9.1	34.3±13.9	*ns*	
FSIQ	87.7±19.2	91.6±21.5	*ns*	
LHA Total score	21.8±12.9	22.7±13.5	*ns*	
LHA Aggression	14.2±7.0	12.6±7.2	*ns*	
LHA Self-directed aggression	2.5±2.9	2.9±3.4	*ns*	
LHA Antisocial behaviour	5.1±5.1	7.2±5.4	0.001	

[a]Mann-Whitney U test

Group comparisons using the Mann-Whitney U Test indicated no significant difference between the outpatient and the forensic group on LHA Total score, or the Aggression and Self-directed aggression subscores. The forensic group, however, scored significantly higher on Antisocial behaviour ($p \leq 0.001$). Again, men and women only differed by a significantly higher score for men on Antisocial behaviour ($p<0.01$), which relates to the difference on this subscale between the two study groups. As seen in Table 2, age was negatively correlated to all LHA scores except the Self-directed aggression score in the forensic group, but not to any of the LHA scores in the outpatient group.

In Table 2, the positive correlations between all LHA subscales and criteria for attention deficits (except the Self-directed aggression subscale), hyperactivity, CD symptoms before the age of 15, and alcohol or drug abuse/dependence are demonstrated. The number of SCID-II PD diagnoses, used as a dimensional variable, was also positively correlated with all LHA subscales. Among the TCI measures of temperament, high Novelty Seeking was the only correlate to the LHA, with the exception of the Self-directed aggression subscore. All three character variables (low Self-Directedness, low Cooperativeness, and high Self-Transcendence) were significantly related to LHA. Lower IQ and lower GAF-scores were specifically correlated with the Self-directed aggression subscale. In contrast to all other studied parameters, ASD symptoms showed a non-linear relation to LHA across the two groups. A lower rate of autistic symptoms was correlated to increased LHA scores in the outpatient group, while the opposite was true for the forensic group. Alcohol and/or drug abuse, as well as CD, were significantly more frequent ($p<0.05$ and $p<0.01$) in the forensic as compared to the outpatient ASD subjects, which could explain this finding.

Table 2. Correlation (Spearman´s rho, two-tailed) between LHA scores, demographical and clinical data

		LHA Total score	LHA Aggression	LHA Self-directed aggression	LHA Antisocial behaviour
		Spearman's rho	Spearman's rho	Spearman's rho	Spearman's rho
Attention deficits	total group	0.39***	0.38***	0.13	0.34***
	outpatients	0.41***	0.38***	0.18	0.42***
	forensic	0.41***	0.39***	0.13	0.44***
Hyperactivity	total group	0.48***	0.48***	0.19**	0.40***
	outpatients	0.49***	0.49***	0.21**	0.44***
	forensic	0.51***	0.46***	0.20	0.51***
Autistic symptoms	total group	-0.07	-0.06	0.04	-0.13
	outpatients	-0.24***	-0.27***	-0.04	-0.21**
	forensic	0.33***	0.27**	0.28**	0.29**
Conduct problems	total group	0.65***	0.55***	0.38***	0.67***
	outpatients	0.74***	0.66***	0.48***	0.71***
	forensic	0.56***	0.53***	0.27	0.56***

Table 2. *continued*

Full scale IQ	total group	-0.07	-0.03	-0.24***	0.01
	outpatients	-0.03	0.03	-0.24**	0.02
	forensic	-0.17	-0.13	-0.27	-0.06
Verbal IQ	total group	-0.08	-0.04	-0.24***	-0.01
	outpatients	-0.06	-0.00	-0.26***	-0.01
	forensic	-0.15	-0.10	-0.25	-0.06
Performance IQ	total group	-0.02	-0.00	-0.21***	0.04
	outpatients	-0.01	0.04	-0.21**	0.05
	forensic	-0.09	-0.06	-0.22	-0.00
GAF	total group	-0.15	-0.09	-0.31***	-0.09
	outpatients	-0.13	-0.09	-0.28***	-0.11
	forensic	-0.18	-0.09	-0.35***	-0.10
Novelty Seeking	total group	0.36***	0.38***	0.10	0.34***
	outpatients	0.41***	0.39***	0.12	0.44***
	forensic	0.29	0.30**	0.11	0.25
Harm Avoidance	total group	-0.00	-0.05	0.17**	-0.05
	outpatients	-0.04	-0.07	0.15	-0.05
	forensic	0.09	-0.03	0.26	0.09
Reward Dependence	total group	-0.11	-0.12	-0.02	-0.07
	outpatients	-0.02	-0.02	0.05	-0.03
	forensic	-0.28	-0.28	-0.16	-0.28
Persistence	total group	0.16	-0.15	0.00	-0.20**
	outpatients	-0.16	-0.16	-0.03	-0.19
	forensic	-0.15	-0.16	0.07	-0.19
Self-Directedness	total group	-0.34***	-0.29***	-0.29***	-0.27***
	outpatients	-0.36***	-0.28***	-0.31***	-0.35***
	forensic	-0.36***	-0.27	-0.37***	-0.31**
Cooperativeness	total group	-0.34***	-0.34***	-0.17**	-0.31***
	outpatients	-0.26***	-0.21**	-0.12	-0.32***
	forensic	-0.53***	-0.50***	-0.31**	-0.49***
Self-Transcendence	total group	0.30***	0.25***	0.21***	0.28***
	outpatients	0.30***	0.26***	0.21**	0.28***
	forensic	0.28	0.30**	0.15	0.22
Number of PDs	total group	0.34***	0.26***	0.28***	0.33***
	outpatients	0.27***	0.25***	0.24**	0.19*
	forensic	0.49***	0.42***	0.38***	0.45***
Alcohol abuse	total group	0.39***	0.32***	0.20***	0.42***
	outpatients	0.42***	0.37***	0.23**	0.43***
	forensic	0.37***	0.36***	0.15	0.32**
Drug abuse	total group	0.49***	0.39***	0.29***	0.53***
	outpatients	0.52***	0.45***	0.35***	0.53***
	forensic	0.44***	0.36***	0.21	0.49***
Psychosis	total group	0.08	0.06	0.04	0.13
	outpatients	0.05	0.08	-0.01	0.03
	forensic	0.13	0.10	0.10	0.17
Depressive disorder	total group	0.03	0.09	0.04	-0.11
	outpatients	0.06	0.06	0.09	-0.03
	forensic	-0.01	-0.04	-0.03	0.06
Bipolar disorder	total group	-0.01	-0.02	0.02	0.00
	outpatients	-0.07	-0.08	0.00	-0.03
	forensic	0.09	0.07	0.04	0.06
Tic disorder	total group	0.04	0.03	0.01	0.07
	outpatients	0.05	0.07	-0.06	0.07
	forensic	0.02	-0.02	0.11	0.02
Age	total group	-0.09	-0.09	-0.13	-0.01
	outpatients	0.11	0.10	-0.06	0.17
	forensic	-0.39***	-0.39***	-0.20	-0.29**
Sex	total group	-0.06	-0.04	0.09	-0.19**
	outpatients	-0.09	-0.13	0.08	-0.14
	forensic	0.08	0.08	0.21	-0.05

[a]Spearman rank correlation
**P<0.01 ***P≤0.001.

Eventually, we tried to identify the most important clinical covariates of aggressive behaviour patterns in a linear regression model (Table 3), using the variables previously identified as significant covariates in the bivariate correlations described above. In the total study group, conduct problems before the age of 15 emerged as the single most important predictor of high adult LHA scores, followed by three other significant, independent predictors: childhood hyperactivity, drug abuse/dependence, and low Cooperativeness. In this model, the independent variables predicted 49 % of variance in the dependent variable (P<0.001).

Table 3. Multiple regression analyses with LHA total score as dependent variable and clinical and demographical variables as predictors

Predictor	**β**	**95 % CI**	**t**
Clinical variables			
Attention symptoms	-0.17	-1.45-0.10	-1.71
Hyperactivity symptoms	0.22	0.16-1.64	2.39*
Alcohol abuse	0.10	-0.96-6.72	1.48
Drug abuse	0.16	0.40-9.04	2.16*
Conduct symptoms	0.31	0.65-1.93	3.97***
FSIQ	-0.08	-0.15-0.03	-1.33
Total number of PDs	0.08	-0.41-1.39	1.08
Temperament and Character Inventory dimensions			
Novelty Seeking	0.10	-0.03-0.25	1.55
Self-Directedness	-0.04	-0.17-0.09	-0.58
Cooperativeness	-0.10	-0.25- -0.04	-2.81**
Self-Transcendence	0.10	-0.03-0.20	1.54
Age	-0.10	-0.26-0.04	-1.44
Sex	-0.01	-3.56-3.05	-0.15
	Adj R^2		F
Full model	0.49		12.9***

[a]Standardised regression coefficient (β) are presented, which indicate the relative magnitude of prediction for each independent variable.
*P<0.05 **P<0.01 ***P≤0.001.

Discussion

The aim of this study was to identify clinical psychiatric symptoms associated with increased aggression in adults. The two study groups (outpatients diagnosed with neuropsychiatric disorders and violent offenders, all with broad clinical psychiatric assessments) were heterogeneous but represent a wide spectrum of psychiatric problems that may be assessed in relation to aggression. The results support that childhood hyperactivity and CD, adult substance abuse, and low Cooperativeness, carry specific associations with increased levels of aggression, also in adults from a non-correctional setting. No other mental diagnostic definition showed as strong associations with aggression as these childhood-onset behavioural disorders, substance abuse, and specific immature personality traits in social interaction. This finding could, of course, be due to the selection in the present study groups, and calls for replication in other general psychiatry groups, but as it is in line with the literature on ASPD in which the role of childhood CD has always been highlighted, we think that it may at least be accepted as a preliminary finding that in this study was consistent across the two study groups.

Severe violent acting-out is a problem in patient groups with ASD (Kristiansson and Sörman, 2008, Anckarsäter et al., 2008). The lack of association between LHA and autistic traits, the relationship being explained by symptoms of conduct disorder and substance abuse, in the present study may be due to LHA rating the number rather than the severity of aggressive

events over the lifetime. A tentative conclusion based on the current literature might be that AD/HD is specifically associated with frequent aggressive behaviours, while autism may entail a risk of, especially stress-related, violent acting out.

In our study groups, low IQ was significantly related to self-injurious behaviours, but contrary to several other studies (Emerson et al., 2001; Harris, 1993), IQ was not related to other forms of aggressive behaviour or antisociality.

The association between low Cooperativeness and aggression replicates previous studies using the TCI (Kim et al., 2006). The character facets reflected in Cooperativeness describe tendencies to make inaccurate interpretations of intentional cues and a bias towards hostile attributions in ambiguous situations. There are robust correlations between these modes of social information processing and aggression (Orobio de Castro et al., 2002). The lack of relationship between any of the temperament scales (e.g. Novelty Seeking) and aggression could be due to the high prevalence of subjects with AD/HD or be understood as a confirmation of Cloninger's model, in which the actual psychosocial functioning is expressing character maturity rather than the patterns of direct reactions to stimuli captured by the temperament scales. Expressed aggressive behaviours, such as those included in the LHA, are expressions of deficient control mechanisms, such as the conceptual deliberations of consequences, mental processes in others and in oneself, and ethics contained in the descriptions of character.

The findings presented call for assessments of aggression-related behaviours in psychiatric investigations and treatment planning, not only in forensic psychiatric settings but also in community-based adult psychiatric services, and clearly demonstrate the importance of childhood and adolescence behavioural aberrations as the strongest predictor of such behaviours in adulthood. Our analyses also suggest hyperactivity, and not attention deficits, as the marker for the increased risk for aggression associated with AD/HD, and that hyperactivity even independently from CD actually carries an increased risk for aggression. Longitudinal epidemiological research has not been able to identify hyperactivity as a predictor of ASPD or criminality in the absence of early CD (Lilienfelt & Waldman 1990), even if claims to the contrary have been made (Mannuzza et al., 2008 see Hofvander et al, 2009 for a full discussion of the method problems involved). The strong relationship between violent criminality and substance abuse has been demonstrated in a variety of settings, in prison surveys (Fazel et al., 2006) as well as in medical facilities (Steadman et al., 1998). Our study supports these findings in an outpatient as well as a forensic psychiatric context.

This study has several important limitations. Statistical shortcomings include pre-hoc assessment of power for the correlational and predictive models applied, and the impossibility of strict Bonferroni or other correction of p-values to the number of analyses performed. Retrospective data on developmental trajectories and childhood-onset disorders from cross-sectional studies must be cautiously interpreted despite access to a wealth of data from medical/psychiatric records and relatives. The LHA builds on self-assessments though aggressive behaviours were also addressed in the clinical psychiatric evaluations and reviews of files and medical records in both study groups reported here. Studies on associations within study groups are sensitive to the composition of the groups, and our two groups have a number of particular features that may have influenced results, not least in the context of autism. Here again, the consistency of findings across both groups strengthen the results, while a need naturally remains for larger and more representative clinical studies and,

optimally, population-based prospective studies on the relation between psychiatric diagnostic concepts and aggressive acting-out.

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Paper III

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Psychiatric and psychosocial problems in adults with normal-intelligence autism spectrum disorders

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Abstract

Background: Individuals with autism spectrum disorders (ASDs) often display symptoms from other diagnostic categories. Studies of clinical and psychosocial outcome in adult patients with ASDs without concomitant intellectual disability are few. The objective of this paper is to describe the clinical psychiatric presentation and important outcome measures of a large group of normal-intelligence adult patients with ASDs.

Methods: Autistic symptomatology according to the DSM-IV-criteria and the Gillberg & Gillberg research criteria, patterns of comorbid psychopathology and psychosocial outcome were assessed in 122 consecutively referred adults with normal intelligence ASDs. The subjects consisted of 5 patients with autistic disorder (AD), 67 with Asperger's disorder (AS) and 50 with pervasive developmental disorder not otherwise specified (PDD NOS). This study group consists of subjects pooled from two studies with highly similar protocols, all seen on an outpatient basis by one of three clinicians.

Results: Core autistic symptoms were highly prevalent in all ASD subgroups. Though AD subjects had the most pervasive problems, restrictions in non-verbal communication were common across all three subgroups and, contrary to current DSM criteria, so were verbal communication deficits. Lifetime psychiatric axis I comorbidity was very common, most notably mood and anxiety disorders, but also ADHD and psychotic disorders. The frequency of these diagnoses did not differ between the ASD subgroups or between males and females. Antisocial personality disorder and

substance abuse were more common in the PDD NOS group. Of all subjects, few led an independent life and very few had ever had a long-term relationship. Female subjects more often reported having been bullied at school than male subjects.

Conclusion: ASDs are clinical syndromes characterized by impaired social interaction and non-verbal communication in adulthood as well as in childhood. They also carry a high risk for co-existing mental health problems from a broad spectrum of disorders and for unfavourable psychosocial life circumstances. For the next revision of DSM, our findings especially stress the importance of careful examination of the exclusion criterion for adult patients with ASDs.

Background

Autism spectrum disorders (ASDs) (or pervasive developmental disorders (PDDs), in the DSM-IV) are impairing developmental disorders characterized by aberrations in the domains of social interaction, communication and stereotyped or repetitive behavior patterns, estimated to affect about 1% of the general population [1]. The DSM-IV includes the following ASDs: autistic disorder (AD) (pervasive problems/deficits in all three domains), Asperger's disorder (AS) (pervasive deficits in social interaction and in behaviours in the presence of a normal verbal development) and pervasive developmental disorder not otherwise specified (PDD NOS). Research criteria for AS by Gillberg & Gillberg (G & G) [2] include the same triad of restrictions but also verbal peculiarities and abnormal motor development. "High-functioning autism" (HFA) is a disputed term sometimes used to describe individuals with AD without concomitant mental retardation [3].

Community-based studies show highly skewed male>female ratios for ASDs [4]. Possible sex differences in the clinical phenotypes have been insufficiently studied [5], and instruments and criteria have been developed and validated mostly on male subjects, which also might have affected the estimated sex ratio. Further, ASDs have mainly been diagnosed among children and adolescents, but increasing attention is directed to their prevalence and clinical presentation among adults. A few long-term prospective follow-up studies have so far shown high diagnostic stability [6,7].

Data on psychosocial life circumstances and psychiatric comorbidity in normal-intelligence adult patients with ASDs are scarce but suggest reduced social functioning, and a substantially better outcome in AS than in autism, probably attributable to better intellectual abilities [7]. Estimated rates of co-existing psychiatric disorders in subjects with normal intelligence ASDs have varied substantially, from 9% to 89% [8]. Attention deficits and hyperactivity have been shown to be common in children with ASDs [4], but studies of the co-occurrence of ADHD and ASDs in adults are few [9,10]. A high rate of chronic tic disorders has been reported in ASD patients [11]. Mood disorders, together with anxiety disorders, have been described as important complications of ASDs in a range of studies [8,12,13].

Autism was until the 1970's conceptualized as the earliest manifestation of schizophrenia [14]. Kolvin [15], among others, provided evidence of a bimodal distribution of onset in "childhood psychosis", which was thought to separate the two conditions. It was even suggested that at least the childhood-onset subtype of schizophrenia was less common in autism than in the general population [16]. Today, autism and schizophrenia are referred to as early and late onset neurodevelopmental disorders [17]. Psychotic symptoms in ASD patients have often come to be regarded as misattributions of autistic phenomena [18]. However, "schizophrenic-type illnesses" represent around one-tenth of all psychiatric comorbid diagnoses in a review by Howlin [8]. Additionally, a number of clinical case reports have described psychotic symptomatology, including auditory hallucinations, paranoid ideas, or delusional thoughts in subjects with ASDs. It seems probable that ASD is one possible vulnerability factor for the development of psychotic symptoms and schizophrenia [19]. A more definitive picture of the life-time prevalences of ASD, psychotic disorders and their overlap will require population-based prospective studies.

We have compiled detailed data on a large group of consecutively referred adults diagnosed with normal-intelligence ASDs to: 1. detail the criteria for the various problem types in the DSM-IV ASD subgroups and between male and female subjects. 2. estimate frequencies of DSM-IV axis I and II diagnoses and describe their diagnostic overlap in adults with normal-intelligence ASDs and 3. explore the psychosocial situation for these subjects.

Methods

Participants in this study were consecutively referred adults with possible childhood-onset neuropsychiatric disabilities at the Henri Mondor-Albert Chenevier hospital in Paris ("the Paris study group") and at the Child Neuropsychiatric Clinic in Gothenburg ("the Gothenburg study group") who subsequently met DSM-IV criteria for

an ASD with normal intelligence. Both clinics are expert diagnostic centers focused on neuropsychiatric assessments of childhood-onset disorders in adults. The Paris site was specifically recruiting patients with AS and other ASDs. For this study, eight patients were also included according to the Paris protocol at the Psychiatric Outpatient Clinic in Malmö.

The total study group of 122 adults (39 from Paris and 83 from Gothenburg) included 82 (67%) men and 40 (33%) women (median age 29 years (yrs), ranging from 16 to 60 yrs). The Gothenburg subjects were significantly older than the Paris subjects (Mann-Whitney U = 1072, p = 0.003) with a median age of 30 yrs (range 19–60 yrs) as compared to 25 yrs (range 16–47 yrs) in Paris. There were no significant differences in sex ratios ($\chi^2 = 1.33$, df = 1, p = 0.30) or full scale IQ (Mann-Whitney U = 1170, p = 0.46) between the two study groups. In Gothenburg 2% of cases were diagnosed with AD, 46% with AS and 52% with PDD NOS. Among the Paris subjects, AD was diagnosed in 8%, AS in 74%, and PDD NOS in 18%. The difference in frequency of AS and PDD NOS diagnoses between Gothenburg and Paris were significant ($\chi^2 = 8.75$, df = 1, p = 0.004 and $\chi^2 = 12.58$, df = 1, p < 0.001). Men and women in the total study group did not differ significantly in age (Mann-Whitney U = 1392, p = 0.18) with the median age being 28 yrs for men and 30 yrs for women. Sex differences within the diagnostic ASD subgroups did not reach significance, as was the case in another study of an adult psychiatric population [10].

The Gothenburg study group includes patients diagnosed with ASD from a previously described study group of adults with childhood-onset neuropsychiatric disorders [9,20]. All subjects were seen on an outpatient basis by clinicians involved in autism research (all included patients had their final diagnoses confirmed by either HA, MR or ML). The individual diagnoses were based on all available information, including current clinical status. Childhood developmental problems were assessed retrospectively, from direct parental report where possible. More than half of the subjects had earlier been diagnosed with anxiety, mood disorders or psychosis and were now secondary or tertiary referrals from specialists in adult psychiatry for additional diagnostic work-up. Childhood medical records, including previous psychiatric or psychological assessments, were provided by the patients or obtained from child medical centers. All subjects were included according to the research protocol for the Gothenburg Neuro-Psychiatry Genetics Project (NPG) or the Paris Autism Research International Sibpair study (P.A.R.I.S.).

The Asperger Syndrome Diagnostic Interview (ASDI) [21] was used in 106 subjects (87%). ASD diagnoses were assigned according to specific assessments of all DSM-IV autistic disorder criteria and the Gillberg & Gillberg (G&G) criteria for AS [2]. In the Gothenburg group, 63 patients (76%) had axis-I disorders assessed by the Structured Clinical Interview for DSM IV – Axis I Disorders (SCID-I) [22]; all other subjects had a structured, DSM-IV-based, clinical interview supplemented with a life-time DSM-IV symptom checklist containing individual criteria or symptom definitions for all relevant axis-I disorders. Axis-II disorders were assessed in 117 patients (96%), in 95 subjects (81%) by the Structured Clinical Interview for DSM IV – Axis II Personality Disorders (SCID-II) [23] and in the others by a structured DSM-IV-based clinical interview. For all disorders, DSM criteria that limited the possibility of assigning other comorbid psychiatric diagnoses were disregarded to allow a comprehensive recording of the pattern of comorbidity.

Somatic status was assessed in all patients. Cases with known medical causes of autism, including genetic syndromes, or injuries of relevance for the mental disorders assessed, were excluded by history, physical examination, and in dubious cases by karyotype, Fragile × PCR and southern blot, and FISH analyses (15q11-q13, 22q11 and 22q13 deletion syndromes). No patient was in need of language interpretation for communication. Three-generation pedigrees were drawn. In the Gothenburg study group, whenever possible, a semi-structured collateral interview (n = 63, 76%) based on the ASDI, the ADHD-RS [24], the "Five to Fifteen" questionnaire [25], and the Wender Utah Rating Scale [26] was performed with a relative who had known the index subject as a child. In the Paris study group the Autism-Tics, ADHD and Other Comorbidities Inventory (A-TAC) [27], was used for collateral interviews (n = 39, 100%). Global intellectual ability was assessed in most cases (n = 114, 93%) using the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (n = 83) or the Wechsler Adult Intelligence Scale-III (WAIS-III) (n = 31) [28,29]. The remaining eight subjects either had normal results from previous tests or well-documented normal development according to school and educational performance but declined participation in new psychometric assessments.

The study was approved by the medical ethical review boards at each site (Gothenburg, Paris and Malmö). All patients included gave written informed consent.

Statistical analyses were performed using the SPSS 15.0 [30]. Since AD was diagnosed only in five subjects, these subjects were described separately and not included in group comparisons between diagnostic groups. Mann-Whitney U test was used for group comparisons of differences in continuous variables, as the data was not normally distributed. Fisher's exact χ^2-test was used to compare differences in frequencies of fulfilled ASD, DSM-

IV and G & G criteria and coexisting psychopathologies. All p-values are two-tailed, and significance was considered at the 5% level.

Results

Autism Spectrum Disorders (Pervasive Developmental Disorders)

The distribution of DSM-IV and G & G criteria across the diagnostic categories and sexes is presented in Table 1. Virtually all subjects (n = 119, 98%) displayed symptoms required for the first DSM-IV and G & G criterion (i.e. social interaction problems, in the DSM-IV also including non-verbal communication deficits). Nonverbal communication problems according to the fifth G & G criterion were very common, described in 89% (n = 108) of all subjects. The AS and the PDD NOS subjects did not differ significantly in the DSM-IV and G & G areas of social interaction and the DSM-IV area of communication.

Other Axis I Psychiatric Disorders "Usually First Diagnosed in Infancy, Childhood, or Adolescence"

A large proportion of all subjects was diagnosed with ADHD (n = 52, 43%, Table 2). Subjects with PDD NOS had significantly more symptoms of inattention (Mann-Whitney U = 1157, p = 0.01) and hyperactivity/impulsivity (Mann-Whitney U = 1136, p = 0.007) compared to subjects with AS. However, the prevalence of the categorical diagnosis of ADHD did not differ significantly between the groups.

The frequency of reading disorder in combination with disorder of written expression (i.e. dyslexia) was 14% (n =

Table 1: Distribution of DSM-IV and Gillberg and Gillberg (G&G) criteria across the diagnostic categories

Type of DSM-IV PDD	Autistic disorder (N=5)		Asperger's disorder (N=67)		PDD NOS (N=50)		AS – PDD NOS[a]		Total (N=122)		Male (N=82)		Female (N=40)		Male – Female[a]	
	N	%	N	%	N	%	χ^2 (df = 1)	p	N	%	N	%	N	%	χ^2 (df = 1)	p
DSM IV criterion A1 "Qualitative impairment in social interaction"	5	100	67	100	47	94	4.13	0.08	119	98	80	98	39	98	0.00	1.00
DSM-IV Criterion A2: "Qualitative impairment in communication"	5	100	34	51	18	36	2.52	0.13	57	47	41	50	16	40	1.08	0.34
DSM-IV Criterion A3: "Restricted, repetitive and stereotyped behaviour, interests, and activities"	5	100	65	97	29	58	27.60	<0.001	99	81	70	85	29	73	2.91	0.14
G&G Criterion 1; "Social interaction problems"	5	100	67	100	47	96	4.13	0.08	119	98	80	98	39	98	0.00	1.00
G&G Criterion 2: "Narrow interests"	5	100	64	96	33	67	17.61	<0.001	102	84	69	84	33	83	0.05	0.80
G&G Criterion 3; "Repetitive routines"	5	100	61	91	25	51	24.77	<0.001	91	75	62	76	29	73	0.14	0.83
G&G Criterion 4: "Speech and language"	5	100	56	84	22	45	20.19	<0.001	83	69	57	70	26	65	0.25	0.68
G&G Criterion 5: "Non-verbal communication problems"	5	100	66	99	37	76	16.33	<0.001	108	89	74	90	34	85	0.73	0.38
G&G Criterion 6: "Motor clumsiness"	5	100	57	85	31	63	8.18	0.005	94	78	60	73	33	83	1.29	0.37

[a]Fisher's exact χ^2 test

Table 2: Frequency of ADHD subtypes and symptoms of inattention and hyperactivity/impulsivity in each of the ASD subtypes

	Autistic disorder (N=5)		Asperger's disorder (N=67)		PDD NOS (N=50)		AS – PDD NOS[a]		Total (N=122)		Male (N=82)		Female (N=40)		Male – Female[a]	
	N	%	N	%	N	%	χ^2 (df = 1)	p	N	%	N	%	N	%	χ^2 (df = 1)	p
Inattentive subtype	2	40	8	12	11	22	2.13	0.21	21	17	14	17	7	18	0.00	1.00
Hyperactive/ impulsive subtype	0	0	5	8	3	6	0.10	1.00	8	7	5	6	3	8	0.09	0.72
Combined subtype	0	0	11	16	12	24	1.04	0.35	23	19	16	20	7	18	0.07	1.00
Any ADHD	2	40	24	36	26	52	3.06	0.09	52	43	35	43	17	43	0.00	1.00
							AS – PDD NOS[b]								Male – Female[b]	
							Z	p							Z	p
Median and range of inattentive criteria met	4 (0–7)		3 (0–8)		6 (0–9)		-2.52	0.01	4 (0–9)		4 (0–9)		3 (0–9)		-0.49	0.63
Median and range of hyperactive/ impulsive criteria met	2 (0–7)		1 (0–9)		3 (0–9)		-2.69	0.007	2 (0–9)		2 (0–9)		2 (0–9)		-0.89	0.37

[a]Fisher's exact χ^2 test; [b]Mann-Whitney U test

Table 3: Lifetime rate of axis-I disorders in adults with autism spectrum disorders (N = 122, if not otherwise specified)

	Criteria met DSM-IV															
	Autistic disorder (N=5)		Asperger's disorder (N=67)		PDD NOS (N=50)		Total (N=122)		AS – PDD NOS[a]		Male (N=82)		Female (N=40)		Male – Female[a]	
	N	%	N	%	N	%	N	%	χ^2 (df = 1)	p	N	%	N	%	χ^2 (df = 1)	p
Attention-Deficit/ Hyperactivity Disorder	2	40	24	36	26	52	52	43	3.06	0.09	35	43	17	43	0.00	1.00
Chronic tic disorders	0	0	14	21	11	22	25	20	0.02	1.00	20	24	5	13	2.33	0.16
Mood disorder	3	60	35	52	27	54	65	53	0.04	1.00	39	48	26	65	3.29	0.08
Psychotic disorders	0	0	10	15	5	10	15	12	0.62	0.58	13	16	2	5	2.94	0.14
Substance related disorders	1	20	4	6	14	28	19	16	10.67	0.002	14	17	5	13	0.43	0.60
Anxiety disorder N = 119	0	0	34	51	25	50	59	50	0.01	1.00	37	45	22	55	1.05	0.34
Obsessive Compulsive Disorder	0	0	14	21	15	30	29	24	1.27	0.29	16	20	13	33	2.50	0.12
Impulse control disorder	0	0	4	6	7	14	11	9	2.17	0.20	6	7	5	13	0.88	0.50
Somatoform disorder N = 119	0	0	2	3	4	8	6	5	1.48	0.40	4	5	2	5	0.00	1.00
Eating disorder N = 119	0	0	2	3	4	8	6	5	1.48	0.40	2	2	4	10	3.29	0.09

[a]Fisher's exact χ^2 test

16). In the Gothenburg group the criteria for this diagnosis was an unambiguous history of deficient reading and writing; the Paris subjects had a formal diagnosis of dyslexia.

Adult Axis I Disorders

The frequencies of the remaining DSM-IV axis-I diagnoses are presented in Table 3. Among the small number of subjects with AD, 80% (n = 4) met criteria for at least one other major axis-I disorder as specified below. In the AS and PDD NOS subgroups all subjects had at least one comorbid axis-I disorder. The most common life-time comorbid condition was mood disorder (n = 65, 53%). One-third of subjects (n = 42, 34%) had been treated with an antidepressant at least once in their lives. Criteria for a bipolar disorder (BP) were met by 10 subjects (8%), five of whom had bipolar I subtype and two bipolar II, while three were coded as unknown subtypes. No subject with AD met criteria for BP. Only three patients (2%) had ever been treated with a mood stabilizer.

A considerable number of patients (n = 15, 12%) met criteria for a psychotic disorder (most often not otherwise specified). Four patients met criteria for a schizophreniform disorder, three for brief psychotic disorder, and one for a delusional disorder. No subject met criteria for schizoaffective disorder. In the entire study group, 18 subjects (15%) had been treated with neuroleptics at least once in their lives.

Sixteen per cent of the subjects (n = 19) met criteria for a substance use disorder (SUD). The PDD NOS group had significantly more SUD-related diagnoses than the AS group (p = 0.002). The majority of diagnoses were related to alcohol (n = 15, 12%), four subjects met criteria for cannabis use disorder, three for amphetamine use disorder, two had a history of taking non-prescribed opiates or analgetics, and one had used anabolic steroids. Another subject, a 27-year-old man with AD, had a history of inhaling solvents.

The second most frequent category of DSM-IV disorders was anxiety disorders. Generalized anxiety disorder was common (n = 18, 15%) as was social phobia (n = 16, 13%). Thirteen subjects (11%) met criteria for panic disorder and/or agoraphobia and seven (6%) met criteria for a specific phobia. Two patients suffered from post traumatic stress disorder (PTSD), and one had an anxiety disorder NOS.

Among patients affected with impulse control disorders, intermittent explosive disorder was the most common diagnosis (n = 7, 6%), followed by kleptomania, pyromania, pathological gambling, trichotillomania, and impulse control disorder NOS, all affecting one patient each.

Personality disorders

Rates for personality disorders (PD) according to DSM-IV are presented in Table 4. Obsessive-compulsive PD (OCPD) was significantly more common in the AS group

Table 4: Lifetime rate of axis-II disorders in adults with autism spectrum disorders (N = 117)

	Criteria met DSM-IV															
	Autistic disorder (N=5)		Asperger's disorder (N=62)		PDD NOS (N=50)		Total (N=117)		AS – PDD NOS[a]		Male (N=77)		Female (N=40)		Male – Female[a]	
	N	%	N	%	N	%	N	%	χ^2 (df = 1)	p	N	%	N	%	χ^2 (df = 1)	p
Personality disorders																
≥ 1 PD	1	20	42	68	30	60	73	62	0.72	0.43	46	60	27	68	0.68	0.43
≥ 2 PD	0	0	25	40	16	32	41	35	0.83	0.43	28	36	13	33	0.18	0.84
≥ 3 PD	0	0	11	18	9	18	20	17	0.00	1.00	13	17	7	18	0.01	1.00
Paranoid	0	0	12	19	10	20	22	19	0.01	1.00	15	20	7	18	0.07	1.00
Schizotypal	0	0	10	16	5	10	15	13	0.90	0.41	12	16	3	8	1.54	0.26
Schizoid	0	0	13	21	12	24	25	21	0.15	0.82	11	14	14	35	6.72	0.02
Histrionic	-	-	-	-	-	-	0	0	-	-	-	-	-	-	-	-
Narcissistic	0	0	1	2	2	4	3	3	0.61	0.59	2	3	1	3	0.00	1.00
Borderline	0	0	4	7	6	12	10	9	1.05	0.34	4	5	6	15	3.24	0.09
Antisocial	0	0	0	0	4	8	4	3	5.14	0.04	3	4	1	3	0.16	1.00
Avoidant	0	0	18	29	11	22	29	25	0.62	0.52	21	28	8	20	0.81	0.50
Dependent	0	0	2	3	4	8	6	5	1.24	0.41	3	4	3	8	0.70	0.41
Obsessive	1	20	25	40	11	22	37	32	4.26	0.04	23	30	14	35	0.32	0.68
PD NOS	-	-	-	-	-	-	0	0	-	-	-	-	-	-	-	-

[a]Fisher's exact χ^2 test

($\chi^2 = 4.26$, df = 1, p = 0.04) and antisocial PD in the PDD NOS group ($\chi^2 = 5.14$, df = 1, p = 0.04). Overall frequency of PDs did not differ between men and women, with the exception of schizoid PD, which was significantly more common among the female subjects ($\chi^2 = 6.72$, df = 1, p = 0.02).

Psychosocial Characteristics

A majority of the subjects (n = 68, 56%) reported that they had been bullied at school. Such victimization was most common among the women ($\chi^2 = 6.09$, df = 1, p = 0.02). The educational level was relatively high in the entire study population. Two thirds (n = 77, 65%) had graduated from upper secondary school, and a quarter (n = 29, 24%) had completed college or university studies. In terms of daily occupation, 43% (n = 50) were employed or were students at the time of the assessment, with no significant differences between males and females. The others had either no organized daily activities, were on sick leave, held a medical pension, or were unemployed. Half of the subjects aged 23 yrs or more had independent living arrangements, as did some of the younger subjects. Nineteen (16%) had lived in a long-term relationship. Men and women did not differ in terms of marriage or cohabitation.

Discussion

Large outcome studies or systematic clinical surveys of adult ASDs are few. To our knowledge, this is one of the first such studies presenting detailed clinical data on a large consecutive group of adults with ASDs and normal intelligence. It includes a wide age span (16–60 yrs), with a relatively large proportion of subjects over 30 yrs of age (42%), and a substantial representation of women.

The purpose of describing the presence of autistic disorder symptoms in all three diagnostic subgroups was to address the important question of the adequacy of the current DSM-IV ASD categories. The interpretation of different patterns of criteria in the three diagnostic groups first has to consider that these criteria were used to assign the diagnoses. Then, as expected, the small group with normal-intelligence AD (equivalent to HFA) had the most pervasive ASD symptomatology, followed by the AS group, while the PDD NOS group exhibited the least number of symptoms. However, one-third of the PDD NOS patients and half of the AS patients met the DSM-IV communication criterion despite the fact that, according to the DSM-IV, only "subtle aspects of social communication" is expected to be impaired in AS, and the criteria for PDD NOS do not even require communication problems. When comparing the distribution of G & G criteria across the subgroups, deficits in the area of "social interaction" were evident in all ASD cases, while the other criteria were all more pronounced in the AS group as compared to the PDD NOS group. A tentative conclusion would be that these findings fit a dimensional model of ASDs and that the high rates for all criteria across the diagnostic categories would speak against their use as differential diagnostic entities.

The proportion of female subjects was high in this consecutively recruited clinical group compared to epidemiological studies [4]. This high representation could suggest that women with ASDs develop more severe social deficits [31] or more concomitant psychopathology. In a group of children and young adults diagnosed with normal-intelligence ASDs, Holtmann and colleagues [5] did not find sex differences in the triad of autism core dysfunctions. Our findings can extend this to an older group of patients.

It is worth noting that referral practices are likely to have enriched our study group with a higher prevalence of comorbid conditions in comparison to the ASD population as a whole. Indeed, many of our patients had previously been in contact with specialists in psychiatry and were then referred to our expert centers. The prevalence of comorbid conditions is also likely to be inflated by our decision to disregard DSM-IV criteria excluding certain diagnoses in the presence of ASD. Nonetheless, this decision was justified by our aim to describe clinical conditions where prevalence would have been zero if strict hierarchical criteria had been followed.

High comorbidity with childhood-onset disorders was expected in our study population. Despite the fact that the current diagnostic classification of ASDs precludes a diagnosis of concomitant ADHD (in DSM-IV) or hyperkinetic disorder (in ICD-10), earlier estimates have reported very high rates of these problems (80–83%) in children with ASDs [4]. In our group, the rate was lower but still substantial. The most common ADHD subtypes were the combined and inattentive forms, which may be due to the different presentation of ADHD in adulthood.

Kanner [32] suggested that the features of the autistic syndrome, for example insistence on sameness, were related to anxiety. Other authors have described patients with ASD as vulnerable to stress because of a restricted repertoire of appropriate coping mechanisms [33]. In agreement with this, anxiety disorders, especially OCD where rates were very similar to a recent study of mostly AS patients [34], were clearly overrepresented as compared to the general population.

Earlier estimates of comorbid depression in autism and AS vary widely, from 4 to 38% [35]. Our high frequency of major depressive disorder might be linked to the higher median age in our study group. This finding and the fact that only a minority of the patients had ever had antide-

pressant treatment would stress the importance of attention to such symptoms in this patient category. The overlap of symptoms between ASDs and depression (e.g. social withdrawal, impaired non-verbal communication) can make diagnoses difficult, and earlier studies have pointed out the difficulties these patients have in verbalizing their changes in mood and describing depression [36].

Psychotic symptoms in ASDs are controversial. Since our study group was clinically recruited, it cannot be considered to be representative for a general ASD population, but the need for revision of the criteria precluding or diffusing the diagnostic possibilities in this field is obvious.

Substance-related disorders, especially those related to alcohol, were no more common in this group than in the general population, but more prevalent among subjects diagnosed with a PDD NOS than among subjects with AS. This, and the fact that antisocial PD was found only in the PDD NOS group, is in line with other studies describing a subgroup of antisocial individuals having atypical autistic features presenting as PDD NOS [37]

Patients afflicted with ASDs often describe themselves in clinical interviews or in self-rate questionnaires in a way that corresponds to PD characteristics [38]. Our findings, with two-thirds of our subjects meeting criteria for at least one PD, confirm this, as well as a preponderance of OCPD and avoidant PDs [20]. Furthermore, the higher rate of OCPD in AS compared to PDD NOS corresponds to the AS group's higher rate of restrictions in repertoires and interests. However, the AS group did not have a higher rate of OCD as compared to the PDD NOS group. Despite the tendency toward more diagnoses of cluster A and C in the total group, the overall conclusion is that categorical PDs provide a rather unspecific description of the maladaptive patterns of personality function in the ASD group.

A large proportion of the subjects, especially the females, had been bullied during their school years. In spite of high levels of education, more than half of the entire ASD group was unemployed, on sick-leave, or had a medical pension. Some 40% were still living with their parents or in community-based group homes. In line with previous studies, only a few had ever had a long-term relationship [5], though marriage or cohabitation was slightly more common among the women. Altogether, the outcome must be considered rather poor, taking the high intellectual ability of the group into account.

Conclusion

ASDs in adulthood may be diagnosed according to criteria reflecting the same triad of socio-communicative restrictions as in children. A wide range of symptoms will be found in all ASD subgroups, questioning the current classification. Patterns of comorbidity are insufficiently described in adult patients with ASD. This study demonstrated the high rates of DSM-IV axis I and II disorders, especially depression and ADHD. Differences between men and women were very few. Our results reflect the indistinct demarcations of the adult clinical neurodevelopmental phenotypes and stress the importance of the clinician's attention to a wide spectrum of psychiatric symptoms. These findings point to the need for a careful reexamination of the exclusion criteria of concomitant disorders for adult patients with ASDs in the next revision of the DSM. In spite of a normal or high intelligence, many subjects with adult ASD have considerable psychosocial impairment.

Limitations

This study has a number of limitations. First, the lack of comparison group. All subjects were, however, consecutively recruited, which gives the study group a representative quality. Second, in order to obtain a reasonable study group size, two groups of patients from different sites were pooled. The groups from the two sites were investigated with almost, but not exactly, the same protocol. The two groups were, however, fairly similar in important variables such as age, sex, and intellectual level.

Both study sites have been involved in a common genetic project, and methods for assessment of subjects with ASDs were established in 1990s. Still, frequencies of disorders differed between sites: whereas subjects with AD were rare in both sites, the frequency of Gothenburg subjects with AS almost equaled that with PDD NOS, but the large majority of the Paris subjects were diagnosed with AS.

Our study group is most likely representative of clinical patients in adult psychiatry, though some prevalences of comorbid psychiatric symptoms may have been overestimated due to the fact that many of these patients had earlier psychiatric contacts. There is a need for population-based studies of ASDs and their overlapping conditions in adults.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

BH, PC, HA,OS, CG, MR and ML designed this study and its protocols. BH, RD, PC, AN, EW, OS, EH, AS, HA, MR and ML collected data through their clinical work. BH performed the statistical analyses and wrote the manuscript together with RD, HA, CG, MR and ML. All authors read and approved the final manuscript.

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Paper IV

The sociocommunicative deficit subgroup in anorexia nervosa: clinical symptoms, autism spectrum disorders, neurocognition, personality, and prognosis in a population-based, longitudinal study

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ABSTRACT

Context: Autism spectrum disorders (ASDs) and reduced capacity for social interaction have been reported in a subgroup of cases with anorexia nervosa (AN). **Objectives:** To characterize the clinical phenotype of this subgroup in comparison to other subjects with AN and controls. **Design:** Longitudinal diagnoses in the autism spectrum were assessed across four phases of independent clinical assessments spanning from the teens to the early thirties. Outcome measures were compared across subjects with AN who had been diagnosed with an ASD at some stage of the project, other subjects with AN, and controls. **Participants:** Fifty-one subjects with teenage-onset AN, 16 of whom had been diagnosed with an ASD at some stage, and 51 age-, gender-, and school-matched controls. **Main outcome measures:** Interviews by the SCID-I and the SCID-II cluster C module and the Asperger Syndrome Diagnostic Interview, self-assessments by the Autism-Spectrum Quotient and the Temperament and Character Inventory, subscales from the Wechsler scales, continuous performance tests, Tower of London, and Happé's cartoons. **Results**: Previous reports of ASDs in this AN study group were replicated, and the diagnostic threshold was reached by about one-third. Inter-rater reliability of ASD diagnoses reached kappa coefficients >0.70 over 10 years. The group with both AN and ASDs had the highest prevalence of personality disorders, the most deviant personality traits, and the lowest Morgan-Russell scores, but the group with AN who had never met criteria for a diagnosis on the autism spectrum also differed significantly from controls on personality traits related to poor interpersonal and neurocognitive functioning. **Conclusions:** A subgroup of subjects with AN meets criteria for ASDs. They may, however, represent an extreme of neurocognitive and personality problems to be found more generally in AN.

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Introduction

Interest in social interaction problems in psychiatric conditions has increased sharply since the formulation of basic concepts such as mentalizing, Theory of Mind (ToM), and empathy in this context in the 1980s[1-3]. Formerly considered to be specific for autism and autism spectrum disorders (ASDs), restrictions in interpersonal interaction and communication have also been reported in groups diagnosed with schizophrenia[4], bipolar disorder[4], obsessive-compulsive disorder (OCD)[5], antisocial behavior disorder[6], personality disorders (PDs)[7], and anorexia nervosa (AN)[8]. Today's nosological systems are not clear on whether to regard such problems as an "endophenotype", carrying susceptibility for these disorders, or as "comorbidity" with the ASDs. The social interaction problems used to be unspecifically referred to as deficits in "empathy" but have now come to be defined with increasing precision as, for example, aberrant or restricted social cognition (referred to as mentalizing or ToM[9,10], as deficient decoding of other persons' emotional communication (resembling the "empathy" term), as restrictions in expressive non-verbal communication (gaze contact, mimicry, and emotional coloring of speech), as deviant semantic and/ or non-shared pragmatic use of language in social exchange[11], as egocentric interests or preoccupations, or as a lack of need for social reinforcement (referred to as low Reward Dependence in Cloninger's personality model[12]).

Most diagnostic concepts used in psychiatry and psychology so far have included heterogeneous aspects of all these types of social interaction problems. A more specific line of demarcation has, however, been drawn between these abilities and the *intentions* behind the social interaction, such as lack of sympathy or moral attitudes in relation to others[13]. Assessment methods for social interaction problems have often lumped these different subsets of restrictions together; diagnostic schemes for ASDs or personality traits related to poor social interaction being two different examples. The development of tests to assess social abilities is also much less advanced than tests of, for instance, executive functions, and those presented so far, such as the "Reading the mind in the eyes" test[14], "Reading the mind in the voice" test[15], gaze-tracking methods[16], or social stories or cartoons[17], provide poor specificity in relation to clinical diagnostics. Nor have they been studied in relation to tests established for affective relatedness in the context of "psychopathy", such as reduced neurophysiological responses or abnormal processing of emotionally charged words[18,19].

The hallmark diagnostic concept describing social interaction problems is the ASDs, referred to as pervasive developmental disorders (PDDs) in the later editions of the DSM system. Here, aberrations in the capacities for 1. social interaction, notably the expression, interpretation, and understanding of emotions; 2. communication, with language that is often peculiar, non-abstract, and formalistic, and 3. flexibility in habits, interests, and behaviors, severe enough to have negative consequences for social relatedness, are diagnosed by the definitions for autism (autistic disorder in the DSM-IV), Asperger syndrome (Asperger's disorder in the DSM-IV), and other autistic-like conditions (i.e. pervasive developmental disorder not otherwise specified, PDD NOS, in the DSM-IV). This subgrouping has been questioned as empirical data to support a taxonomic distribution of problems in the spectrum are lacking. Recent epidemiological studies point to a prevalence for the ASDs of about 1% in all children[20, 21]. Heritable factors have been shown to explain more than 70% of the inter-individual variance in ASDs or related traits[22]. The ASDs have classically been assumed to be stable conditions due to the interaction between a large number of genetic and epigenetic factors and "environmental" factors influencing the early development of the central nervous system. Almost all of the more severe forms of ASDs remain as severe handicaps into

adulthood[23], while the prognosis in more high-functioning or atypical cases, though less studied, is known to include at least subgroups with such an improvement that diagnostic criteria are no longer met at follow-up[24]. In the literature on personality, correlations over time of about 0.3 to 0.4 in trait estimates or a stability of about 50% for categorical definitions of social interaction deficits have been reported[25,26].

Observations in twin studies of autistic-like traits in "unaffected" siblings who did not have problems severe enough to reach diagnostic thresholds have distinguished a "broader phenotype" associated with the ASDs[27]. In this paper, we will refer to this broader phenotype, which corresponds to a lower-most end in a normal distribution of social interaction faculties[28-30], as "autistic-like traits". Such traits seem to be over-represented among relatives of autistic children, scientists, music students with absolute pitch, and, in the broadest sense, among men as compared to women[31-33]. They are also involved in personality development and may form a schizoid temperament affecting character development in a manner equivalent to what is seen in PDs[7,34]. Conversely, eating problems, just as sleep disorders and perceptual aberrations, are clinically important aspects of ASDs that hitherto have not been sufficiently captured by the systematic research and diagnostic criteria in the field[35].

AN is a severe eating disorder characterized by rigorous regimes or food refusal periods and distorted ideas about weight and body. Onset is generally during the teen period, and the disorder is more common in women, affecting about 0.3% of girls and a tenth of that proportion among boys. For long, a clinical notion of restrictions in social interaction has been discussed in the literature on AN, and a "social cognitive endophenotype", described by methods ranging from brain physiology over psychometric tests to clinical assessments, was recently proposed to characterize a subgroup of subjects with AN[36]. Many questions remain to be answered on the connection between AN and sociocommunicative deficits, however. Does it express a shared genetic and/or neurodevelopmental susceptibility with a premorbid social cognitive endophenotype that contributes to initiating the eating problems in the teens, or is it rather an effect of AN-related, distorted ideas on central issues of social life, such as eating and body? Or is it an effect of depletion of essential nutrients involved in brain metabolism or neurotransmission through starvation or restricted diet? It seems that social interaction and communication problems may be completely absent in some cases with severe AN. At least two studies have so far described a subgroup of AN cases with clear-cut deficits that meet criteria for an ASD[37,38].

Deficits in such a specific subgroup may, however, fail to show up in studies that merely compare samples of AN subjects to controls. A study by Tchanturia et al[39] could not demonstrate differences on story comprehension and cartoon tasks for ToM between 20 women with AN and 20 age- and sex-matched controls, although their report did stress that there was a subgroup within the AN group with a clear ToM impairment that the study did not have power to demonstrate statistically. Another study, by Kucharska-Pietura and coworkers[40], compared recognition of facial and vocal stimuli that expressed specific emotions in 30 women with AN and a matched control group, reporting poor emotional recognition in the AN group. This was most marked for negative emotions in faces and for both positive and negative emotions in voices. In the review by Zucker and coworkers[36], different models of conceptualizing social cognitive phenotypes in AN were compared to the definitions of the ASDs, leading to the proposal that the ASDs and AN share similarities in social information processing. It also stressed the possibility of using our knowledge about social interaction deficits in ASD to understand problems in AN, and, conversely, to use the

knowledge about restrictive eating patterns and other eating deviances in AN as models for studying eating deviances in ASD.

Personality and PDs have traditionally been used to describe deviances in cognitive abilities and interpersonal relatedness. In AN, a personality profile including restrictions in the ability to identify and describe emotional states, referred to as alexithymia, has been identified[41], which is probably most developed in the subgroup of AN patients with empathy problems or ASDs[42]. Normal-intelligence adults with ASDs often meet DSM criteria for cluster C PDs and describe a personality structure with low Reward Dependence, high Harm Avoidance, and an immature character profile in Cloninger's temperament and character model[7,43].

We have now used the fourth phase of a longitudinal follow-up of the population-based Gothenburg group of subjects with teenage AN and matched controls referred to above[37], including new diagnostic assessments of ASDs and related traits made blindly to the previous diagnostic work-up at, on average, 18 years after the onset of AN, to provide a detailed clinical description of the social interaction deficit phenotype in AN from a longitudinal, inter-expert, and cross-methodological perspective.

The aims of the present study were to (1) replicate previous findings of overrepresentations of ASDs and PDs among AN cases as compared to controls and describe the longitudinal development of such diagnostic overlaps, (2) describe the longitudinal stability of ASD assessments in this group, (3) provide details on specific ASD symptoms, personality profiles, neurocognition, and prognosis in the AN subgroup meeting diagnostic criteria for an ASD, and (4) assess whether ASD-related traits are also over-represented among AN cases without ASD diagnoses as compared to controls.

Methods

Earlier assessments

Fifty-one subjects (3 men, 48 women) with adolescent-onset AN according to DSM-III-R criteria were originally recruited in a screening of all schools in Gothenburg[44,45]. Half the AN group consisted of a total population cohort (minus 1) born in 1970 and living in the city of Gothenburg, Sweden, in 1985. All 51 cases (48 female, 3 male) have met the DSM-III-R and DSM-IV criteria for AN. For each AN case, the school nurse selected the healthy, gender-matched schoolmate closest in age to the index child (COMP group). All 51 AN cases and 51 COMP subjects were examined in depth together with their mothers at the mean age of 16 years. That initial study will be referred to as AN Study I. The whole study group was subsequently followed up after 6 years (AN Study II), 10 years (AN Study III), and, in the present study, 18 years after the onset of AN (AN Study IV).

In AN Study I, a detailed developmental history was obtained by interviewing the mother. An evaluation was made of pregnancy, obstetrical, and other medical records. On the basis of de-identified case notes on premorbid history, the 102 subjects were assigned diagnoses of DSM-III-R PDs and ASDs by a senior psychiatrist who was blinded to group status[45]. In the AN Study II, at mean age 21 years, and in AN Study III, at mean age 24 years, all 51 individuals in the AN group and the 51 COMP subjects were interviewed.

Present study- AN Study IV

All 51 individuals in the AN group and their 51 comparison subjects were followed up in AN Study IV. Forty-four AN cases agreed to a personal interview and six were interviewed over the phone. In one AN case, the mother did not want us to see her daughter, who had persisting AN, but both agreed to a collateral interview with the semi-structured instruments used with the other subjects.

All 51 COMP subjects participated in AN Study IV. Forty-eight were interviewed in person and three over the phone.

The longitudinal study and recruitment procedures have been thoroughly described in previous publications[8,37,44,45].

Each phase has thus included an assessment of personality traits and autistic features by a psychiatrist blinded to case or control status and to previous assessments. In the first phase, schizoid or autistic features were assessed by case notes containing no mention of weight or feeding. The focus was on the premorbid phase, especially early childhood[45]. In each of the subsequent phases, a new psychiatrist made a structured clinical assessment. A high degree of blinding to case-control status has been possible to achieve as more than 90% of AN subjects have been weight-restored at each follow-up. In AN Study II, the SCID-II[46] and a checklist for autistic features according to the criteria for PDDs in the DSM-III-R and the research criteria for Asperger syndrome presented by Gillberg and Gillberg in 1989[47] were used[48]. In AN Study III, the SCID-II, the Asperger Syndrome/high-functioning autism spectrum Diagnostic Interview (ASDI)[49], the Y-BOCS[50], and the OCD module from SCID-I were used[8]. For the longitudinal analyses presented in this paper, previous diagnoses were recoded so that diagnoses of obsessive-compulsive PD (OCPD) and/or empathy deficits were lumped together and referred to as autistic-like traits, while a conclusive diagnosis of "schizoid disorder" (according to the definitions proposed by Sula Wolff[51]), was referred to as a PDD NOS. In individuals who had received different diagnoses within the autism spectrum on different follow-up occasions, the most severe one was used (i.e. autistic disorder rather than Asperger syndrome, Asperger syndrome rather than PDD NOS).

Diagnostic procedures

The assessment of social interaction problems in AN Study IV included the clinical interviews referred to above, and, in addition, self-ratings and psychometric tests. The interviews included the Cluster C module of the SCID-II (as few subjects had previously scored positive for any of the Cluster A or B PDs) in combination with the ASDI, which contains 20 specific interview questions or expert ratings exploring each of the six Gillberg and Gillberg research criteria for Asperger syndrome/high-functioning autism. Three ratings are possible: "does not apply" (coded as 0), "probably applies to some extent" (coded as 0.5), and "applies definitively" (coded as 1). Sum scores may thus be calculated for each criterion and for the whole interview (with a maximum score of 20). At the end of the interview, we specifically asked about perceptual aberrations (hypo- and hypersensibilities), without adding points to the score for this issue. Based on all the available information provided during the interview, the 12 DSM-IV criteria for autistic disorder (A1) were assessed in a last step. As the interviewer was blind to previous diagnostic assessments, the rating of ASD criteria only focused on the present timeframe and the anamnestic information provided by the subjects themselves during the course of the interview. All subjects were carefully instructed not to provide any information on eating habits, which thus were not assessed along with other ritualistic behaviors or ASDI criteria.

Self-rating instruments

The self-ratings included the Autism Spectrum Quotient (AQ)[52], the Temperament and Character Inventory (TCI)[53], and questions assessing criteria for attention-deficit/hyperactivity disorder (AD/HD), and tics according to the DSM-IV algorithms. The AQ is a self-report instrument designed to measure the degree, on a continuum, to which an individual has traits associated with the ASDs. It comprises 50 questions, divided into five areas with ten questions each: social skills, attention switching, attention to detail, communication, and imagination. The TCI assesses the following personality dimensions: Harm Avoidance (HA), Novelty Seeking (NS), Reward Dependence (RD), Persistence (P), Self-Directedness (SD), Cooperativeness (C), and Self-Transcendence (ST). Raw scores for each dimension and its subscales were transformed into T-scores by comparison to gender- and age-matched norm groups (as described by Brändström and colleagues[54]).

Neurocognitive tests

The neuropsychological assessments performed in AN Study IV included tests of attention and working memory using the Wechsler Adult Intelligence test - III (WAIS-III)[55], computerized measures of attentional processes with the Test of Variables of Attention (TOVA)[56], the Tower of London (ToL)[57] test of executive functions, especially planning and organization, and the mental and non-mental cartoons test by Francesca Happé[58]. The neurocognitive assessment procedures are further described in Gillberg et al (in press).[59].

Statistical analyses

Mann-Whitney U tests were used to test for differences between two groups and Kruskal-Wallis Test for differences between three groups in continuous variables. Fisher´s exact χ^2-test was used to compare differences between the AN subgroups in frequencies of coexisting axis I and II disorders. Correlations were calculated by the Spearman rank method. The non-parametric tests were used due to the skewed non-normal distributions of the samples. For analyses of diagnostic agreement across assessments, Cohen´s kappas were calculated. All p-values are two-tailed, and significance was considered at the 5% level for the hypothesis-based group comparison. The comparison between instruments in the final paragraph of the Results section is descriptive and therefore not corrected for multiple comparisons. It contains 234 correlations, meaning that 12 would be randomly significant on the 5% and two on the 1% level. Only correlations on the later level are therefore indicated as significant in the Table and discussed as such in the text.

Ethics

The study was approved by the regional ethical review board at the University of Gothenburg (register # Ö 529-02). The subjects participated voluntarily after giving their informed consent.

Results

1. ASDs in AN cases as compared to COMP cases

As in the previous phases of the project, autistic features and disorders were over-represented among the AN cases as compared to the controls (referred to as COMP subjects in the following). Scores in the ASDI ranged from 0 to 16.5 (out of 20 possible) with a skewed distribution towards the lower end and an overall median of 2. The median ASDI score was 2.5 among cases and 1 among COMP subjects (p=0.010). AN cases also had higher scores than COMP subjects in all ASDI domains (corresponding to the six Gillberg and Gillberg

criteria), a difference that was statistically significant for social interaction problems, monomanic interests, routines and rituals, and non-verbal communication. For verbal communication problems and motor clumsiness, the differences were non-significant. The motor clumsiness domain consists of one question only, which may explain why this comparison did not reach statistical significance.

The number of DSM-IV autistic disorder criteria (A1-A3) ranged from 0 to 7 (out of 12). The median number of DSM-IV criteria was 1 among AN cases and 0 among COMP subjects ($p<0.001$). Seven AN cases and one COMP subject met four or more DSM-IV ASD criteria. Sixteen AN cases out of 49 vs. five out of 48 COMP subjects fulfilled the Social interaction criterion, three AN cases vs. zero COMP subjects the Communication criterion, and 14 AN cases vs. two COMP subjects the Lack of flexibility criterion. All three DSM-IV domains differed significantly between cases and COMP subjects. DSM-IV criteria for a diagnosis in the autism spectrum were met in 14 AN cases (autistic disorder in one case, Asperger´s disorder in four, and PDD NOS in nine) and in one COMP subject (PDD NOS) according to the assessments in this phase of the project. In contrast, sub-threshold autistic-like traits, considered to be part of the normal variation rather than a pathological condition, were equally common among AN cases (9/51) and COMP subjects (10/51).

According to the SCID-II interviews, five AN cases and zero COMP subject met criteria for an avoidant PD. Five cases and two COMP subjects met criteria for OCPD. No subject met criteria for a dependent PD. AN cases met significantly more SCID-II criteria for avoidant and obsessive PDs than COMP subjects ($p=0.004$ and 0.004, respectively). There was no corresponding difference between AN cases and COMP subjects in dependent PD criteria.

2. Test-retest ASD diagnoses

In total, 17 AN cases and one COMP case had been assigned an ASD diagnosis on at least one of the four assessment occasions spanning from the teens into the early thirties. As described in the previous section, 14 of these 17 AN cases were diagnosed as having an ASD at the present study (AN Study IV).

In one of the AN cases and in the one COMP case, the ASD diagnoses were not assigned until after life events impacting brain functioning. In the AN case, empathy problems had been noted earlier, but after suffering a severe traumatic brain injury at about 20 years of age, she has repeatedly displayed social interaction problems considered to correspond to a PDD NOS. One COMP subject had been assigned a diagnosis of PDD NOS in the two most recent phases of follow-up after having suffered a severe cannabis-related psychotic episode. These two subjects were omitted from further analyses in this report, as their social interaction problems had clear adult-age exogenous causes (even if these certainly may have acted on an underlying susceptibility), leaving us with a subgroup of 16 out of 50 AN cases (32%) assigned an ASD diagnosis in at least one phase of the project (referred to as AN+ASD in the following sections, while the AN cases who have never been assigned an ASD diagnosis will be referred to as the AN-ASD group).

Thirteen of the AN+ASD cases were thus diagnosed with an ASD in this fourth phase of the project. Six subjects had ASDs at all four phases. Seven cases with ASD diagnoses assigned in the later phases of the project had been diagnosed with Tourette syndrome, OCD, and/or OCPD at one or several previous phases. In contrast, three subjects with previously assigned ASD diagnoses did not meet the diagnostic criteria in the later or latest phases of the project. One of two subjects with AS at AN Study I and AN Study II was not found to have an ASD

in any of the two following steps, while the other had AS at AN Study III but only autistic-like traits (i.e. not meeting diagnostic criteria for an ASD diagnosis) in AN Study IV. Both these subjects had created social situations "congruent with" their personalities. Another case of ASD "in remission" was associated with a significant decline in social functioning during active AN that subsequently improved once weight was restored. This subject did not personally participate in the new assessments of ASDs at AN Study IV but had a telephone evaluation in which no ASD diagnosis was assigned.

ASD diagnoses in the last study phase were compared to all those in all previous phases after exclusion of the diagnoses in AN Study IV that were not blind to previous assessments and of the two subjects with documented brain injury, yielding a Cohen's kappa at 0.75 as compared with AN Study III and 0.70 with AN Study II, while the agreement with the premorbid diagnoses recorded at AN Study I were considerably lower, 0.23, due to the much lower prevalence at this phase. The agreement between ASD diagnoses in AN Study II and AN Study III was 0.80.

3. ASD symptoms, personality profiles, neurocognition, and prognosis in the AN+ASD group

ASD symptoms

Details on autistic symptoms according to the DSM-IV and the Gillberg and Gillberg criteria are given in Table 1, comparing the three subgroups as described in the previous section (AN+ASD n=16, AN-ASD n=34, and COMP, n=50, as the one case and one control with exogeneous causes of ASD-like dysfunctions were omitted from further analyses). Varying total numbers in the Tables are due to missing information in one or a few individuals from each subgroup.

Table 1. Comparison of DSM-IV and Gillberg and Gillberg criteria in the two AN groups and the controls

	AN+ASD (n=16)	AN-ASD (n=34)	Controls (n=50)	Group comparisons	
DSM-IV	median (range)	median (range)	median (range)	$\chi2(df=2)$[a]	p
"Qualitative impairment in social interaction"	2 (0-4) [b***, d***]	0 (0-2.5)	0 (0-2.5) [e**]	30.88	0.000
"Qualitative impairment in communication"	0 (0-1) [b**, d***]	0 (0-0.5)	0 (0) [e*]	21.90	0.000
"Restricted, repetitive and stereotyped behavior, interests, and activities"	0.75 (0-2) [b**, d***]	0 (0-1)	0 (0-1) [e**]	22.63	0.000
ASDI interviews	(n=13)	(n=33)	(n=46)	Group comparisons	
Gillberg and Gillberg	median (range)	median (range)	median (range)	$\chi2(df=2)$[a]	p
"Social interaction problems"	2 (0-4) [b***, d***]	0 (0-3)	0 (0-2) [e*]	20.83	0.000
"Narrow interests"	1 (0-3) [b*, d***]	0 (0-2)	0 (0-2) [e**]	14.61	0.001
"Repetitive routines"	0.5 (0-2) [b**, d***]	0 (0-1)	0 (0-2) [e*]	14.93	0.001
"Speech and language"	1 (0-3.5) [b**, d**]	0 (0-1.5)	0 (0-3)	12.04	0.002
"Non-verbal communication problems"	3 (0-5) [b**, d***]	0.5 (0-3) [c*]	0 (0-3.5) [e***]	23.79	0.000
"Motor clumsiness"	0 (0-1)	0 (0-1)	0 (0-1)	1.39	0.499

For each subcriterion, 0.5 was assigned when "applies to some extent" and 1.0 when "applies fully"
[a]Kruskal-Wallis Test; [b]Mann-Whitney U-test AN+ASD vs. AN-ASD; [c]AN-ASD vs. COMP; [d]AN+ASD vs. COMP; [e]AN vs. COMP; *<0.05, **<0.01, ***<0.001

The AN+ASD group had their most pronounced problems in social interaction and lack of flexibility according to the DSM-IV. In the DSM-IV, non-verbal communication deficits form

a part of the social interaction criterion. These subjects also met Gillberg and Gillberg criteria for non-verbal communication problems and for both monomanic interests and routines and rituals. In contrast, verbal communication problems were only present in a few subjects and did not characterize the AN+ASD group as a whole.

Personality profiles

The self-rating instruments AQ and TCI were compared across AN cases with or without ASDs and COMP subjects, both by an overall Kruskal-Wallis analysis of overall differences in variance and by subsequent Mann-Whitney tests for differences between any of the three groups or between all AN cases and COMP subjects (Table 2). There were significant group differences between AN groups and the COMP subjects for all AQ scores (the only exception being Imagination, with a borderline p-value just above the 0.05 significance level) and for several personality dimensions according to the TCI, especially Novelty Seeking and Self-Directedness. However, Novelty Seeking was unexpectedly high in the COMP group.

Table 2. Personality traits according to the AQ and the TCI in the two AN groups and the controls

Domain	AN+ASD (n=16)	AN-ASD (n=34)	Controls (n=50)	Group comparison	
Autism Spectrum-Quotient	median (range)	median (range)	median (range)	$\chi2(df=1)$ [a]	p
Social skill	4 (0-8) [b**, d***]	1 (0-7)	1 (0-4) [e*]	13.17	0.001
Attention switching	4 (0-8) [b*, d***]	2 (0-7) [c*]	1 (0-5) [e***]	15.07	0.001
Attention to detail	4 (0-10)	5 (0-10) [c*]	4 (0-7) [e**]	7.46	0.024
Communication	2 (0-4) [b**, d**]	1 (0-3)	0 (0-4)	11.04	0.004
Imagination	4 (0-5) [d*]	3 (0-7)	2 (0-6)	5.00	0.082
Total AQ	19 (0-30) [b*, d***]	12 (0-26) [c**]	9 (0-19) [e***]	17.72	0.000
	AN+ASD (n=13)	AN-ASD (n=31)	Controls (n=47)	Group comparison	
Temperament and Character Inventory	median (range)	median (range)	median (range)	$\chi2(df=1)$ [a]	p [d]
Novelty Seeking	53 (20-62) [d*]	51 (24-70) [c**]	59 (36-80) [e***]	10.67	0.005
Harm Avoidance	54 (27-79) [d*]	49 (32-81)	44 (32-65)	5.52	0.063
Reward Dependence	46 (20-65) [d*]	47 (15-65)	53 (18-65) [e*]	5.78	0.058
Persistence	51 (28-74)	55 (34-74)	50 (33-68)	0.78	0.676
Self-Directedness	43 (10-61) [d***]	49 (14-67)	53 (24-62) [e**]	11.72	0.003
Cooperativeness	46 (20-61)	53 (28-64)	53 (16-66)	3.12	0.214
Self-Transcendence	45 (30-73)	43 (30-73)	43 (32-70)	1.33	0.515

[a]Kruskal-Wallis Test; [b]Mann-Whitney U-test AN+ASD vs. AN-ASD; [c]AN-ASD vs. COMP; [d]AN+ASD vs. COMP; [e]AN vs. COMP *<0.05, **<0.01, ***<0.001

Neurocognition

Similar analyses were subsequently performed for results on the neurocognitive tests (Table 3). Again, AN cases differed from COMP subjects, most significantly on arithmetic, total Tower of London, TOVA commission score, and Happé's mental cartoons.

Table 3. Group differences on neuropsychological variables between the three groups

Domain	AN+ASD (n=12)	AN-ASD (n=29)	Controls (n=44)	Group comparison	
WAIS-III	median (range)	median (range)	median (range)	$\chi2(df=1)$ [a]	p
Arithmetics	7 (5-15) [d*]	11 (5-16)	12 (6-15)	6.82	0.033
Digit Span	9 (4-12)	9 (6-14)	10 (6-19)	2.15	0.341
Letter-Digit Sequencing	10 (5-15)	10 (4-17)	10 (7-16)	0.76	0.684
Coding (Digit Symbol)	10 (6-14)	13 (5-16)	12 (6-17)	4.42	0.110
WMI	97 (69-121) [d*]	101 (75-130)	102 (86-141)	4.07	0.131

Table 3. *continued*

	AN+ASD (n=12)	AN-ASD (n=28)	Controls (n=43)	Group comparison	
Tower of London	median (range)	median (range)	median (range)	$\chi2(df=1)$[a]	p
Correct	108 (84-120)	102 (78-132)	102 (78-132)	0.42	0.813
Move	102 (68-112)	97 (68-124)	104 (70-124)	1.64	0.441
Initiation	101 (90-148)	109 (88-148)	104 (86-148)	1.96	0.375
Execution	101 (60-116)	98 (70-120)	102 (68-120)	3.57	0.168
Total	99 (60-118)	96 (60-114) [c*]	102 (68-128) [e*]	6.31	0.043

	AN+ASD (n=12)	AN-ASD (n=26)	Controls (n=42)	Group comparison	
TOVA	median (range)	median (range)	median (range)	$\chi2(df=1)$[a]	p
Omissions	109 (40-109)	109 (40-109)	109 (40-109)	2.57	0.277
Commissions	97 (77-113) [d**]	107 (68-119)	111 (75-123)	6.31	0.043
Response	105 (74-125)	109 (74-126)	106 (41-129)	0.85	0.655
Variability	90 (40-112)	102 (40-115)	99 (43-120)	3.38	0.185

	AN+ASD (n=12)	AN-ASD (n=29)	Controls (n=43)	Group comparison	
Happe´s mental and non-mental cartoons	median (range)	median (range)	median (range)	$\chi2(df=1)$[a]	p
non-mental cartoons time	9.3 (4.6-29.0)	8.6 (2.6-25.0)	7.6 (2.6-12.8) [e*]	4.21	0.122
non-mental cartoons correct	7 (1-15) [b*, d*]	11 (2-15)	11 (0-15)	5.82	0.055
mental cartoons time	9.0 (5.2-32.0)	8.4 (2.2-38.2)	7.4 (2.8-12.8) [e*]	3.94	0.139
mental cartoons correct	7 (2-14) [d**]	10 (3-15)	11 (3-15) [e*]	7.95	0.019

[a]Kruskal-Wallis Test; [b]Mann-Whitney U-test AN+ASD vs. AN-ASD; [c]AN-ASD vs. COMP; [d]AN+ASD vs. COMP; [e]AN vs. COMP; *<0.05, **<0.01, ***<0.001

Prognosis

The AN+ASD subgroup had significantly lower Morgan-Russell scores than the AN-ASD group but no other severity measure differed between the ASD-positive and -negative AN cases. Nor did the AN+ASD cases have more axis I disorders, even if a tendency towards more psychotic disorders was noted in this group (two subjects vs. none, for details, see Table 4).

Table 4. Measures of severity and comorbid diagnoses

	AN+ASD (n=15-16)	AN-ASD (n=34)		Group comparison
Continuous variables	median (range)	median (range)		p [a]
Onset (yrs)	14.5 (10.0-17.2)	14.0 (10.5-17.0)		ns
Minimum BMI	14.9 (8.9-19.0)	15.2 (9.4-20.9)		ns
Morgan-Russel	9 (4-12)	11 (5-12)		0.005
SR AD	0 (0-7)	1 (0-6)		ns
SR HD	1 (0-9)	1 (0-4)		ns
	AN+ASD (n =15-16)	AN-ASD (n=34)	Controls (n=51)	Group comparison
Dichotomous variables	n (%)	n (%)	n (%)	p [b]
Mood disorder	16 (100%)	33 (97%)	16 (31%)	ns
Psychotic disorder	2 (13%)	0 (0%)	1 (2%)	ns (0.089)
Childhood AD/HD	0 (0%)	0 (0%)	0 (0%)	-
Avoidant PD	3 (20%)	2 (6%)	0 (0%)	ns
Dependent PD	0 (0%)	0 (0%)	0 (0%)	-
Obsessive-Compulsive PD	3 (20%)	4 (12%)	2 (2%)	ns

[a]Mann-Whitney U-test; [b]Fischer´s exact test

4. Social problems in the non-ASD AN group (AN-ASD)

The AN cases who had never been assigned an ASD diagnosis nevertheless had significantly higher ASDI scores than the COMP subjects for the fifth Gillberg and Gillberg criterion non-verbal communication problems (Table 1).

The AN group without ASDs scored in between the AN+ASD group and the COMP subjects in all personality scales, and differed significantly from the COMP group on Attention switching, Attention to detail, Total AQ, and Novelty Seeking, but not on Self Directedness.

On the overall Tower of London score, used to assess executive functions, the AN group without ASDs even showed significantly lower scores than both the other groups.

5. Convergence between different measures of social interaction deficits

Correlations (Spearman´s rho) between AQ/TCI and the neurocognitive variables were subsequently plotted and showed significant associations between the AQ Social skills score and the WAIS-III Arithmetics (rho=-0.296, p=0.006), between the AQ Attention switching score and the TOVA commissions (rho=-0.290, p=0.009), between the AQ Imagination score and the number of correct mental cartoons (rho=-0,341, p=0.001), between the TCI Harm Avoidance score and the time to decipher the Non-mental cartoons (rho=0.303, p=0.006), and finally between the TCI Self-Directedness score and the WAIS-III Arithmetics (rho=0.291, p=0.008).

Discussion

This report has used a longitudinal, population-based cohort of AN cases and matched controls followed into adulthood and assessed for ASDs in four consecutive phases, most recently also by structured interviews and self-assessments of personality, other mental health problems and outcome, and by neurocognitive tests, to identify and describe the subgroup of AN cases who also have socio-communicative problems (the "social cognitive endophenotype" recently proposed by Zucker and coworkers[36]). Our first aim was to replicate previous quantifications of this subgroup by a new wave of clinical assessments blind to previous diagnostics and case or control status. The previously described subgroup meeting ASD criteria was replicated in this new phase of examinations, although the clinical assessments focused on the current situation and functioning rather than on the life-time perspective or childhood development and functioning. All four waves of the project thus unanimously showed that a considerable subgroup among AN cases have socio-communicative deficits corresponding to DSM-IV definitions of ASDs (PDDs) and the Gillberg and Gillberg research criteria for Asperger syndrome/high-functioning ASDs.

The inter-rater consistency of these diagnostics was remarkable in view of the long periods between assessments. As comparison, PDs have generally been found to have a correlation of around 50% over time[26]. The study also showed that it is possible to assess ASDs and their dysfunctions or traits reliably in adults without access to collateral or other types of information on childhood development. In spite of the overall consistency, it was clear, however, that diagnoses of subclasses within the autism spectrum (such as autistic disorder, Asperger's disorder and PDD NOS) have much less consistency, at least among normal-intelligence adults, and that the differentiation from OCPD and other OCD-related clinical presentations is uncertain. OCPD was also the only PD that differed significantly between AN cases and controls across the four phases of the present project.

The proportion of AN cases who met criteria for an ASD was around one-third of all AN cases in the present population-based cohort. Classic autism was rare, however. Sub-threshold autistic traits that do not meet diagnostic criteria did not differ between cases and controls in this study. That some autistic traits were found in about one fifth of controls is consistent with the notion of ASDs and autistic traits as personality disorders or features, as presented in several questionnaire-based reports during recent years[28,60]. To our knowledge, this is the first study assessing such traits in healthy subjects clinically, and the prevalence figures resemble prevalences of PDs reported from clinical assessments of healthy subjects[61].

The various symptom types defined on the autism spectrum were all more common among AN cases than among controls apart from verbal peculiarities (Gillberg and Gillberg criterion number four) and motor clumsiness. The lack of significance for the latter difference may be explained by the small range of variation in the ASDI scale, while the former may be due to the large over-representations of women among both cases and controls, as ASDs in women seem to be less often characterized by the "Asperger-typical" pedantic, stiff, and formalistic verbal communication. Even if the ASDI is built on criteria developed mostly for young children with AS, with a strong male preponderance, it worked well in this sample and provided meaningful information that was also coherent with other types of clinical assessments, previous diagnoses, and self-rating scales.

The "social cognitive endophenotype" among subjects with AN (and/or several other mental disorders) has not yet been systematically studied in order to establish specific diagnostic instruments. As proxies, scales that assess Asperger syndrome criteria (such as the ASDI) or cognitive styles associated with the ASDs (such as the AQ) come closest. We have used several such instruments in the present study and as they converge to a substantial degree, we conclude that they may all be used to study ASD-related traits in AN, but that a longitudinal, expert, all-data diagnosis according to the proposed LEAD principle remains the golden standard to aim for in this kind of studies. In large-scale epidemiological studies, however, the AQ and other self-rating scales provide results that may be interpreted in terms of the proposed endophenotype or specific subgroup of socio-communicative deficits among AN cases.

The TCI has previously been very useful in the study of personality variants associated with neurodevelopmental disorders such as the ASDs and AD/HD[7]. A similar picture emerged here, where the AN+ASD subjects described themselves as the least mature in Self-Directedness. This group was also significantly lower than the controls in Reward Dependence and Novelty Seeking and higher in Harm Avoidance. It is noteworthy that the AN-ASD subgroup did not differ from controls in TCI personality dimensions (besides a lower Novelty Seeking), but had significantly higher AQ scores (totally and in two subscales), lower Tower of London results, and significantly more non-verbal communication problems than controls, indicating that socio-communicative problems among subjects with AN are not restricted to the subgroup meeting diagnostic criteria for an ASD.

A wide range of neurocognitive tests have been established for the assessment of executive functions, such as the computer-based continuous performance tests. In comparison, it has proved much more difficult to establish tests that measure social interaction and communication abilities. The cartoons test by Happé and coworkers[58] is one of the most serious attempts, and the AN group performed significantly lower compared to controls on this test. In this study, a comparatively strong negative correlation was found between this test and self-assessments of Imagination and the total score in the Baron-Cohen instrument. In

contrast, Happe's cartoons did not relate to the TCI results, besides a correlation between Harm Avoidance and slower decryptation of the non-mental cartoons. Nor were the correlations to the mental pictures specific (even if there were no similar correlations to the non-mental cartoons), as the same AQ scales also correlated with dysexecutivity according to the Tower of London test.

In this study, the AN+ASD subgroup performed comparatively well on measures of attention, working memory, planning, and organization. The significantly lower results on the WAIS-III subtest Arithmetics could be due to specific difficulties in calculation.

There are several limitations to this study. The first and most important is, of course, the small number of AN and COMP cases. The advantages provided by their representativeness and the longitudinal diagnostics are easily countered by the limited number of subjects, which precludes many conclusions to be drawn from the analyses, especially from the "negative" comparisons that did not yield significant differences between the three groups of AN cases with or without ASDs and the controls. The definitions of ASDs have mainly been developed on childhood-aged boys and so have the instruments used to assess these conditions. In addition, many instruments used in this area make use of parental information rather than clinical assessments (such as the DISCO and the ADI), assess life-histories and development rather than the current state, and target subjects with severe forms of ASDs, often combined with mental retardation, rather than disorders in adults of normal intelligence (such as the ADOS). The instruments used for this study have comparatively small sets of published validation data and were developed and validated mostly on boys. More standardized tests of social interaction, preferentially in unstructured situations, and non-verbal communication are urgently needed in psychiatric research and diagnostics.

To conclude, the ASD subtype among AN cases was replicated in this new follow-up phase of the longitudinal Gothenburg AN project. Longitudinal diagnostic reliability was high. The ASD subgroup was characterized by social interaction and non-verbal communication deficits, lack of flexibility, personality immaturity, especially in relation to self direction, low reward dependence, high harm avoidance and deficits in executive and social cognitive functions. AN subjects who had never met criteria for an ASD diagnosis nevertheless had significantly higher scores on the Autism Quotient than controls, and also differed from the normal controls in neurocognitive measures.

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