Autistic-like traits

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AUTISTIC-LIKE TRAITS

Sebastian Lundström

Malmö 2011
My heart leaps up when I behold
My heart leaps up when I behold
A rainbow in the sky:
So was it when my life began;
So is it now I am a man;
So be it when I shall grow old,
Or let me die!
The Child is father of the Man;
And I could wish my days to be
Bound each to each by natural piety.

William Wordsworth

Romanska fågor
Inne i den valliga romska kyrkan trängdes turisterna
i halvmörkret.
Valv gapade bakom valv och ingen överblick.
Några ljuslägor fladdrade.
En ängel utan ansikte omfamnade mig
och viskade genom hela kroppen:
"Skäms inte för att du är människa, var stolt!
Inne i dig öppnar sig valv bakom valv oändligt.
Du blir aldrig färdig, och det är som det skall."
Jag var blind av tårar
och föstes ut på den solsjudande piazzan
tillsammans med Mr och Mrs Jones, Herr Tanaka och
Signora Sabatini
och inne i dem alla öppnade sig valv bakom valv oändligt.

Tomas Tranströmer
## Contents

**Abstract** ................................................................................................................................................................. 7  
**Svensk sammanfattning** ............................................................................................................................................. 11  
**Acknowledgements** .................................................................................................................................................... 9  
**List of papers** ............................................................................................................................................................. 11  
**Abbreviations** .......................................................................................................................................................... 13  
**Introduction** ............................................................................................................................................................ 15  
**Background** ............................................................................................................................................................. 16  
  - Autism - development of the concept ................................................................................................................... 16  
    - Leo Kanner and Hans Asperger ......................................................................................................................... 16  
    - Nosology ............................................................................................................................................................ 17  
  - Autistic disorder (AD) ......................................................................................................................................... 18  
  - Asperger’s syndrome (AS) ................................................................................................................................. 19  
  - The autism spectrum disorders (ASDs) ............................................................................................................. 19  
**Epidemiology** .......................................................................................................................................................... 23  
**Diagnostic methods** ............................................................................................................................................... 24  
**Learning disabilities** ............................................................................................................................................. 24  
**Causes behind ASDs** ............................................................................................................................................ 25  
  - Genetic effects .................................................................................................................................................. 26  
  - Environmental effects ...................................................................................................................................... 26  
**Cognitive processes** ............................................................................................................................................... 29  
  - Central coherence ............................................................................................................................................. 29  
  - Theory of Mind .................................................................................................................................................. 29  
  - Executive functioning ..................................................................................................................................... 30  
  - Special abilities ................................................................................................................................................ 30  
**Organizations** .......................................................................................................................................................... 30  
**Broader autism phenotypes and autistic-like traits** .......................................................................................... 31  
  - Broader autism phenotypes ............................................................................................................................. 31  
  - Autistic-like traits (ALTs) ................................................................................................................................. 32  
**Co-existence** ........................................................................................................................................................... 34  
**Distribution of ALTs** ............................................................................................................................................. 34  
**ALTs and ASDs** ..................................................................................................................................................... 35  
**Aims of the present thesis** ................................................................................................................................. 37  
**Specific aims:** ......................................................................................................................................................... 37  
**Methods** ................................................................................................................................................................. 38  
**Subjects** ................................................................................................................................................................. 38  
  - CATSS-17k (Papers I and IV) .......................................................................................................................... 38  
  - CATSS-11k (Papers II and III) .......................................................................................................................... 38  
  - STAGE (Paper II) .............................................................................................................................................. 39  
  - TEDS (Paper III) ............................................................................................................................................... 39  
**Representativeness** ................................................................................................................................................ 39  
**Measures** ............................................................................................................................................................... 40  
  - A-TAC (Papers I-IV) ......................................................................................................................................... 40  
  - CAST (Paper III) .............................................................................................................................................. 41  
  - DSM-IV-based checklists for ASDs and other conditions (Paper II) ............................................................. 41  
**Twin methodology** ................................................................................................................................................. 43  
**Heritability** ............................................................................................................................................................. 43  
**Analytical methods** .............................................................................................................................................. 45  
  - Chronbach’s α (alpha) ..................................................................................................................................... 45  
  - Mann-Whitney U-test ...................................................................................................................................... 46
Appendix

Main finding 3 – co-existence.............................................................................................................................. 73

Main finding 4 - paternal age ............................................................................................................................... 75

Main finding 5 – extreme analyses .......................................................................................................................... 76

The connection between ASDs and ALTs.............................................................................................................. 76

Limitations.................................................................................................................................................................. 78

Representativeness.................................................................................................................................................. 78
Source of data ......................................................................................................................................................... 78
Lack of clinical neurodevelopmental diagnoses..................................................................................................... 79
Psychometric method problems............................................................................................................................ 79

Measurement............................................................................................................................................................ 80

Conclusions ............................................................................................................................................................... 81

Future directions .................................................................................................................................................... 81

Genetic and environmental factors are far from causal.......................................................................................... 81

ALTs provide a new approach to the genetic etiology of ASDs ............................................................................. 82

References............................................................................................................................................................... 84

Appendix I .............................................................................................................................................................. 102

Appendix II .............................................................................................................................................................. 103
Abstract

Introduction
Autism spectrum disorders (ASDs) are neurodevelopmental disorders characterized by restrictions in social interaction, understanding, and communication, by stereotyped patterns of repetitive behaviors, and by narrow interests. ASDs, which affect about 1% of the population, are predominantly genetic, but no single explanation has been found. On the contrary, a multitude of developmental trajectories are possible. In relatives of individuals with ASDs, autistic-like traits (ALTs, i.e. traits that are less pronounced than, but qualitatively similar to, ASD symptoms) occur more frequently than expected by chance. When studied in the general population, ALTs have shown high internal consistency, dimensional distributions, and hereditary influence. It is, however, unclear if ASDs are the extreme end of a continuum of ALTs, if ALTs are psychiatrically relevant, and if ALTs share etiological factors with ASDs.

Methods
This thesis employs three nation-wide twin studies to pursue the following aims:

1. To establish the distribution of ALTs and provide estimates of the genetic and environmental effects involved.
2. To describe the relationships between ALTs and other types of mental problems, including shared etiology.
3. To clarify whether ALTs are influenced by increasing paternal age, which is a known risk factor for ASDs.
4. To determine whether there is a demarcation in the genetic effects between ASDs and ALTs.

Results
1. ALTs are dimensionally distributed in 46% of all 9- and 12-year-old twins, and genetic effects account for 68% of the variation in ALTs.
2. Increasing levels of ALTs are related to an increased risk of concomitant mental health problems in both adults and children. In addition, common genetic and environmental etiological factors were found behind ALTs and phenotypically different mental health problems.
3. Increasing paternal age increases the risk for ALTs and ASDs alike.
4. No demarcation could be discerned between the genetic effects on ASDs and ALTs, implying a continuum from ASDs to ALTs predominantly affected by genes.

Conclusion
Taken together, the results of this thesis suggest that ASDs can be viewed as the extreme end of ALTs, or that ALTs are truly a ‘shadow’ of ASDs in persons with sub-threshold problems with social interaction, communication, and behavioral flexibility, and that ALTs may be crucial for understanding mental health problems and for scientific attempts to identify etiological factors behind ASDs.
Svensk sammanfattning

Introduktion
Autismspektrumstörningar (ASDs) är neuroutvecklingsrelaterade tillstånd som karakteriseras av begränsningar i social interaktion, förståelse och kommunikation samt av stereotypa och repetitiva beteenden. ASDs, med en prevalens på cirka 1% i befolkningen, har framför allt en genetisk bakgrund. Det finns inte någon enskild förklaring till ASDs. Däremot finns det ett flertal möjliga utvecklingsvägar som kan leda till tillståndet. Hos släktingar till personer med ASDs finner man oftare än förväntat autismliknande drag (ALTs), det vill säga egenheter och problem som är mindre uttalade men kvalitativt lika ASD-symptomen. ALTs i befolkningen har i studier visat sig ha en hög intern konsistens, dimensionell distribution och vara starkt påverkade av genetiska faktorer. Det är oklart om ASDs kan hänföras till den yttersta änden på ett kontinuum av ALTs, om ALTs är psykiatriskt relevanta, eller om ALTs delar etiologiska faktorer med ASDs.

Metod och Syften
I denna avhandling används tre nationella tvillingstudier för att uppnå följande syften:
1. Att beskriva distributionen av ALTs och uppskatta de bakomliggande genetiska och miljömässiga effekterna.
2. Att beskriva relationen mellan ALTs och andra typer av mentala hälsoproblem och en eventuell gemensam etiologi.
3. Att klargöra om ALTs är influerade av stigande paternell ålder, vilket är en känd riskfaktor för ASDs.
4. Att undersöka om det finns en klar etiologiska avgränsning mellan ALTs och ASDs.

Resultat
1. ALTs är dimensionellt distribuerade och förekommer hos 46% av alla 9 och 12 år gamla tvillingar. Genetiska effekter förklarar 68% av variansen i ALTs.
2. Ökande nivåer av ALTs är relaterade till en ökad risk för andra mentala problem hos både vuxna och barn. Vidare är ALTs och de samvarierande tillstånden delvis påverkade av samma genetiska och miljömässiga faktorer.
3. Ökande ålder hos fäderna ökar risken för både ASDs och ALTs.
4. Ingen klar avgränsning mellan ALTs och ASDs kunde skönjas, vilket tyder på att det finns ett kontinuum mellan ALTs och ASDs.

Konklusion
Resultaten från denna avhandling tyder på att ASDs kan ses som en extrem av ALTs, och att ALTs kan ses som en ‘skugga’ av ASDs hos personer med svårigheter inom socialt samspel och kommunikation eller med stereotypa och repetitiva beteenden. Vidare kan ALTs vara viktiga för att förstå psykiska problem och för vetenskapliga försök att identifiera etiologiska faktorer bakom ASDs.
Acknowledgements
On bus 130, between Malmö and Lund on a cold spring day in 2006, the notion of a doctoral thesis was planted in my head.

This thesis is the product of contributions from many people (in some cases more than 17,220) and could obviously not have been completed without all the consenting parents of twins in Sweden. Thank you!

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Eva Carlström, who generously and gladly introduced me to CATSS and had the patience to endure all my questions about data handling.

Agneta Brimse and Monika Montell provided laughter and wisdom and immaculate secretarial support, at times also during evenings and weekends.

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Cecilia – life is richer in all aspects since I met you.
List of papers

I  Henrik Anckarsäter, Sebastian Lundström, Linnea Kollberg, Nora Kerekes, Eva Carlström, Niklas Långström, Patrik Magnusson, Linda Halldner, Sven Bölte, Christopher Gillberg, Clara Gumpert, Maria Råstam, Paul Lichtenstein.
The Child and Adolescent Twin Study in Sweden (CATSS).
Submitted for publication.

II  Sebastian Lundström, Zheng Chang, Nora Kerekes, Clara Hellner Gumpert, Maria Råstam, Christopher Gillberg, Paul Lichtenstein, Henrik Anckarsäter.
Autistic-like traits and their relation to mental health problems in two nation-wide twin cohorts of children and adults.

III  Sebastian Lundström, Claire MA Haworth, Eva Carlström, Christopher Gillberg, Jonathan Mill, Maria Råstam, Christina M Hultman, Angelica Ronald, Henrik Anckarsäter, Robert Plomin, Paul Lichtenstein, Abraham Reichenberg.
Trajectories leading to autism spectrum disorders are affected by paternal age: findings from two nationally representative twin studies.

IV  Sebastian Lundström, Zheng Chang, Maria Råstam, Christopher Gillberg, Henrik Larsson, Henrik Anckarsäter, Paul Lichtenstein.
Autism spectrum disorders and autistic-like traits: similar etiology in the extreme end and the normal variation.
Submitted for publication.

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<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AD</td>
<td>Autistic Disorder</td>
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<tr>
<td>AD/HD</td>
<td>Attention Deficit/Hyperactivity Disorder</td>
</tr>
<tr>
<td>ADI-R</td>
<td>Autism Diagnostic Interview-Revised</td>
</tr>
<tr>
<td>ADOS</td>
<td>Autism Diagnostic Observation Schedule</td>
</tr>
<tr>
<td>AIC</td>
<td>Akaike's Information Criteria</td>
</tr>
<tr>
<td>ALTs</td>
<td>Autistic-Like Traits</td>
</tr>
<tr>
<td>AS</td>
<td>Asperger's Syndrome</td>
</tr>
<tr>
<td>ASDs</td>
<td>Autism Spectrum Disorders</td>
</tr>
<tr>
<td>A-TAC</td>
<td>Autism-Tics, AD/HD, and other Co-morbidities inventory</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
</tr>
<tr>
<td>AQ</td>
<td>Asperger Quotient</td>
</tr>
<tr>
<td>CAST</td>
<td>Childhood Autism Spectrum Test</td>
</tr>
<tr>
<td>CATSS</td>
<td>Child and Adolescent Twin Study in Sweden</td>
</tr>
<tr>
<td>CD</td>
<td>Conduct Disorder</td>
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<tr>
<td>CES-D</td>
<td>Center for Epidemiologic Studies Depression Scale</td>
</tr>
<tr>
<td>CIs</td>
<td>Confidence Intervals</td>
</tr>
<tr>
<td>DCD</td>
<td>Developmental Coordination Disorder</td>
</tr>
<tr>
<td>DF</td>
<td>Degrees of Freedom</td>
</tr>
<tr>
<td>DF-analyses</td>
<td>DeFries and Fulker-analyses</td>
</tr>
<tr>
<td>DISCO</td>
<td>Diagnosis of Social and Communication Disorder Schedule</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorder</td>
</tr>
<tr>
<td>DZ</td>
<td>Dizygotic</td>
</tr>
<tr>
<td>EQ</td>
<td>Empathizing Quotient</td>
</tr>
<tr>
<td>FLEX</td>
<td>Flexibility module in A-TAC</td>
</tr>
<tr>
<td>GAD</td>
<td>Generalized Anxiety Disorder</td>
</tr>
<tr>
<td>GEE</td>
<td>Generalized Estimating Equations</td>
</tr>
<tr>
<td>ICCs</td>
<td>Intra-Class Correlations</td>
</tr>
<tr>
<td>K-SADS-PL</td>
<td>Kiddie-Schedule for Affective Disorders and Schizophrenia for</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>--------------</td>
<td>-------------</td>
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<tr>
<td>LANG</td>
<td>Language module in A-TAC</td>
</tr>
<tr>
<td>MZ</td>
<td>Monozygotic</td>
</tr>
<tr>
<td>NDP</td>
<td>NeuroDevelopmental Problems</td>
</tr>
<tr>
<td>NOIR</td>
<td>Nominal, Ordinal, Interval, and Ratio</td>
</tr>
<tr>
<td>ODD</td>
<td>Oppositional Defiant Disorder</td>
</tr>
<tr>
<td>PDD</td>
<td>Pervasive Developmental Disorder</td>
</tr>
<tr>
<td>PDD-NOS</td>
<td>Pervasive Developmental Disorder Not Otherwise Specified</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver Operating Characteristics</td>
</tr>
<tr>
<td>SES</td>
<td>Socio-Economic Stratum</td>
</tr>
<tr>
<td>SOC</td>
<td>Social module in A-TAC</td>
</tr>
<tr>
<td>SQ</td>
<td>Systemizing Quotient</td>
</tr>
<tr>
<td>SRS</td>
<td>Social Responsiveness Scale</td>
</tr>
<tr>
<td>STAGE</td>
<td>Screening Twin Adults: Genes and Environment study</td>
</tr>
<tr>
<td>TC</td>
<td>Tetrachoric Correlations</td>
</tr>
<tr>
<td>TD</td>
<td>Tic Disorders</td>
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<td>TEDS</td>
<td>Twin’s Early Development Study</td>
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</table>
Introduction

Autism spectrum disorders (ASDs) are neurodevelopmental disorders characterized by restrictions in social interaction, understanding, and communication, by stereotyped patterns of repetitive behaviors, and by narrow interests. These restrictions are often accompanied by abnormal responses to sensory and visual stimuli and by mental problems related to neurodevelopment, such as learning disabilities, attention deficit/hyperactivity disorder, and motor dyscoordination. About 1% of all children have problems severe enough to meet criteria for an ASD, which in most cases will persist into adulthood and in many cases be complicated by other forms of mental health problems. There is no single explanation for ASDs. On the contrary, numerous trajectories towards the development of ASDs are possible. Twin studies have clearly documented that the liability for ASDs is predominantly genetic. Specific genetic syndromes are diagnosed in a substantial subgroup of all cases with ASDs combined with learning disability, and new, rare genetic syndromes linked to ASDs and other neurodevelopmental problem constellations in small groups are continuously described. Some genetic variants have also been linked to the overall liability for ASDs, even if their unique effect size is marginal. The majority of genetic variants and the way they influence the development of ASDs (through genetic, neurobiological, and environmental interactions) remain unknown. In current nosological systems, three types of ASDs are acknowledged: (1) ‘autistic disorder’, (2) ‘Asperger’s disorder’, and (3) ‘pervasive developmental disorder not otherwise specified’ or ‘atypical autism’, largely differentiated by the age at onset of language problems and the number and types of diagnostic criteria fulfilled. A unified ASD diagnosis will probably be accepted in the near future. The ASDs have been proposed to express reduced or ‘different’ abilities to form mental representations of persons’ inner lives, Gestalts from pieces of information, and/or cognitive executive functions. The diagnostic criteria are supposed to be interpreted in relation to the general developmental level, meaning that verbal communication deficits, for instance, may manifest as anything total lack of verbal communication to mere difficulties in understanding puns, irony, or metaphors. Relatives of persons with ASDs have been found to have less pronounced, but qualitatively similar, problems and features, referred to as ‘broader autistic phenotypes’ or autistic-like traits (ALTs), more often than expected by chance alone. During the last decade, several scales designed to capture ALTs and other manifestations of low social responsivenes, empathy, and socio-communicative abilities have shown high internal consistency, dimensional distribution, and genetic influence when measured in the general population. It remains to be established, however, how these interindividual
Introduction
differences in socio-communicative abilities relate to the ASDs. That is, are they ‘autistic’ in the sense that they express autistic symptoms and are related to ASDs, or do they only resemble the ASDs to some extent without sharing their etiology, relation to other mental health problems or known risk factors? Furthermore, ALTs is a noted feature in mental health settings, but it is unclear if ALTs are relevant for mental health issues by increasing the risk for other types of mental health problems, and if ALTs share common susceptibilities with phenotypically different mental health problems. This thesis will address these issues and provide some clues to their answers.

Background

Autism - development of the concept
In 1911, the Swiss psychiatrist Eugene Bleuler coined the term ‘autism' to describe schizophrenic patients who withdrew from reality and became self-absorbed\(^1\). Autism has thus long been associated with schizophrenia and regarded as a variant of schizophrenia characterized by impoverished social relatedness and communication (‘negative symptoms’). For long, childhood conditions that today would be referred to as ASDs were also labeled ‘childhood schizophrenia’\(^2\).

Leo Kanner and Hans Asperger
In 1943, the Austrian-born psychiatrist Leo Kanner at Johns Hopkins University Hospital published a paper on childhood autism named “Autistic disturbances of affective contact”, where he described a condition very similar to modern forms of autism or ASDs. The paper contained case vignettes on 11 children. Kanner suggested that “the outstanding 'pathognomonic,' fundamental disorder is the children’s inability to relate themselves in the ordinary way to people and situations from the beginning of life”\(^3\). In addition, Kanner noticed stereotyped motor mannerisms, language and communication deviances, and ‘an obsessive desire for sameness’. The paper concluded by stating that “we must, then, assume that these children have come into the world with innate inability to form the usual, biologically provided affective contact with people, just as other children come into the world with innate physical or intellectual handicaps”. Oddly, Kanner later changed his notion and suggested that autism was an emotional disorder caused by parental emotional coldness\(^4\).

\(^1\) Mash & Barkley 2003  
\(^2\) Wolff 2004  
\(^3\) Kanner 1943  
\(^4\) Kanner & Eisenberg 1955, Eisenberg & Kanner 1956
Introduction

In 1944, the Viennese pediatrician Hans Asperger, independently of Kanner, described children showing problems similar to those described by Kanner. Asperger’s children, however, were not as severely disabled as those described by Kanner. On the contrary, he noted that some of the children had a vast vocabulary and high intelligence, coupled with circumstantial and narrow interests based on learning rather than understanding. There were several similarities between Kanner’s and Asperger’s case vignettes: both authors described (1) male preponderance, (2) social isolation, egocentricity and a lack of interest for other people’s emotions or thoughts, (3) communication deficits, (4) lack of gesture, imperfect eye contact, (5) lack of imaginary play, (6) repetitive behaviors, (7) peculiar reactions to sensory stimuli, (8) motor clumsiness, (9) behavioral problems (aggressiveness and destructivity), and (10) special skills within certain areas.

Asperger wrote all his works in German and remained unknown for the broader scientific community until Lorna Wing introduced his writings in the early 1980s, adding a notion of high-functioning autism, i.e., autism in persons with normal or even high intelligence, and a spectrum of autism-related conditions. Meanwhile, clinical researchers formulated their own definitions of Asperger’s syndrome (AS), notably those by Carina Gillberg and Christopher Gillberg and by Peter Szatmari.

Nosology

The first (1952) and second (1968) editions of the Diagnostic and Statistical Manual of Mental Disorder (DSM) viewed autism as belonging in a childhood schizophrenia continuum (a prominent scientific journal edited by Leo Kanner and Stella Chess was actually named The Journal of Autism and Schizophrenia.).

In 1978, Michael Rutter proposed four criteria for childhood autism: “(1) onset before the age of 30 months, (2) impaired social development that has a number of special characteristics and is out of keeping with the child’s intellectual level, (3) delayed and deviant language development that also has certain defined features and is out of keeping with the child intellectual level, and (4) insistence on sameness, as shown by stereotyped play patterns, abnormal preoccupations, or resistance to change.” Rutter’s criteria greatly influenced the definition of autism in the third edition of the DSM (DSM-III), where infantile autism became an independent diagnosis under the general category

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5 Asperger 1944  
6 Frith 1991  
7 Wing 1981a  
8 Wolff 2004  
9 Gillberg & Gillberg 1989  
10 Szatmari et al. 1989a  
11 APA (DSM I) 1952, APA (DSM II) 1968  
12 Rutter 1978
of pervasive developmental disorders (PDDs). An additional diagnosis, applicable to those who had once met all criteria for infantile autism but no longer did so, residual infantile autism, was included in the DSM-III. The term ‘infantile’ was chosen to reflect the early age of onset.

In 1981, Wing suggested that a triad of impairments, namely impairments in social interaction, social communication, and in social imagination were the core elements of autism. In the revised version of the DSM-III (DSM-III-R) the diagnosis of autism was based on 16 criteria encompassing social disturbance, communicative disturbances, and restricted and repetitive behaviors. Also, autism was moved from Axis I (identifying clinical disorders) to Axis II (identifying personality disorders and mental retardation), and the criterion requiring age at onset before 30 months was removed.

The fourth version of the DSM (DSM-IV) was released in 1994. The DSM-IV has continued to use PDDs as an umbrella term that now includes autistic disorder (AD), Asperger’s disorder (here referred to as Asperger’s syndrome, AS), pervasive developmental disorders not otherwise specified (PDD NOS), childhood disintegrative disorder, and Rett’s disorder. The PDD disorders were defined by twelve symptoms for AD, organized in accordance with Wing’s triad, each containing four individual symptoms. The DSM-IV was the first DSM version to include a definition of AS. Age at onset before three years of age was re-introduced as a criterion for the AD diagnosis. It has been argued, however, that the age of onset might not be an optimal inclusion factor as it is not a behavioral criterion, and, unless a correct developmental and medical history can be obtained in cases examined after the age of three, the diagnosis may be uncertain.

**Autistic disorder (AD)**

AD is the severe, extreme end of the PDDs as described in the DSM-IV. A diagnosis of AD requires the presence of severe early deficits in social interaction, communication, and behavioral flexibility (Table 1). Note that pervasive restrictions must be present in all three domains for a diagnosis of AD. Also, the onset must be before the age of three.

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13 APA (DSM III) 1980, Kaplan & Sadock 2000
14 Kaplan & Sadock 2000
15 Wing 1981b
16 APA (DSM-III-R) 1987
17 APA (DSM-IV) 1994
18 Gillberg 1990
Table 1. Diagnostic criteria for AD (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

Asperger's syndrome (AS)

The DSM-IV refers to AS as Asperger's disorder. In the DSM-IV, AS differs from AD as neither communication deficits nor a significant cognitive delay before the age of three is required (Table 2). The differentiation is thus largely based on the development of

\[19\] APA (DSM-IV) 1994
Introduction

age-adequate speech at the age of three and the absence of verbal communication difficulties, which has created some confusion in relation to the previously well-documented verbal peculiarities, semantic-pragmatic communication deviance, and outright dysfunctions in verbal communications related to emotional and abstract terms in AS\textsuperscript{20}.

Table 2. Diagnostic criteria for AS (DSM- IV)

<table>
<thead>
<tr>
<th>Criteria (A)</th>
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<tbody>
<tr>
<td>Qualitative impairment in social interaction, as manifested by at least two of the following:</td>
</tr>
<tr>
<td>(a) 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</td>
</tr>
<tr>
<td>(b) failure to develop peer relationships appropriate for developmental level</td>
</tr>
<tr>
<td>(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)</td>
</tr>
<tr>
<td>(d) lack of social or emotional reciprocity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Criteria (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restricted repetitive and stereotyped patterns of behaviour, interests, and activities, as manifested by at least one of the following:</td>
</tr>
<tr>
<td>(a) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus</td>
</tr>
<tr>
<td>(b) apparently inflexible adherence to specific, non-functional routines or rituals</td>
</tr>
<tr>
<td>(c) stereotyped and repetitive motor-mannerisms (hand- or finger-flapping or twisting or complex whole-body movements)</td>
</tr>
<tr>
<td>(d) persistent preoccupation with parts of objects</td>
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</table>

<table>
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<tr>
<th>Criteria (C)</th>
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<tbody>
<tr>
<td>The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning</td>
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<table>
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<th>Criteria (D)</th>
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<tbody>
<tr>
<td>There is no clinically significant delay in language (e.g., single words used by age 2 years, communicative phrases used by age 3 years)</td>
</tr>
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</table>

<table>
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<tr>
<th>Criteria (E)</th>
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<tbody>
<tr>
<td>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</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Criteria (F)</th>
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</thead>
<tbody>
<tr>
<td>Criteria are not met for another Pervasive Development Disorder or Schizophrenia</td>
</tr>
</tbody>
</table>

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

Peculiarities and dysfunctional aspects of verbal communication, including delayed development or deviances in development of language, such as absence of spoken words until the emergence of formally well-developed phrases, had been included among the criteria for AS proposed by Gillberg & Gillberg (Table 3)\textsuperscript{21}. These criteria also differ from the DSM-IV criteria by including motor clumsiness and narrow interests that exclude other activities or are repetitive and fact-based.

\textsuperscript{20} Klin et al. 2005, Landa 2000, Szatmari et al. 1989b
\textsuperscript{21} Gillberg & Gillberg 1989
**Introduction**

**Table 3. Gillberg & Gillberg research criteria for AS**

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

Another set of criteria for AS was published by Szatmari\textsuperscript{22} at about the same time as those by Gillberg & Gillberg. The Szatmari research criteria are generally more inclusive than those proposed by Gillberg & Gillberg. They acknowledge ‘difficulties’ in social interaction instead of ‘inability’ or ‘lack of’ and include features that may encompass the normal variation of personalities, like being ‘a loner’, but also rely on the classic notion of autism as self-absorption and include deviant verbal skills.

\textsuperscript{22} Szatmari et al. 1989a
Table 4. Szatmari's research criteria for AS

All
(1) Solitary (at least two of the following items)
   (a) No close friends
   (b) Avoid others
   (c) No interest in making friends
   (d) A loner
(2) Impaired social interaction (at least two of the following items)
   (a) Approaches others only to have own needs met
   (b) A clumsy social approach
   (c) One-sided response to peers
   (d) Difficulty sensing feeling of others
   (e) Detached from feelings of others
(3) Impaired nonverbal communication (at least one of the following)
   (a) Limited facial expression
   (b) Unable to read emotions from facial expressions
   (c) Unable to give message with eyes
   (d) Does not look at others
   (e) Does not use hands to express oneself
   (f) Gestures are large and clumsy
   (g) Comes too close to others
(4) Odd speech (at least two of the following)
   (a) Abnormalities in inflection
   (b) Talks to much
   (c) Talks to little
   (d) Lacks of cohesion to conversation
   (e) Idiosyncratic use of words
   (f) Repetitive patterns of speech

Pervasive developmental disorder not otherwise specified (PDD NOS)
PDD NOS/atypical autism refers to individuals who exhibit deficits in social interaction in combination with communication difficulties or reduced behavioral flexibility but do not meet full criteria for AD or an AS. Thus, a diagnosis of PDD NOS can be considered when a dysfunction is present but the number of criteria met is below the diagnostic threshold. The criteria are provided in Table 5. From a clinical point of view it should be acknowledged that it is difficult to find a demarcation between PDD NOS and schizoid personality disorder, where the diagnostic formulations (e.g. “... chooses solitary
Introduction

activities...lack of close friends...") are reminiscent of those described for ASDs, and between PDD NOS and extremes in normal personality that do not meet overall criteria for ‘disordered’. In people with learning disabilities and low IQ, the demarcation of PDD NOS is even more unclear.

Table 5. Diagnostic criteria for PDD NOS (DSM-IV)

<table>
<thead>
<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td>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.</td>
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The autism spectrum disorders (ASDs)

In 1979, Lorna Wing and Judith Gould conducted a large clinical study in a borough of London where they examined all children with known physical or mental handicaps. The primary aim of the study was to explore how many of these children displayed core features of autism (impairment in social interaction and/or the development of verbal or non-verbal language, and repetitive and stereotyped activities). Their main finding was that core features of autism did not necessarily co-vary, and the authors suggested that classical autism is a subgroup in a spectrum characterized by deficits in social interaction and communication, and that these deficits may occur regardless of level of intelligence. This dimensional model, that allowed for non-specificity (i.e. overlap with other psychiatric conditions), was later corroborated in a Swedish study where autism and autistic features were noted together with other clinical conditions and with varying degrees of severity. The findings reported by Wing and Gould eventually generated the term ASDs, sometimes used interchangeably with the term ‘autistic continuum’. The notion of a spectrum led to a widening of the criteria, whereby individuals with deficits who formerly did not reach the diagnostic threshold were included, and opened up for the PDD NOS category. Although the term ‘ASDs’ is not yet formally acknowledged as a diagnostic taxonomy, it is commonly used in clinical settings and scientific papers. In this thesis it will be used synonymously with the DSM-IV PDD concept as an umbrella term for AD, AS, and PDD NOS.

23 APA (DSM-IV) 1984
24 Wing & Gould 1979
25 Gillberg et al. 1986, Steffenburg & Gillberg 1986
26 Wing 1988
27 Gillberg 1991
Introduction

Epidemiology
During the last 30 years, the reported prevalence of ASDs has steadily increased. For instance, the first epidemiological study conducted on autism reported a prevalence of 4.5/10,000\textsuperscript{28}, while recent studies have reported prevalence figures around 1\% for ASDs\textsuperscript{29}. This increase in prevalence can to a large extent be attributed to the changes in diagnostic criteria and to a growing public and professional awareness of ASDs\textsuperscript{30}. While no study has been able to test whether there has also been a true rise in either the prevalence or the incidence of ASDs\textsuperscript{31}, it should be noted that some studies have suggested that the ASD prevalence is higher in some immigrant groups\textsuperscript{32}, but the reasons for this phenomenon remain unknown\textsuperscript{33}. Infections during pregnancy or infancy and nutritional effects are among the proposed mechanisms that could explain a true increase in the prevalence of ASDs\textsuperscript{34}.

Diagnostic methods
No blood tests, physical examinations, or genetic tests can be used to diagnose ASDs accurately\textsuperscript{35}. Clinical assessments therefore include: (1) structured interviews, like the ‘Diagnosis of Social and Communication disorder schedule’ (DISCO)\textsuperscript{36} and ‘the Autism Diagnostic Interview-Revised’ (ADI-R)\textsuperscript{37}, assessing early neurodevelopment, milestones, toddler behavior, and the current situation by parents or care-givers, (2) clinical observations of autistic symptoms, with, for instance, ‘the Autism Diagnostic Observation Schedule’ (ADOS)\textsuperscript{38}, (3) a cognitive, test-based evaluation of IQ and specific cognitive functions proposed to be affected in ASDs, and (4) a broad psychiatric evaluation, like ‘the Kiddie-Schedule for Affective Disorders and Schizophrenia for school age children-Present and Lifetime Version’ (K-SADS-PL)\textsuperscript{39}, for differential diagnostics and possible overlaps with other psychiatric conditions, and, finally, (5) clinical genetics to rule out (or confirm) the presence of Fragile X, Angelmans syndrome, 15-q duplication, Cornelia de Lange, or other specific genetic syndromes with known

\textsuperscript{28} Lotter 1966
\textsuperscript{29} Baird et al. 2006, Gillberg et al. 2006
\textsuperscript{30} Wing & Potter 2002
\textsuperscript{31} Fombonne 2009
\textsuperscript{32} Gillberg et al. 1987, Goodman & Richards 1995,
\textsuperscript{33} Fombonne 2003
\textsuperscript{34} Landrigan 2010
\textsuperscript{35} Gillberg & Coleman 2000
\textsuperscript{36} Leekam et al. 2002
\textsuperscript{37} Lecavalier et al. 2006
\textsuperscript{38} Lord et al. 2000a
\textsuperscript{39} Kaufman et al. 1997
Introduction

associations with ASDs (sometimes described as ‘syndromic autism’)\(^{40}\), and a general medical work-up to exclude other medical conditions compromising central nervous system functioning. Since it is generally unfeasible to conduct clinical assessments by these principles in large-scale epidemiological studies, brief questionnaires tapping into the core deficits of ASDs or assessing traits thought to be related to the ASDs through measures of interindividual differences in socio-communicative abilities have been developed. Examples of scales developed to screen for ASDs and to measure ASD symptoms include the ‘Childhood Autism Spectrum Test’ (CAST)\(^{41}\) and the ‘Autism – Tics, AD/HD, and other Co-morbidities inventory’ (A-TAC)\(^{42}\), while the ‘Social Responsiveness Scale’ (SRS)\(^ {43}\) is an example of a scale constructed to reflect the general variation in social relatedness and communicative abilities. The Asperger Quotient’ (AQ), initially developed as a screening tool\(^ {44}\), was later completed by the ‘Systematizing and Empathizing Quotients’ (SQ & EQ) to be applicable in the general population and to reflect also the theoretical opposite distribution of the ASDs, i.e. good socio-communicative abilities\(^ {45}\). The screening questionnaires have most often been validated in relation to clinical diagnoses of ASDs and correspond dimensionally to an increased liability (i.e. probability or risk) for ASDs. Several instruments may be rated either by parents, teachers, or the subject, though the knowledge of systematic differences by information source is scarce, and deficits in meta-cognition and self-awareness have been proposed as a core problem in subjects with ASDs\(^ {46}\) (and to some extent in some of their relatives), which could influence the reliability of questionnaires.

Learning disabilities

Learning disabilities (especially the type of general learning disability with a low IQ formerly referred to as mental retardation) are often concomitant with ASDs; a recent study suggested that about 10% of individuals with an ASD also had this type of learning disability\(^ {47}\). This figure will increase considerably (up to about 60%) if only subjects meeting the narrow criteria for AD are taken into account\(^ {48}\). As we have reason to believe that social and communicative deficits exist on a spectrum, it is important to keep in mind that the deficits may differ depending on the general developmental level. In clinical practice, the social and communicative abilities should be estimated in

\(^{40}\) O’Hare 2009  
\(^{41}\) Williams et al. 2005, Williams et al. 2006  
\(^{42}\) Hansson et al. 2005  
\(^{43}\) Constantino et al. 2003  
\(^{44}\) Baron-Cohen et al. 2001  
\(^{45}\) Baron-Cohen et al. 2003, Baron-Cohen & Wheelwright 2004  
\(^{46}\) Lombardo et al. 2007  
\(^{47}\) Fernell & Gillberg 2010  
\(^{48}\) Levy et al. 2009
Introduction

relation to the cognitive level. For those at the most severe end of the learning disabilities continuum, a diagnosis may have to be based on social reactions displayed via facial expression, eye contact, or body gestures\(^49\). For instance, a child with mental retardation might be mute or in need of basic speech therapy, while a high-functioning individual may be exceptionally gifted academically and show deficits only in the understanding of certain usages of words or phrases, such as puns or metaphors\(^50\).

**Gender differences**

There is a male preponderance in all ASDs\(^51\) with an overall male:female ratio about 4:1\(^52\). The male over-representation is less pronounced in ASD subgroups with mental retardation and most extreme in ‘narrow’ AS combined with high intelligence\(^53\). Simon Baron-Cohen has proposed that the ASDs may be an extreme variant of the 'male brain', meaning that boys are better at systemizing \((if \ x \ \ then \ y)\) while girls are better in empathizing (the attribution of mental states to others), and that persons with ASDs are far better at systemizing than at empathizing\(^54\). Though this line of reasoning would explain some of the male preponderance in ASDs, there might, on the other hand, be a tendency towards rating boys as more 'autistic' than girls\(^55\), possibly because ASDs in girls may present differently than in males, and/or because high-functioning girls with ASDs may have access to compensatory abilities that mask their autistic problems to a larger extent\(^56\). ASDs may thus remain unidentified longer in girls than in boys\(^57\). In addition, it should be noted that a major share of all research on ASDs so far has been conducted on boys, including the studies that form the basis for the development of diagnostic criteria, i.e. the field trials of the prevailing diagnostic system\(^58\). Thus, it is wise to be cautious about applying the present knowledge about ASDs to groups of girls.

**Causes behind ASDs**

**Genetic effects**

Twin studies have consistently reported that the liability for ASDs to a large extent is genetic in origin, with one of the highest, if not \textit{the} highest, heritability estimates for any

\(^{49}\) Wing 1998
\(^{50}\) Lord et al. 2000b
\(^{51}\) Volkmar & Pauls 2003
\(^{52}\) Fombonne 2005
\(^{53}\) Steffenburg & Gillberg 1986, Volkmar et al. 1993
\(^{54}\) Baron-Cohen 2002
\(^{55}\) McLennan et al. 1993, Pilowsky et al. 1998
\(^{56}\) Mash & Barkley 2003
\(^{57}\) Kopp & Gillberg 1992
\(^{58}\) Volkmar et al. 1994, Buitelaar et al. 1999
mental health problem, trait, or feature\textsuperscript{59}. The only study with enough statistical power to confidently estimate the role of hereditary factors behind ASDs found that genetic effects accounted for 80% of the variation\textsuperscript{60}. Furthermore, the sibling recurrence risk is high: 4.5% in a study using strict criteria\textsuperscript{61} and 10.5% when a looser definition was used\textsuperscript{62}.

It is now generally accepted that virtually all mental disorders, including the ASDs, are due not to single or even a few genetic effects but affected by a plethora of genetic factors and/or largely unknown interplay between genes and environmental effects that cause effects rather by non-linear than by linear or additive means\textsuperscript{63}. This notion is particularly compelling for the ASDs, behind which a great number of pathways have been suggested\textsuperscript{64}. For the ASDs, deleterious mutations were first the obvious hypothesis, e.g. the Fragile X trinucleotide repeat mutation. Several other mutations in genes encoding proteins important for synaptogenesis have been linked to autism\textsuperscript{65}, and over a hundred rare genetic syndromes have today been linked with autism, but all of them have also been linked to learning disabilities with low or very low IQ\textsuperscript{66}, and each of these syndromes are present only in a very small number of ASDs, limiting their general explanatory value. Effects of common genetic variants on the ASDs have been sought, first, in association studies of candidate genes with known variants (so-called polymorphisms, often single nucleotide polymorphisms or repeat polymorphisms) that sometimes but far from always have been linked to altered functions in brain transmitter systems\textsuperscript{67}. These genes seem promising when trying to identify the etiology of ASDs and probably interact, with each other as well as with other unidentified genes\textsuperscript{68}. Lately, very large genome-wide association studies have included copy number variants that are of specific interest but also found to have low explanatory value\textsuperscript{69}. A recent genome-wide association study took advantage of one of the largest samples in the world (more than 10,000 individuals out of which 3,101 were probands) to identify common genetic risk factors for ASDs. The authors found a common genetic variant on 5p14.1 with an odds ratio of 1.19\textsuperscript{70}, which means that this common variant increases the

\textsuperscript{59} Bailey et al. 1995, Folstein & Rutter 1977, Lichtenstein et al. 2010
\textsuperscript{60} Lichtenstein et al. 2010
\textsuperscript{61} Jorde et al. 1991
\textsuperscript{62} Constantino et al. 2010
\textsuperscript{63} Cook & Scherer 2008, Kendler 2005
\textsuperscript{64} Abrahams & Geschwind 2008
\textsuperscript{65} Durand et al. 2007, Jamain et al. 2003
\textsuperscript{66} Betancur 2011
\textsuperscript{67} Cook et al. 1997, Yirmiya et al. 2001
\textsuperscript{68} Abrahams & Geschwind 2008
\textsuperscript{69} Pinto et al. 2010
\textsuperscript{70} Wang et al. 2009
risk for ASDs with 19%. It should be noted, however, that since the prevalence of ASDs is 1%, the probability of an ASD in terms of percent is 1.19% if the common genetic variant is present. In other words, if the common variant is present, the probability for not developing an ASD is 98.81%. In addition, de novo mutations (i.e. sporadic mutations not inherited from the parents), which have been suggested as a risk factor for ASDs, are only present in a small part of ASDs\textsuperscript{71}.

To sum up, we now know that genetics play a large role in the etiology of ASDs, but research into specific mechanisms has so far ended up with mutations and genetic syndromes that may have large effects in individual cases (so called ‘syndromic autism’) but together account for only about 10% of the individuals with ASDs\textsuperscript{72}, and are probably more related to the severe and somewhat atypical forms of autistic disorders with low or very low IQ than to the broader spectrum, let alone to the general variation in socio-communicative abilities. Taken together, known genetic syndromes, copy number variants, and mutations do not account for more than about 20% of all ASDs\textsuperscript{73}.

**Environmental effects**

A part of the variance of ASDs (about 20%) is explained by environmental factors\textsuperscript{74}. The literature on environmental factors leading to ASDs or involved in the pathogenesis of ASDs is sparse, but thalidomide embryopathy\textsuperscript{75}, prematurity\textsuperscript{76}, intrauterine stress\textsuperscript{77}, herpes encephalitis\textsuperscript{78}, and fetal alcohol syndrome\textsuperscript{79} have all been linked to ASDs in cases or case series. Autistic-like symptoms may arise in severely deleterious environments. Case studies of Romanian adoptees revealed that features very similar to autism were over-represented\textsuperscript{80}, but the condition of the adoptees improved gradually when they were placed in foster homes\textsuperscript{81}.

\textsuperscript{71} Sebat et al. 2007  
\textsuperscript{72} Lintas & Persico 2009  
\textsuperscript{73} Abrahams & Geschwind 2008  
\textsuperscript{74} Lichtenstein et al. 2010  
\textsuperscript{75} Strömland et al. 1994  
\textsuperscript{76} Buchmayer et al. 2009  
\textsuperscript{77} Wilkerson et al. 2002  
\textsuperscript{78} Ghaziuddin et al. 2002  
\textsuperscript{79} Harris et al. 1995  
\textsuperscript{80} Rutter 1998  
\textsuperscript{81} Rutter et al. 1999
Cognitive processes

Central coherence
The weak central coherence theory, introduced by Uta Frith refers to the ability (or inability) to see the 'big picture' and to form Gestalts out of parts and pieces of information. Basically, the theory postulates that individuals with ASDs have a processing style that is prone to focus on details instead of on the whole context. Several studies have investigated this style of processing and found that individuals with ASDs indeed are better at narrow, detail-focused tasks and at identifying details that may be overlooked by other persons who give priority to the overall scheme (such as the embedded figures task)\(^\text{82}\). For instance, individuals with ASDs generally show low sub-test scores on comprehension and high scores on block design\(^\text{83}\).

Theory of Mind
Another cognitive trait, commonly proposed to be the 'core' deficit in autism, is hampered development of the ability to form a 'theory of mind' or to 'mentalize', i.e. to attribute mental states to others in order to predict their behavior (generally assessed by so called 'false belief tests' where it is necessary to understand that other people's behaviors are guided not by reality but by their, sometimes mistaken and false, notions of reality). The understanding of false beliefs and the ability to form a Theory of Mind normally develops between three and four years of age. Mentalizing is also referred to as 'meta-cognition', i.e. the process to think about thinking in yourself and in others, thereby extracting global form and/or meaning about persons. The mentalizing process, which is an unconscious and automatic activity\(^\text{84}\), is supposedly diminished in individuals with ASDs, but it is necessary to understand that most - if not all - subjects with ASDs and a normal or near-normal overall IQ will be able to solve false belief tasks, for example, but may do so by different strategies that may be more energy-consuming or stressful, and are likely to have more complex problems with mentalizing as based on social perceptions and abstract reasoning.

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\(^{82}\) Happé & Frith 2006
\(^{83}\) Siegel et al. 1996
\(^{84}\) Frith 2003
Executive functioning

Executive functioning is a wide concept that basically refers to the independent, purposive, and self-serving strategies that enable a person to plan and execute tasks\(^{85}\). The planning ability and mental flexibility (as measured by perseveration and regulatory difficulties) are impaired in individuals with ASDs, while there is ambiguous evidence regarding inhibitory tasks, like the Stroop test\(^{86}\). It may be argued that executive functions by definition are deficient in all conditions referred to as ‘mental disorders’, but more specific problems in ASDs are obviously related to inhibitory functions, strategy formation, and adaptation within the three main problem areas of the ASDs.

Special abilities

Kanner described ‘islets of ability’ in individuals with ASDs and extraordinary skills, such as absolute pitch\(^{87}\), memory, and mathematical abilities\(^{88}\). Savant capabilities, i.e. an extraordinary proficiency in one or more areas far beyond the developmental level, have been described in children with autistic problems and have been estimated to occur in as many as 28% of individuals with ASDs\(^{89}\). At least in some cases, such skills may be understood as expressions of weak central coherence that by freeing attention from overall structures enables an unusually strong focus on details.

Organizations

Since autism in the 1980s started to attract more general interest in the research community, a large number of regional, national, and international organizations working with or created by and for individuals with ASDs have been developed. One of the largest is The National Autistic Society (www.autism.org.uk), which provides extensive information about ASD-related topics for individuals with ASDs, their families, employers, teachers, support groups, networks, and the general public. While some of these organizations are mainly led by parents and researchers, others are founded and developed by user groups, especially on the web, where internet communities of (sometimes self-identified) persons with ASDs provide a picture of what it means to ‘have’ an ASD or to be an ‘Aspie’ (their own term) that is not fully consistent with that described by the researchers. The users are, for example, more likely to define ASDs as ‘differences’ rather than as ‘disorders’ or ‘dysfunctions’, to conceptualize the differences in strictly cognitive terms, and to emphasize possible advantages involved in autistics.

\(^{85}\) Lezak et al. 2004
\(^{86}\) Hill 2004
\(^{87}\) Heaton et al. 2008
\(^{88}\) Rimland 1978
\(^{89}\) Howlin et al. 2009
like ways of functioning cognitively. It will prove interesting to see how the user’s self-descriptions will influence future research in the field.

**Broader autism phenotypes and autistic-like traits**

ASDs can be construed as the phenotypical expression of a lower-most extreme end of a continuum of socio-communicative abilities that are dimensionally distributed in the general population\(^{90}\). An extension of this conception is that features similar to those described in the ASDs (as in Tables 1-5) may occur also in the normal variation as a ‘broader autism phenotype’ or ‘autistic-like traits’ (ALTs). Both concepts relate to problems described among the ASDs but reported in individuals who do not meet formal criteria for an ASD. The research on the broader autism phenotype has mainly been conducted in family studies as a condition among relatives of probands with ASDs, while ALTs have been studied as continuous variations in the general population. Today, the broader autism phenotype is defined as an extension of the ASDs, while ALTs are thought of as interindividual differences in features commonly described in relation to ASDs. It should be acknowledged, however, that both concepts have been used interchangeably, which would seem to be appropriate since no evidence or theory today indicates that the broader autism phenotype and the ALTs are qualitatively distinct or even different from each other.

**Broader autism phenotypes**

In the concluding remarks of his original paper\(^ {91}\), Kanner wrote: “For the most part, the parents, grandparents and collaterals are persons strongly preoccupied with abstractions of a scientific, literary or artistic nature, and limited in genuine interest in people”. In addition, short characteristics are given of the patients’ parents and grandparents, such as “absorbed in thinking”, “mildly obsessive”, “obsessive preoccupations with details” and “mostly living with himself” i.e. features described as being part of the autism spectrum\(^ {92}\). Asperger also noticed these phenomena among the parents and described characteristics like "reclusiveness", "eccentric", "lone wolf"\(^ {93}\).

Although we now know that ASDs are not associated with a specific social class\(^ {94}\), most of the assessed children in the initial studies had highly educated families from the upper socio-economic stratum (SES), most probably because of referral bias.

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\(^{90}\) Gillberg 1992  
\(^{91}\) Kanner 1943  
\(^{92}\) Gillberg 1995  
\(^{93}\) Frith 1998  
\(^{94}\) Gillberg & Schaumann 1982, Wing 1980
Introduction

In 1975, a study reported a history of speech disorder in five out of 19 families with a member with a known ASD\textsuperscript{95}. In an extension of the study, it was shown that two out of 18 fathers and ten out of 19 mothers had seen a physician for psychiatric reasons\textsuperscript{96}. In 1977, Susan Folstein and Michael Rutter\textsuperscript{97} assessed a group of twins, primarily to determine concordance rates for ASDs in co-twins of 11 monozygotic (MZ) and ten dizygotic (DZ) twins affected by ASDs. A subordinate finding, at the time, was that twin pairs supposedly discordant for ASDs were not totally discordant. On the contrary - out of the seven MZ pairs ‘discordant’ for ASDs, only two pairs were ‘truly’ discordant for ASD-related features. In the five remaining MZ pairs, all co-twins showed cognitive difficulties, four showed language difficulties, and, in addition, poor coordination skills and hyperactivity were reported in the case vignettes. All of the ten DZ twins were discordant for ASDs; only one pair was concordant for learning disabilities. ASD-related features were noted in one co-twin (a delayed motor milestone) and another DZ co-twin later developed an unknown psychiatric disorder. Among non-twin siblings and parents, psychiatric, cognitive and reading disabilities, and/or ASD-characteristics were frequently reported.

More recent studies investigating the broader autism phenotype have found social and communicative impairments, both severe and subtle, in relatives of probands with ASDs\textsuperscript{98} to a larger extent than expected by chance alone, and a specific scale has been developed for assessing such traits in relatives\textsuperscript{99}. In addition, tendencies towards a lower central coherence have been shown among relatives\textsuperscript{100}.

**Autistic-like traits (ALTs)**

In his 1991 Emanuel Miller memorial lecture, Christopher Gillberg hypothesized that ASDs might be construed as the lower end of a normal variation of an empathy quotient\textsuperscript{101}. This line of reasoning was supported by the pedigree studies described above but remained unexplored until John Constantino and Richard Todd\textsuperscript{102} showed that ALTs (measured with an early version of the SRS\textsuperscript{103}) in an adolescent twin sample were dimensionally distributed and about as heritable as the ASDs (76% of the

\textsuperscript{95} Bartak et al. 1975  
\textsuperscript{96} Cox et al. 1975  
\textsuperscript{97} Folstein & Rutter 1977  
\textsuperscript{99} Dawson et al. 2007  
\textsuperscript{100} Happé et al. 2001  
\textsuperscript{101} Gillberg 1992  
\textsuperscript{102} Constantino & Todd 2000  
\textsuperscript{103} Constantino et al. 2003
Introduction

Phenotypical variation could be explained by genetic factors. These findings were later confirmed (albeit with some variations in the heritability estimates, which were as low as 48% in one study) in a larger sample using the same measure and have been confirmed by various research groups using other methods of measurement and other age groups (ranging from 2-17 years, with heritability estimates ranging from 40-76%)

Already in Asperger’s original papers, his syndrome was conceptualized as a personality deviance, and a model using interindividual variation in traits to describe the problems encountered by persons diagnosed with ASDs has remained a parallel branch to the newer scientific attempts to use specific cognitive ‘dysfunctions’ to model the ASDs. Sula Wolff used ‘schizoid personality’ to characterize children with ASDs, and Robert Cloninger’s temperament and character model has been used to link the ASDs to the normal variation in personality traits related to social reinforcement, interaction, and empathy.

Using systematic assessments of personality disorders, very high prevalences from all the three ‘clusters’ specified in the DSM (odd and eccentric, dramatic, and anxious), were also found among persons with ASDs.

Based on today’s scientific literature as reviewed here, it seems reasonable to conclude that the ASDs encompass about 1% of the population and are defined around a ‘core’ of classic autism, which is often combined with severe learning disabilities and has a prevalence in the range of per milles. The liability of having an ASD is to a large extent genetic (80%). This heritability estimate is close to that derived from clinical groups of twins diagnosed with autism (91%). When using personality scales that measure the broad variation of interindividual social interaction and communication abilities, somewhat lower heritability estimates, around 50%, are found. Based on the features assessed by the different instruments used to diagnose ASDs and assess ALTs (i.e. symptoms of ASDs), it seems reasonable to assume that these are essentially similar phenotypical expressions. This may not so easily be assumed for instruments assessing personality traits. It is important to keep in mind that personality remains a questioned concept in children and adolescents, which underscores the need for studies comparing personality to ASDs and ALTs in population-based cohorts of adults.

104 Constantino & Todd 2003
107 Söderström et al. 2002
108 Anckarsäter et al. 2006
109 Lichtenstein et al. 2010
110 Bailey et al. 1995
111 Anckarsäter & Cloninger 2007
Introduction

Co-existence
Mental disorders, such as attention-deficit/hyperactivity disorder (AD/HD), mood disorders, schizophrenia, developmental coordination disorder (DCD), and personality disorders, seem to be present in one form or another in the majority of subjects diagnosed with an ASD\textsuperscript{112}. In addition, individuals with AD/HD\textsuperscript{113}, internalizing problems\textsuperscript{114}, and conduct disorder (CD)\textsuperscript{115} often report problems corresponding to the ALTs. By employing twin methodology, it has been possible to resolve whether also ALTs are etiologically related to traits of various mental disorders. This research has recently started, and several recent studies have demonstrated shared genetic and environmental influence between ALTs and AD/HD\textsuperscript{116}, anxiety\textsuperscript{117}, clumsiness\textsuperscript{118}, and behavioral problems\textsuperscript{119}.

Distribution of ALTs
A nation-wide study using the DSM-IV criteria for AD reported that 35\% of the whole population displayed an ALT to some degree\textsuperscript{120}. The contemporary concept of ALTs describes deficits occurring on the left-hand side of a normal distribution of mental abilities of relevance for social interaction and communication. We do not, however, know if the opposite of 'lack of social reciprocity' is just 'not lacking' or if there is a continuum of positive social reciprocity. Figure 1 depicts the possible distribution of socio-communicative abilities and ALTs in the general population. It is important to recognize that the majority of individuals with ALTs do not experience problems from all three areas of the triad, which may indicate that the associations between the three domains of the triad may differ between the ALTs and the ASDs and be less pronounced among ALTs\textsuperscript{121}. This notion is supported by twin studies, where low genetic and environmental correlations within the triad have been demonstrated in the general population\textsuperscript{122}. Only one study has so far examined if the correlations between the three domains of the triad are low also when measuring more pronounced ALTs, such as those below the 10\textsuperscript{th} percentile of ALTs. Such a tendency was found, but with too large confidence intervals (CIs) to allow any firm conclusions\textsuperscript{123}. In view of the fact that

\textsuperscript{112} Gillberg & Billstedt 2000, Hofvander et al. 2009, Simonoff et al. 2008,
\textsuperscript{113} Rommelse et al. 2009
\textsuperscript{114} Kanne et al. 2009
\textsuperscript{115} Gilmour et al. 2004
\textsuperscript{116} Reiersen et al. 2008, Ronald et al. 2008a
\textsuperscript{117} Hallett et al 2009, Hallett et al. 2010
\textsuperscript{118} Moruzzi et al. 2011
\textsuperscript{119} Hoekstra et al 2007b
\textsuperscript{120} Anckarsäter et al. 2008
\textsuperscript{121} Abraham & Geschwind 2008, Happé & Ronald 2008
\textsuperscript{122} Ronald et al. 2006a
\textsuperscript{123} Ronald et al. 2006b
problems in all triad areas are required for a diagnosis of AD, it seems obvious that the degree of convergence is larger in narrowly defined ASDs than among more broadly defined ALTs.

Figure 1.

ALTs and ASDs

It would seem obvious that sub-threshold symptoms (i.e. ALTs) may be thought of as less pronounced expressions of the same etiological factors as over-threshold symptoms - as long as no actual threshold has been found. In psychiatry, however, the burden of proof has historically come to lie with those who think that there is a continuum ranging from the normal variation into disordered states both in symptoms and etiology, rather than with those who claim a discontinuity, i.e. that the ‘disorder’ is a specific taxon delineated from the normal distribution. There are, however, several sources of support for the notion of a continuity from the ASDs through the ALTs; one high-risk autism locus (5p14.1)\textsuperscript{124} has also been associated with the normal variation of social

\textsuperscript{124}Wang et al. 2009
communication deficits\textsuperscript{125}. In a sample of 3,400 twin pairs, no genetic or environmental thresholds could be discerned in the distribution of autistic symptoms, indicating continuity between ALTs and ASDs\textsuperscript{126}. Still, the relatively small sample size and the lack of clinically validated cut-offs preclude conclusions to be drawn on the basis of this one study alone. Furthermore, factor analytic approaches have failed to show discontinuities between ASDs and ALTs\textsuperscript{127}. On the other hand, a recent genome-wide association study failed to identify single nucleotide polymorphisms associated with both ALTS and ASDs\textsuperscript{128}. The relationship between ALTs and ASDs therefore remains unclear, and this thesis aims to employ three nation-wide twin studies to investigate whether ASDs is best viewed as the extreme end of a continuum of ALTs.

\textsuperscript{125}St Pourcain et al. 2010
\textsuperscript{126}Ronald et al. 2006b
\textsuperscript{127}Constantino et al. 2004
\textsuperscript{128}Ronald et al. 2010b
Aims of the present thesis

Specific aims:
1. To establish the distribution of autistic-like traits and provide estimates of genetic and environmental effects for autistic-like traits. (Paper I)
2. To describe the relationships between autistic-like traits and other mental problems, including shared etiology. (Paper II)
3. To clarify whether autistic-like traits are also influenced by a known risk factor for autism spectrum disorders, i.e. increasing paternal age. (Paper III)
4. To determine whether there is an etiological demarcation between the autism spectrum disorders and autistic-like traits. (Paper IV)
Methods

Subjects
This thesis is based on four sets of data: two from the ‘Child and Adolescent Twin Study in Sweden’ (CATSS) (CATSS-11k, n=11,222, a subset of the larger CATSS-17k, n=17,220), one from the ‘Twin’s Early Development Study’ (TEDS, n=13,524) conducted in the United Kingdom, and, finally, one from the ‘Screening Twin Adults: Genes and Environment’ study (STAGE, n=18,349) made in Sweden. All three studies have targeted nation-wide populations.

CATSS-17k (Papers I and IV)
The nation-wide CATSS-9/12 study addresses parents of Swedish 9- or 12-year-old twins and is ongoing since 2004. As of January 2010, 8,610 parental informants have participated in telephone interviews for 17,220 individual twins (referred to here as CATSS-17k), representing the cohorts born between July 1, 1995 and December 31, 2000. During the first three years of the study, both 9- and 12-year-old twins (born July 1992-June 1998) were included in order to achieve a large enough cohort to permit meaningful analyses after three years of data collection. The reason for choosing these age groups was that most of the major child psychiatric and neurodevelopmental problem constellations have been established by this age, while the biopsychosocial problems associated with puberty and adolescence most often have not yet emerged. The overall response rate is 80%. Fifty-one % are males, and zygosity is determined by a validated algorithm with >95% predictive value compared to DNA-testing. The telephone interviews are carried out by interviewers from a professional company, ‘Intervjubolaget’. The CATSS is the largest child psychiatric twin study in the world. Biological samples for DNA extraction are currently being collected from all participating twins. Paper I provides an extensive overview of the methodology, cohorts, and results from the project.

CATSS-11k (Papers II and III)
CATSS-11k is the subset of the first six year cohorts included in the CATSS (twins born between July 1992 and June 1998, n=11,222). The CATSS-11k has been linked to the medical birth registry providing information on birth weight, which was controlled for as a potential confounder in Paper III.

129 Lichtenstein et al. 2010
Methods

STAGE (Paper II)
The STAGE cohort is a cross-sectional study consisting of 18,349 adult twins born between 1959 and 1985. The study started in May 2005, when all eligible twins (a total of 42,582) were approached by letters with logon information to a website containing the questionnaires to be answered. For subjects who were not attracted by this procedure, a telephone interview with a trained interviewer was proposed. The overall response rate in STAGE was 47% (40% men and 60% women). Zygosity was determined by an algorithm with a 95% predictive value.

TEDS (Paper III)
TEDS is an ongoing, longitudinal, British study of twins born between 1994 and 1996 in England and Wales. Participants were identified through birth records containing notes of all twin births. Twins enrolled in the TEDS have been examined in connection with their 2nd, 3rd, 4th, 7th, 9th, 10th, and 12th birthdays. When the twins were first assessed at age two, information could be retrieved for 13,732 twin pairs out of roughly 15,000 pairs eligible for inclusion. Due to attrition and limitations in the admission of twins to all stages of the study, the final study group for Paper III contained 13,524 individuals, assessed in connection with their 9th birthday, adding up to a response rate of 49% when compared to the original 13,732 twin pairs (49% males). Zygosity was assessed by a validated algorithm with 96% predictive value.

Representativeness
The CATSS is a nation-wide study with an 80% response rate, while the response rate was 47% in STAGE and 49% in TEDS. In CATSS, non-responders differed from responders by having fathers (36.8% vs 31.1%) and mothers (45.1% vs 44.7%) who to a larger extent had been unemployed from the birth of the twins until the time of the telephone interview. Furthermore, non-responders were more likely to have divorced fathers (16.4% vs 12.4) and mothers (16.4% vs 12.5%), to come from larger families (defined as four or more children) (11.1% vs 6.9%), and to have fathers (6.9% vs 6.3%) and mothers (7.1% vs 4.5%) treated in open or inpatient psychiatric care. This may to some small extent bias the results in Papers I-IV towards over-inclusion of less problem-prone children. In STAGE, non-responders were more likely to be male, have a diagnosed psychiatric disorder, a parent born outside Sweden, criminal convictions,
lower intellectual functioning (measured by conscription records), and lower education\textsuperscript{135}. In TEDS, non-responders have not been systematically analyzed, but there is reason to assume that the non-responders show similar characteristics as those described for CATSS and STAGE, perhaps even to a still larger extent, since the attrition rate is overall larger in TEDS. Generally in the scientific literature, non-responders have been reported to be older, belong to a lower SES, move more often\textsuperscript{136}, and display lower cognitive functioning\textsuperscript{137}. While it seems reasonable to assume that psychiatric problems may be over-represented in non-responders, the evidence for this assumption is inconclusive and likely to vary between conditions\textsuperscript{138}. Though no studies known to this author have been aimed at determining if individuals with sub-threshold traits (i.e. ALTs) to a larger extent are non-responders, adult individuals with ASDs in combination with significant learning disabilities are probably under-represented in STAGE for obvious reasons. In adult surveys of mental health by self-response questionnaires, a higher response-rate among persons interested in psychology and thereby more observant of themselves than the average person inflate prevalence estimates.

**Measures**

Three main assessment measures were used in this thesis to identify ASDs and to assess ALTs continuously from the lowest possible level and into the diagnostic spectrum: (1) the Autism – Tics, AD/HD, and other Co-morbidities inventory (A-TAC\textsuperscript{139}), (2) the Childhood Autism Spectrum Test (CAST\textsuperscript{140}), and (3) 12 DSM-IV-based questions for adults, similar to the DSM-items in the A-TAC, but not formally validated for use among adults.

AD/HD, anxiety, and conduct problems were explored by means of the relevant A-TAC modules\textsuperscript{141}. For adults in STAGE, DSM-IV-based checklists were used for AD/HD, anxiety, and depression. To provide a continuous measure of depressive traits, an 11-item version of the Iowa version of the Center for Epidemiologic Studies Depression Scale (CES-D)\textsuperscript{142} was employed. An overview of the instruments used is given in Table 6.

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\textsuperscript{135} Furberg et al. 2008  
\textsuperscript{136} Roman-Clarkson et al. 1988, Ware et al. 2006  
\textsuperscript{137} Van Beijsterveldt et al. 2002  
\textsuperscript{139} Hansson et al. 2005, Larson et al. 2010  
\textsuperscript{140} Allison et al. 2007, Williams et al. 2006  
\textsuperscript{141} Larson et al. 2010  
\textsuperscript{142} Carpenter et al. 1998
Methods

Table 6. Measures of psychopathology used in the studies

<table>
<thead>
<tr>
<th>Target condition</th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV</th>
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<td>A-TAC and DSM-IV-based items</td>
<td>A-TAC and CAST</td>
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<td>A-TAC and DSM-IV-based items</td>
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<tr>
<td>Conduct disorder and substance abuse</td>
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<td>Depression</td>
<td>A-TAC</td>
<td>A-TAC and DSM-IV-based items</td>
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<td>CES-D</td>
</tr>
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<td>Other psychopathology</td>
<td>A-TAC</td>
<td>A-TAC and DSM-IV-based items</td>
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</table>

A-TAC (Papers I-IV)

The A-TAC is a parental telephone interview designed for large-scale epidemiological research and consists of 227 items organized into theoretically defined modules (i.e. concentration and attention, impulsiveness and activity, social interaction, language), which target all major clinical diagnoses in child and adolescent psychiatry. The A-TAC has been clinically validated in two phases\(^{143}\). Questions refer to a lifetime perspective and should be answered with a comparison to peers in mind. For each module the parent is also asked whether or not problems associated with the endorsed symptoms have led to dysfunction at school, among peers, or at home, and/or to suffering on the part of the child. Items are scored “no” (score 0), “yes, to some extent” (score 0.5), and “yes” (score 1.0). Finally, for each symptom/problem endorsed, the age at onset and persistence of problems are asked for.

In two published validation studies of the A-TAC, Receiver Operating Characteristics (ROC) curves are plotted for the prediction of clinical ASD diagnoses by the A-TAC scales. The ROC curve is a graphical composite measure of the sensitivity and specificity at each possible cut-off in a continuous scale to discriminate between noise and signal.

\(^{143}\) Hansson et al. 2005, Larson et al. 2010
Methods

(i.e., in this case, a diagnosis of ASD). The area under the curve (AUC) ranges from 0 to 1.0, where 0.5 means not better than random at discriminating between noise and signal. Generally, an AUC above 0.8 is considered to indicate a good prediction and above 0.9 as excellent. By looking at specific regions of the ROC-curve it is possible to establish one (or several) inflection points. The inflection point is a cut-off on the continuous scale where the psychometric properties (sensitivity and specificity) for this particular scale-step are seen. The optimal inflection point would be a scale-step where the sensitivity is 1.00 and the specificity 1.00. In psychiatric settings, however, there is almost always a trade-off between sensitivity and specificity.

The ASD-module in the A-TAC consists of 17 items, 12 of which reflect the DSM-IV symptom criteria for AD. In this thesis, three different approaches have been used to identify ASDs by means of the A-TAC for various purposes. Psychometric characteristics are available for the three different scales and cut-offs based on the two published validation studies. First, a cut-off of 4.5 points has been used for the 12 DSM-IV items yielding an AUC of 0.96. Second and third, two different cut-offs (4.5 and 8.5, respectively) were applied to the full A-TAC ASD scale containing 17 items. The lower cut-off yields a sensitivity 0.96 and specificity of 0.88, and at the higher cut-off, the corresponding figures are 0.71 and 0.95, respectively\(^{144}\). The two scales (thus ranging from 0-12 and 0-17, respectively) were also used as continuous measures of ALTs.

The AD/HD-module in the A-TAC consists of 18 items that closely follow the DSM-IV criteria for AD/HD\(^{145}\). This scale has excellent validity for identifying AD/HD (AUC 0.94), with a cut-off score at 8, yielding a sensitivity of 0.87 and a specificity of 0.88\(^{146}\). For anxiety, the module used in Paper II contains six items and has a ROC of 0.78, and the module used in Paper I has three items with a cut-off at 1. The total scores of each individual were also used as dimensional measures of AD/HD and anxiety. Five DSM-IV-based items were used to assess and identify conduct problems. By using both the second validation study and a study group of 66 institutionalized adolescents\(^{147}\), the AUC for identifying CD could be calculated to 0.90 with an optimal cut-off at 2. In Paper II, however, we chose to categorize subjects who scored 1.5 or higher as cases to achieve a reasonable prevalence of conduct problems, since the DSM-IV definition of CD is rarely met in 9- and 12-year-old children.

\(^{144}\) Larson et al. 2010  
\(^{145}\) APA (DSM-IV) 1994  
\(^{146}\) Larson et al. 2010  
\(^{147}\) Ståhlberg et al. 2010
Methods

For the remaining conditions in the A-TAC (described in Paper I), detailed data from the validation studies is provided in Hansson et al\textsuperscript{148}. The scales that have not been formally validated (eating problems, memory, perception, anxiety, and planning) are detailed and discussed in Paper I. The A-TAC is attached to the web-version of the Larson et al. article\textsuperscript{149}, where it can be downloaded for free and is available for non-commercial use.

CAST (Paper III)

The CAST is a parental self-rating screening instrument for ASD designed for epidemiological research\textsuperscript{150}. It consists of 37 items, 31 of which measure ASD symptoms. Items are scored 1 for ASD-positive responses, and 0 for negative ones. The cut-off score for possible ASD, 15 or higher, is reported to yield a 100% sensitivity and a 97% specificity to identify research diagnoses with a 50% positive predictive value in the validation study group\textsuperscript{151}.

DSM-IV-based checklists for ASDs and other conditions (Paper II)

The 12 items assessing ASDs and the 18 items assessing AD/HD used in the adult self-rate study correspond to the A-TAC, ASD, and AD/HD scales, adapted to adulthood and the self-rate format. The ASD scale had a modest internal consistency with a Chronbach’s $\alpha$ of 0.63, and subjects who had 7 points or more were considered to meet criteria for an ASD diagnosis, yielding a prevalence of 0.5%. The AD/HD scale had an excellent consistency with a Chronbach’s $\alpha$ of 0.84. Subjects who responded "yes, to some extent" or "yes" to six or more questions in the hyperactivity or in the inattentive dimension were tentatively assumed to meet a research diagnosis of AD/HD according to the cut-off used in the DSM-IV. This yielded a prevalence of 2.2%. Six DSM-based items corresponding to generalized anxiety disorder (GAD), preceded by the question whether the subject had ever experienced symptoms of anxiety and worrying lasting for one month or more, were used for the identification of anxiety disorder. The cut-off for a possible GAD is 3 points plus an affirmative answer to the question of duration, yielding a prevalence of 4.5%. Nine items were used to identify possible major depression. As in the DSM-IV, the cut-off for a possible lifetime major depression was 5 plus affirmative answers to the C criterion (i.e. that the symptoms were causing clinically significant suffering) and the E criterion (i.e. that the symptoms were not better accounted for by bereavement), yielding a lifetime prevalence of 13.4%. For the continuous analyses,

\textsuperscript{148}Halleröd et al. 2010, Hansson et al. 2005, Larson et al. 2010,
\textsuperscript{149}Larson et al. 2010
\textsuperscript{150}Williams et al. 2006
\textsuperscript{151}Williams et al. 2005
depressive traits were measured by an 11-item version of the Iowa version of the CES-D\textsuperscript{152}, a measure widely used in epidemiological settings to screen for depression. With the exception of the CES-D, none of the measures used in the adult STAGE study has been formally validated as a self-rate adult instrument. They are, however, based on DSM-IV items, and the AD/HD and anxiety scales have previously been described\textsuperscript{153}.

**Twin methodology**

Francis Galton introduced twin methodology in the scientific world by suggesting that twins reared apart could be used to disentangle genetic and environmental effects\textsuperscript{154}. Twin methodology capitalizes on the fact that MZ twins (coming from a single split fertilized egg) share 100\% of their genetic material, while DZ twins (coming from separately fertilized eggs), on an average share 50\% of their segregating alleles. By comparing the within-pair resemblance of MZ to that of DZ twins, conclusions about the etiology of the examined trait can be drawn and decomposed into three variance components: genetic (A, the part of phenotypic variance that is attributable to genetic factors), shared environment (C, non-genetic factors that make the twins similar), and unique environment/non-shared environment (E, non-genetic factors that make the twins different). For instance, if a phenotype is solely affected by genes, the twin pair correlation for MZ twins would be 1.00, while the correlation for DZ twins would be 0.50. If, however, the phenotype is solely affected by C or E, a twin correlation of 1.00, or 0.00 for both MZ and DZ twins would be expected\textsuperscript{155}. During the past decade, twin research has moved from simply answering the question of the underlying etiology of one trait\textsuperscript{156} to multivariate analyses (genetic and environmental co-variation and testing of gene-environment interactions), and children-of-twin studies (to study transmission of traits over generations), to name but a few areas. The twin methodology relies on the equal environment assumption (i.e. that the environmental exposure causes similar effects for MZ and DZ twins). If, for instance, MZ twins are treated more similarly than DZ twins, and this actually leads to making them more similar, heritability will be falsely inflated by an environmental contribution. This has, however, been tested for psychiatric disorders\textsuperscript{157}, spatial ability, and aggression\textsuperscript{158} without evidence of violations of the equal environment assumption. Furthermore, MZ twins reared apart show very

\textsuperscript{152}Carpenter et al. 1998  
\textsuperscript{153}Frisell et al. 2010  
\textsuperscript{154}Galton 1875, Boomsma et al. 2002  
\textsuperscript{155}Neale et al. 2003  
\textsuperscript{156}Boomsma et al. 2002  
\textsuperscript{157}Kendler et al. 1993  
\textsuperscript{158}Derks et al. 2006
similar correlations to MZ twins reared together\textsuperscript{159}, and MZ twins mislabeled as DZ twins show similar correlations on dietary patterns as those correctly classified as MZ twins\textsuperscript{160}. There are even indications that MZ twins in some respects actually show greater differences than DZ twins\textsuperscript{161}, and that these discrepancies may be ascribed to the fact that MZ and DZ twins are not invariably exposed to a similar intrauterine environment\textsuperscript{162}.

**Heritability**
The A variance component in twin methodology is also called heritability. As stated above, heritability refers to the phenotypic variance among individuals attributable to genetic factors. It is crucial to recognize that heritability does not refer to the genetic composition of one individual - it refers to the genetic contribution to the difference between people in an examined trait\textsuperscript{163}. For instance, in Paper I, ALTs were found to have a heritability of 0.68. This does not mean that 68% of ALTs are genetic. The correct interpretation is that 68% of the difference in ALTs across the population is due to genetic factors. A related issue concerns the generalization of heritability estimates; it is important to acknowledge that heritability estimates are valid for the measured population, at the time of the measurement, and may not automatically translate into other populations.

**Analytical methods**
All analyses for this thesis were performed in SAS 9.1 or SAS 9.2 and Mx\textsuperscript{164}. Table 7 presents an overview of statistics used in the papers, and the applied methods are briefly described below.

\textsuperscript{159} Bouchard et al. 1990  
\textsuperscript{160} Gunderson et al. 2006  
\textsuperscript{161} Plomin et al. 2008  
\textsuperscript{162} Martin et al. 1997  
\textsuperscript{163} Plomin et al. 2008  
\textsuperscript{164} Neale et al. 2003
### Methods

#### Table 7. Statistics used in this thesis

<table>
<thead>
<tr>
<th></th>
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<tr>
<td>Bivariate twin analyses</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremes analyses</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

**Chronbach’s α (alpha)**

The Chronbach’s α is a way to measure the internal consistency of a scale. That is, all items should optimally reflect a unified construct. The Chronbach’s α is a composite measure for the correlations between all items and generates a correlation coefficient reflecting the degree of overall convergence between the items. Generally, a Chronbach’s α of 0.7-0.8 is regarded as satisfactory in research settings.\(^{165}\)

**Mann-Whitney U-test**

The Mann Whitney U-test is a non-parametrical statistical test used to detect if the mean value difference between two groups is statistically significant when the data is not normally distributed (i.e. skewed).

**Intra-class/Tetrachoric correlations**

Intra-class correlations (ICCs) are correlation coefficients used to describe how much two measured units (i.e. a pair of twins) resemble each other on one variable. It is commonly used on grouped data (i.e. to compare if the correlation coefficient differs between groups of MZ and DZ twins), where paired observations are not meaningful. Like a standard Pearson correlation, ICCs range from -1 to +1, where 0 means no correlation, but differ by having pooled mean values and standard deviations. The reason for this is that the ICCs measure the same quantity twice, i.e. how much variable X in twin 1 resembles variable X in twin 2. Tetrachoric correlations (TC) are the categorical (binary) equivalent to the ICC. Both ICCs and TCs are calculated by the PROC CORR procedure in SAS.

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\(^{165}\) Bland & Altman 1997
Methods

Cross-twin, cross-trait correlations
The cross-twin, cross-trait correlation is a standard Pearson correlation, where a measure of trait X in twin 1 is correlated with a measure of trait Y in twin 2 (in Paper II, we correlated ALT-score in twin 1 with AD/HD-score in twin 2). A positive correlation indicates that the traits co-vary (i.e. if the ALT-score is high, the AD/HD-score is probably also high). Furthermore, if the correlation is higher for MZ than for DZ twins, a positive genetic covariance is implied (i.e. genetic factors influencing ALTs probably also affect AD/HD-traits). These calculations are done via the PROC CORR procedure in SAS.

Generalized estimating equations (GEE) and mixed models
In twin research, the difference in genetic relatedness between MZ and DZ twins is what renders it possible to draw conclusions about the etiology of a trait or a disorder. Sometimes, however, it is desirable to use twin samples to answer questions irrelevant to twin methodology (as in Papers II and III). By employing GEE and mixed models, it is possible to account for correlations within twin pairs (genetic or environmental), taking the independence of the twins into account, GEE models can be fitted with standard statistical procedures as a logistic regression (Papers II and III), via the PROC GENMOD procedure, or, as a mixed model, on a one-way analysis of variance test (Paper III) via the PROC MIXED procedure in the SAS.

Univariate twin analyses
Univariate analyses refer to the estimation of the genetic and environmental variance components (A, C, and E) of a single phenotype in the population. By applying the Falconer formula on the ICCs or TCs, a crude measure of the variance components can be estimated: \( A = 2(r_{mz} - r_{dz}) \), \( C = r_{mz} - A \), \( E = 1 - (A + C) \). To obtain a more exact measure of genetic and environmental influences and generate CIs, a structural equation modeling program such as Mx is used. Mx, which is freely available at [http://www.vcu.edu/mx/](http://www.vcu.edu/mx/), is the standard statistical program used to analyze twin data. Univariate ACE analyses can be done in two ways; first, in a categorical fashion, where A, C, and E are estimated by including cases and controls from the whole population, and the concordance rates are compared between MZ and DZ twins, thus measuring the variance of the underlying liability of the condition in the general population. The second approach takes advantage of continuous data and includes the whole variation of the examined trait (in this thesis ALTs), thus making it possible to estimate A, C, and E for the underlying liability for the trait.

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166 Neale et al. 2003
Methods

**Bivariate analyses**

Bivariate analyses estimate the extent of covariance between two or more traits and if this covariance is due to the environmental and/or genetic influences\(^{167}\). The bivariate analysis is based on the cross-twin, cross trait correlation and is mainly displayed via genetic correlations \((r_a)\), shared environmental correlations \((r_c)\), and non-shared environmental correlations \((r_e)\). A perfect genetic correlation (1.00) between trait x and trait y indicates that all genetic influences on trait x also influence trait y.

**Extreme analyses**

DeFries and Fulker\(^{168}\) proposed a model (DF-analyses) to analyze twin data in extreme-scoring groups in order to assess the heritability for an extreme trait. In DF-analyses, probands (individuals with ASDs) are identified, and the continuous score of the co-twin is used to obtain heritability estimates. A mean standardized quantitative trait score is calculated by dividing the scores (quantitative traits) of the co-twins (subtracting the population mean) with the proband mean (subtracting the population mean). This score ranges from 0.00-1.00, where 0.00 is the population mean and 1.00 is the proband mean.

This estimate is basically a correlation coefficient between the full variation of a quantitative trait in the co-twin of a proband and the narrowly defined extreme end condition in the proband. These correlations in MZ and DZ twins can then be used to estimate genetic (commonly called ‘group heritability’) and environmental contributions in the same fashion as for any quantitative trait. To estimate the ‘group heritability’, a regression model predicting the score of the co-twin can be used\(^{169}\). The regression can be expressed as \(C = B_1P + B_2R + D\), where ‘C’ is the co-twin score, ‘P’ the proband score, ‘R’ the genetic relatedness (1.0 for MZ and 0.5 for DZs), ‘B2’ is a regression coefficient estimating the group heritability, and ‘D’ is a regression constant. The genetic estimation accounts for all possible genetic contributions (e.g. dominance, epistasis, or additive effects) shared between the extreme end condition and the variance in the quantitative trait. Therefore, if the extreme group correlations show a pattern of dominance (i.e. a MZ correlation more than twice as high as the DZ correlation), group heritability is to be restrained to the value of the MZ correlation.

\(^{167}\) Plomin et al. 2008
\(^{168}\) DeFries & Fulker 1985
\(^{169}\) DeFries & Fulker 1988
Methods

Nature of data
The NOIR-concept (Nominal, Ordinal, Interval, and Ratio) was introduced in 1946 and proposed as a guideline for how to statistically cultivate different types of data\textsuperscript{170}. For instance, ordinal data should only be used for simple statistics, like summary statistics. The suggestions presented in the paper have met a lot of criticism (but also support), and an interesting review highlights the main points\textsuperscript{171}. The continuous scales used in this thesis are created out of ordinal data (i.e. categorical data, logically ordered) but the statistics are traditionally used with interval data (the difference between two values represents a fixed distance), for instance, the difference between 5 and 7 is the same as that between 11 and 13) or ratio data (same as interval data but with a clear definition of 0, like weight). The usage of one-way analysis of variance, on ordinal data, provides a valid estimate about whether two groups differ statistically. The quandary, however, lies in the interpretation of the results. An example, if the mean of three groups, measured on an ordinal scale, is 2, 4, and 6 points, it is not correct to assume that the difference between 2 and 4 is the same as that between 4 and 6, or that 4 is twice as much as 2. Thus, the interpretation of an analysis of variance or t-test can inform us if there are significant differences between groups, but cannot specify the actual difference between these groups.

Power/Multiple testing
Power analyses test the probability for a type II error (failure to reject the null hypothesis when it in fact is false, which means that a true difference cannot be observed). No a priori power analyses were conducted in CATSS, STAGE, or TEDS as all three studies are prospective, nation-wide, and thought to include a sufficient number of participants. The CATSS is also continuously including new twins. Also, the wide variety of different scales and measures would make one power analysis impossible. Multiple testing increases the risk that the observed difference between two (or more) groups will be due to chance alone (type I error). For instance, a test between A1 and A2 might yield a p-value of 0.05 (which means that the probability of obtaining the same, or a more extreme value, on the condition that the null hypothesis is true, is 5%, i.e. there is a 5% chance of committing a type I error). However, if 100 tests were performed simultaneously (between A1 –A2, A1-A3 ... A1-A100) and all p-values were 0.05, then five of the estimates would be wrong according to chance. In Paper I, we tested for

\textsuperscript{170} Stevens 1946
\textsuperscript{171} Velleman & Wilkinson 1993
Methods

gender differences in all 14 conditions, and the results for all conditions were <0.0001, suggesting that it would be unreasonable to assume that the observed differences arose by chance alone.

Ethical aspects
Both the CATSS and STAGE studies have ethical approval from the Karolinska Institute Ethical Review Board: Dnr 03-672, 2010/507-31/1, and 03-224. The TEDS has ethical approval from King's College London ethics committee: Dnr 05/Q0706/228 (196/05) and PNM/09/10-104.

No adverse effects are expected by the results presented in this thesis. Some issues, however, need to be addressed. First, in Paper II we report that ALTs increase the risk for various mental health problems, and that ALTs are present in a large proportion of both children and adults. Today, web-based ‘assessments’ of ALTs are widely available to everyone, and since it is possible that individuals may assess themselves and draw conclusions regarding their own risk for concomitant mental health problems, it is important to stress that our results are not applicable on an individual level but merely reflect an association found on a group level. Second, in Paper IV, our results suggest that co-twins of twins with ASDs have a higher degree of ALT than the normal population, and that the genes that affect ASDs are also important for the ALTs. This may be perceived as stigmatizing, but very similar phenomena (like the broad autism phenotype) have been described several times in the scientific literature without, to the best of the author’s knowledge, any reported adverse effects. Third, in Paper III we report that increasing paternal age is a risk factor for ASDs and ALTs, although this risk is relative considering that the majority of individuals with ASDs do not have a father aged more than 50 years at the time of conception. Only 2.5% and 3%, respectively, of the ASD-cases had fathers of that age. Furthermore, the actual risk estimates were 3.7% and 1.9%, meaning that the risk for not having a child with ASD, if the father is above 50, is 96.3% and 98.1%, respectively. Again, this is an effect found on a group level that by no means can sustain inferences on an individual level. Fourth, the establishment of databases containing personal information on children and adults may be considered to encroach on the individual integrity. However, the participants (or their parents) are protected by informed consent, and with respect to the risks to confidentiality and integrity, raw data is entered into computer files utilizing identification numbers that cannot be linked to individuals.


Results

Paper I: Basic prevalence figures for ALTs and estimates of genetic and environmental effects

Paper I aims to establish the distribution of ALTs and provide estimates of genetic and environmental effects for ALTs.

Of all 17,220 individuals included in the CATSS-17k, 46.1% showed at least one ALT “to some extent” according to the A-TAC score (Table 8). Using the more narrow DSM-IV score, the corresponding figure is 29%. The difference is due to the high prevalence of the two items “Do other people easily influence him/her?”, and “Does he/she dislike changes in daily routines?”, included in the A-TAC based on their screening properties, but not in the DSM-IV. The three ASD-modules (language, social interaction, and flexibility) each affected about 25% of the population, meaning that they contribute about equally to the ALTs, and that there is a considerable overlap between the three problem types, but far from a perfect match.

ICCs (i.e. the correlation coefficient within twin pairs) were consistently higher between MZ twins than between DZ twins, indicating genetic influences (Table 9). This was confirmed by the univariate analyses (i.e. estimating the heritability of one trait), showing an overall heritability estimate for ALTs of 0.68, meaning that the interindividual variation in ALTs to 68% is explained by genetic effects. Specific analyses for the three problem areas language, social interaction, and flexibility, showed slightly lower heritability estimates, ranging from 55% for social interaction problems, 62% for language deficits, and 63% for the flexibility module. Higher heritability estimates were consistently noted among boys than among girls.
Table 8. The cumulative distribution of ALTs

<table>
<thead>
<tr>
<th>A-TAC module</th>
<th>Max Score</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
<th>2.5</th>
<th>3.0</th>
<th>3.5</th>
<th>4.0</th>
<th>4.5-5*</th>
<th>5.5-6</th>
<th>6.5-7</th>
<th>7.5-8</th>
<th>≥8.5*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social interaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexibility</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Girls Boys</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


*4.5 and 8.5 are validated cut-offs which yield a sensitivity of 0.96 and 0.71 and a specificity of 0.88 and 0.95, respectively.

Table 9. ICCs and estimates of genetic and environmental effects for ALTs

<table>
<thead>
<tr>
<th>A-TAC module</th>
<th>Intra-class correlations</th>
<th>Estimates of genetic and environmental effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MZ</td>
<td>DZ</td>
</tr>
<tr>
<td>-----------------</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASD combined</td>
<td>0.65</td>
<td>0.53</td>
</tr>
<tr>
<td>Language</td>
<td>0.63</td>
<td>0.55</td>
</tr>
<tr>
<td>Social interaction</td>
<td>0.51</td>
<td>0.52</td>
</tr>
<tr>
<td>Flexibility</td>
<td>0.59</td>
<td>0.45</td>
</tr>
</tbody>
</table>
The overlap between ASDs and other conditions assessed in the A-TAC was substantial (Table 10). For instance, roughly 25% of those who screened positive for an ASD also screened positive for AD/HD.

**Table 10. Overlap between ASDs and other types of problems**

<table>
<thead>
<tr>
<th>A-TAC module</th>
<th>ASD</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD/HD</td>
<td>25%</td>
</tr>
<tr>
<td>Tics</td>
<td>13%</td>
</tr>
<tr>
<td>Motor control</td>
<td>17%</td>
</tr>
<tr>
<td>Learning disabilities</td>
<td>22%</td>
</tr>
<tr>
<td>Eating disorder</td>
<td>10%</td>
</tr>
<tr>
<td>Separations</td>
<td>20%</td>
</tr>
<tr>
<td>Compulsions</td>
<td>18%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>16%</td>
</tr>
<tr>
<td>Defiance</td>
<td>16%</td>
</tr>
<tr>
<td>Conduct</td>
<td>20%</td>
</tr>
<tr>
<td>Memory</td>
<td>11%</td>
</tr>
<tr>
<td>Perception</td>
<td>34%</td>
</tr>
<tr>
<td>Planning</td>
<td>20%</td>
</tr>
</tbody>
</table>

**Additional data from the analyses for Paper I**

In order to “establish the distribution of autistic-like traits...” (the first of the aims of this thesis), some additional analyses were performed based on the data-set used in Paper I. First, the specific questions in the A-TAC are listed together with the distribution of answers in order to present the content of the rating of ALTs (Table 11), second, gender-specific cumulative distributions of ALTs are given to provide distributions of problems by gender.

The 17 ASD items are given in Table 11, organized in descending order by frequency, from the most to the least prevalent item. In the next column (’ASDs removed’), the prevalences of the items among subjects who do not meet the research criteria for an ASD (the high cut-off for ASD, 8.5 or more points) are presented to illustrate the relative expression of the different problems among sub-threshold cases only as compared to all cases, and in the last column (’ASDs and learning disabilities removed), subjects with learning disabilities are also removed to present the variation among subjects with normal intelligence only. As indicated by the ‘#’, the order of prevalence of the different
Results

ASD symptoms/ALTs did not change when ASDs and learning disabilities were removed. When just ASDs were included, however, the order changed. The items “Does he/she dislike changes in daily routines?” and “Does he/she have difficulties behaving as expected by peers?” were affirmed by more than 90%.

The cumulative distribution of ALTs by gender
Out of the 8,787 boys, 51.5% displayed some kind of ALT (Table 12), while the corresponding figure for the 8,433 girls was 41.7% (Table 13). Consistently, through the three subscales, boys displayed more ALTs than girls. No subscale struck out as noticeably more or less prevalent in one of the genders.

Distribution of DSM-IV items
When only DSM-IV items were included, 29% reported “yes” or “yes, to some extent” to one or more the DSM-items. Figure 2 also illustrates that we cannot know if there is a socio-communicative continuum of ‘hyper-sociability’.

Figure 2. The distribution of DSM-IV items in relation to a hypothetical normal distribution of background socio-communicative abilities
Table 11. Distribution of ALTs per item. (*DSM-items)

<table>
<thead>
<tr>
<th>Module</th>
<th>All</th>
<th>0.5-1</th>
<th>#</th>
<th>0.5-1</th>
<th>#</th>
<th>0.5-1</th>
<th>#</th>
<th>0.5-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do other people easily influence him/her?</td>
<td>SOC</td>
<td>77.6</td>
<td>22.4</td>
<td>1</td>
<td>78.1</td>
<td>21.9</td>
<td>1</td>
<td>78.4</td>
</tr>
<tr>
<td>Does he/she dislike changes in daily routines?</td>
<td>FLEX</td>
<td>88.3</td>
<td>11.7</td>
<td>2</td>
<td>89.1</td>
<td>10.9</td>
<td>2</td>
<td>89.4</td>
</tr>
<tr>
<td>Does he/she get absorbed by his/her interests in such a way as being repetitive or too intense?</td>
<td>FLEX</td>
<td>89.8</td>
<td>10.2</td>
<td>3</td>
<td>90.5</td>
<td>9.5</td>
<td>3</td>
<td>90.7</td>
</tr>
<tr>
<td>Does he/she get absorbed by details?</td>
<td>FLEX</td>
<td>89.9</td>
<td>10.1</td>
<td>4</td>
<td>90.7</td>
<td>9.3</td>
<td>4</td>
<td>90.9</td>
</tr>
<tr>
<td>Does he/she talk in too high a pitch or too quietly?</td>
<td>LANG</td>
<td>90.3</td>
<td>9.7</td>
<td>5</td>
<td>90.8</td>
<td>9.2</td>
<td>5</td>
<td>91.0</td>
</tr>
<tr>
<td>Does he/she have difficulties keeping “on track” when telling other people something?</td>
<td>LANG</td>
<td>90.5</td>
<td>9.5</td>
<td>6</td>
<td>91.3</td>
<td>8.7</td>
<td>6</td>
<td>91.9</td>
</tr>
<tr>
<td>Was his/her language development delayed or doesn’t he/she speak at all?</td>
<td>LANG</td>
<td>90.9</td>
<td>9.1</td>
<td>7</td>
<td>91.5</td>
<td>8.5</td>
<td>7</td>
<td>91.9</td>
</tr>
<tr>
<td>Does he/she have difficulties behaving as expected by peers?</td>
<td>SOC</td>
<td>93.9</td>
<td>6.1</td>
<td>8</td>
<td>94.8</td>
<td>5.2</td>
<td>8</td>
<td>94.9</td>
</tr>
<tr>
<td>Can he/she only be with other people on his/her terms?</td>
<td>SOC</td>
<td>94.4</td>
<td>5.6</td>
<td>9</td>
<td>95.1</td>
<td>4.9</td>
<td>9</td>
<td>95.3</td>
</tr>
<tr>
<td>Does he/she exhibit considerable difficulties interacting with peers?</td>
<td>SOC</td>
<td>94.6</td>
<td>5.4</td>
<td>10</td>
<td>95.4</td>
<td>4.6</td>
<td>10</td>
<td>95.7</td>
</tr>
<tr>
<td>Does he/she like to repeat words and expressions or does he/she use words in a way other people find strange?</td>
<td>LANG</td>
<td>95.9</td>
<td>4.1</td>
<td>11</td>
<td>96.5</td>
<td>3.5</td>
<td>11</td>
<td>96.7</td>
</tr>
<tr>
<td>Has he/she ever engaged in strange hand movements or walking high on tiptoe when he/she was happy or upset?</td>
<td>FLEX</td>
<td>96.5</td>
<td>3.5</td>
<td>12</td>
<td>97.0</td>
<td>3.0</td>
<td>12</td>
<td>97.1</td>
</tr>
<tr>
<td>Has he/she difficulties with pretend play or does he/she imitate considerably less than other children?</td>
<td>LANG</td>
<td>96.7</td>
<td>3.3</td>
<td>13</td>
<td>97.4</td>
<td>2.6</td>
<td>13</td>
<td>97.5</td>
</tr>
<tr>
<td>Does he/she get absorbed by routines in such a way as to produce problems for himself or for other?</td>
<td>FLEX</td>
<td>96.8</td>
<td>3.2</td>
<td>14</td>
<td>97.5</td>
<td>2.5</td>
<td>14</td>
<td>97.6</td>
</tr>
<tr>
<td>Does he/she have difficulties participating in discussions with others?</td>
<td>LANG</td>
<td>97.3</td>
<td>2.7</td>
<td>15</td>
<td>98.1</td>
<td>1.9</td>
<td>15</td>
<td>98.3</td>
</tr>
<tr>
<td>Is he/she uninterested in sharing joy, interests, and activities with others?</td>
<td>SOC</td>
<td>98.1</td>
<td>1.9</td>
<td>16</td>
<td>98.7</td>
<td>1.4</td>
<td>16</td>
<td>98.7</td>
</tr>
<tr>
<td>Does he/she have difficulties expressing emotions and reactions with facial gestures, prosody, or body language?</td>
<td>SOC</td>
<td>98.3</td>
<td>1.7</td>
<td>17</td>
<td>98.9</td>
<td>1.1</td>
<td>17</td>
<td>99.0</td>
</tr>
</tbody>
</table>
## Results

### Table 12. Cumulative distribution of ALTs in boys

<table>
<thead>
<tr>
<th>A-TAC module</th>
<th>Max score</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
<th>2.5</th>
<th>3.0</th>
<th>3.5</th>
<th>4.0</th>
<th>4.5-5</th>
<th>5.5-6</th>
<th>6.5-7</th>
<th>7.5-8</th>
<th>8.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD combined</td>
<td>17</td>
<td>48.5</td>
<td>65.9</td>
<td>77.7</td>
<td>84.2</td>
<td>88.7</td>
<td>91.3</td>
<td>94.5</td>
<td>95.3</td>
<td>96.0</td>
<td>96.6</td>
<td>97.4</td>
<td>98.2</td>
<td>98.6</td>
<td>100</td>
</tr>
<tr>
<td>Language</td>
<td>6</td>
<td>72.5</td>
<td>85.1</td>
<td>92.9</td>
<td>95.8</td>
<td>97.4</td>
<td>98.2</td>
<td>98.9</td>
<td>99.3</td>
<td>99.6</td>
<td>99.9</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social interaction</td>
<td>6</td>
<td>69.3</td>
<td>86.9</td>
<td>93.4</td>
<td>95.7</td>
<td>97.2</td>
<td>98.0</td>
<td>98.6</td>
<td>99.1</td>
<td>99.5</td>
<td>99.9</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexibility</td>
<td>5</td>
<td>71.7</td>
<td>84.9</td>
<td>92.4</td>
<td>95.2</td>
<td>97.2</td>
<td>98.1</td>
<td>98.9</td>
<td>99.2</td>
<td>99.6</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 13. Cumulative distribution of ALTs in girls

<table>
<thead>
<tr>
<th>A-TAC module</th>
<th>Max score</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
<th>2.5</th>
<th>3.0</th>
<th>3.5</th>
<th>4.0</th>
<th>4.5-5</th>
<th>5.5-6</th>
<th>6.5-7</th>
<th>7.5-8</th>
<th>8.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD combined</td>
<td>17</td>
<td>59.3</td>
<td>76.3</td>
<td>86.1</td>
<td>90.7</td>
<td>93.9</td>
<td>95.4</td>
<td>96.6</td>
<td>97.6</td>
<td>98.1</td>
<td>98.4</td>
<td>99.0</td>
<td>99.3</td>
<td>99.5</td>
<td>100</td>
</tr>
<tr>
<td>Language</td>
<td>6</td>
<td>78.9</td>
<td>90.8</td>
<td>96.3</td>
<td>98.0</td>
<td>99.0</td>
<td>99.2</td>
<td>99.5</td>
<td>99.6</td>
<td>99.8</td>
<td>99.9</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social interaction</td>
<td>6</td>
<td>75.9</td>
<td>91.5</td>
<td>96.2</td>
<td>97.7</td>
<td>97.7</td>
<td>99.0</td>
<td>99.4</td>
<td>99.6</td>
<td>99.8</td>
<td>99.9</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexibility</td>
<td>5</td>
<td>82.0</td>
<td>92.0</td>
<td>96.4</td>
<td>98.0</td>
<td>98.9</td>
<td>99.3</td>
<td>99.6</td>
<td>99.7</td>
<td>99.9</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results

**Paper II: Relationships between ALTs and other mental problems**

Paper II aims to describe relationships between ALTs and other mental problems, including possible shared etiological genetic and/or environmental effects.

Logistic regression models were used to calculate the risk for AD/HD, anxiety, conduct problems, depression, and substance abuse across increasing levels of ALTs in both the CATSS-11k and the STAGE. The risk for concomitant mental health problems increased monotonically by severity of ALTs (i.e. consistently increasing step by step, with a larger relative risk increase by each step of ALTs). These relationships remained strong after adjusting for zygosity, SES, learning disabilities, and age (Table 14).

Genetic influences were important for all traits related to other mental disorders (Table 15) albeit more modest in STAGE, where non-shared environmental effects (i.e. environmental effects making the twins less similar) were more pronounced. No shared environmental effects (i.e. effects making the twins more similar) could be discerned in CATSS or STAGE.

The phenotypic correlation (i.e. the degree to which two traits co-vary in the population) between ALTs and AD/HD traits was 0.52 in CATSS and 0.46 in STAGE (Figure 3), meaning that about half of the variation for ALTs is due to etiological factors *common* with AD/HD traits, i.e. these etiological (genetic or environmental) factors influence both ALTs and AD/HD traits. Of these correlations, 71% in CATSS and 46% in STAGE were accounted for by genetic effects influencing both conditions. The phenotypic correlations between ALTs and anxiety traits were more modest both in CATSS and STAGE, while common genetic effects again accounted for 92% and 55% of the correlation. For ALTs and depressive traits, roughly half of the correlation was accounted for by common non-shared environmental effects. Sixty-eight percent of the correlation between ALTs and substance abuse was accounted for by common genetic effects, as was 81% of the correlation between ALTs and conduct problems. The model fitting estimates and full statistics are given in the Appendix I and II.
Table 14. The adjusted odds ratios between number of ALTs and the risk for concomitant psychopathology

<table>
<thead>
<tr>
<th>CATSS-11k</th>
<th>STAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD/HD</td>
<td>Anxiety</td>
</tr>
<tr>
<td>N</td>
<td>10 760</td>
</tr>
<tr>
<td>ASD</td>
<td>99.7 (62.1-160.1)</td>
</tr>
<tr>
<td>ALT5</td>
<td>40.6 (23.7-69.6)</td>
</tr>
<tr>
<td>ALT4</td>
<td>25.4 (16.8-38.4)</td>
</tr>
<tr>
<td>ALT3</td>
<td>8.3 (5.8-12.0)</td>
</tr>
<tr>
<td>ALT2</td>
<td>4.4 (3.3-5.8)</td>
</tr>
<tr>
<td>ALT1*</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Reference category

Table 15. Estimates of genetic and environmental effects for ALTs and mental health problems

<table>
<thead>
<tr>
<th>CATSS-11k</th>
<th>STAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALTs</td>
<td>AD/HD</td>
</tr>
<tr>
<td>A</td>
<td>0.70 (0.66-0.73)</td>
</tr>
<tr>
<td>C</td>
<td>0.00 (0.00-0.03)</td>
</tr>
<tr>
<td>E</td>
<td>0.30 (0.27-0.33)</td>
</tr>
</tbody>
</table>
**Results**

**Figure 3.** Phenotypical correlation between ALTs and AD/HD traits, anxiety traits, depressive traits, conduct problems, and substance abuse

![Phenotypic correlation with ALTs](image.png)

* Unique environmental factors that are *common* to both ALTs and other problem types
** Genetic factors that are *common* to both ALTs and other problem types

**Additional data from the analyses for Paper II**

The distribution of ALTs in STAGE is presented here in order to serve as an adult comparison to the distribution of ALTs in CATSS.

Of all 16,695 adult individuals who responded to the self-rate questionnaire in STAGE, 86.3% reported at least some kind of ALT measured in a lifetime perspective (Table 16). The distribution between the three domains was somewhat similar. Items in the language dimension, however, were the least common, while about half of the population reported one social interaction and flexibility criterion, at least “to some extent”, during a phase in their life.
Table 16. The cumulative distribution of ALTs among adults in STAGE

<table>
<thead>
<tr>
<th>DSM-IV criteria</th>
<th>Max Score</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
<th>2.5</th>
<th>3.0</th>
<th>3.5</th>
<th>4.0</th>
<th>4.5-5</th>
<th>5.5-6</th>
<th>6.5-7</th>
<th>7.5-8</th>
<th>≥8.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD combined</td>
<td>12</td>
<td>14.7</td>
<td>28.9</td>
<td>47.3</td>
<td>61.8</td>
<td>74.3</td>
<td>82.7</td>
<td>89.4</td>
<td>92.9</td>
<td>95.8</td>
<td>98.2</td>
<td>99.3</td>
<td>99.7</td>
<td>99.9</td>
<td>100</td>
</tr>
<tr>
<td>Language</td>
<td>4</td>
<td>48.8</td>
<td>76.3</td>
<td>92.3</td>
<td>96.8</td>
<td>98.9</td>
<td>99.6</td>
<td>99.9</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social interaction</td>
<td>4</td>
<td>46.4</td>
<td>64.6</td>
<td>87.9</td>
<td>95.9</td>
<td>98.6</td>
<td>99.5</td>
<td>99.9</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexibility</td>
<td>4</td>
<td>39.5</td>
<td>64.2</td>
<td>83.3</td>
<td>92.4</td>
<td>97.2</td>
<td>98.7</td>
<td>99.6</td>
<td>99.9</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results

Paper III: Risk factors for ASDs and ALTs

Paper III aims to clarify whether ALTs are also influenced by a known risk factor for ASDs, i.e. increasing paternal age.

To explore the previously known risk factor for ASDs, increasing paternal age, in relation to ALTs in two cohorts (CATSS-11k and TEDS), logistic regression modeling was used to calculate the effect of paternal age on the risk for ASDs in the offspring. Odds ratios adjusted for maternal age, zygosity, SES, and, in the Swedish cohort, birth weight, are provided in Table 17. An U-shaped relationship could be discerned (i.e. offspring of both younger and older fathers showed elevated rates of ASDs) in both cohorts. But only the highest paternal age group in the Swedish cohort showed a statistically significant risk increase. The overlapping CIs warrant caution when interpreting the results.

Table 17. Association between paternal age and ASDs

<table>
<thead>
<tr>
<th>Paternal Age Group, years</th>
<th>Non-ASD cohort</th>
<th>ASD cases</th>
<th>Risk</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CATSS-11k</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>467</td>
<td>15</td>
<td>32:1000</td>
<td>1.93 (0.87-4.30)</td>
<td>0.105</td>
</tr>
<tr>
<td>25-34*</td>
<td>6235</td>
<td>80</td>
<td>12:1000</td>
<td>1.00</td>
<td>---</td>
</tr>
<tr>
<td>35-44</td>
<td>3690</td>
<td>56</td>
<td>15:1000</td>
<td>1.21 (0.79-1.85)</td>
<td>0.380</td>
</tr>
<tr>
<td>45-50</td>
<td>358</td>
<td>9</td>
<td>25:1000</td>
<td>1.90 (0.73-4.92)</td>
<td>0.185</td>
</tr>
<tr>
<td>≥51</td>
<td>108</td>
<td>4</td>
<td>37:1000</td>
<td>3.37 (1.02-11.14)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

| TEDS                     |                |           |      |                      |         |
| <25                      | 467            | 6         | 13:1000 | 1.91 (0.88-4.17)     | 0.101   |
| 25-34*                   | 6577           | 38        | 6:1000  | 1.00                 | ---     |
| 35-44                    | 3968           | 17        | 4:1000  | 0.81 (0.41-1.58)     | 0.547   |
| 45-50                    | 376            | 3         | 8:1000  | 1.66 (0.47-5.82)     | 0.425   |
| ≥51                      | 104            | 2         | 19:1000 | 3.59 (0.37-34.46)    | 0.26    |

*Reference category

An U-shaped association was observed between paternal age categories and ALT scores in both the CATSS-11k and TEDS cohorts when all individuals meeting a research diagnosis for an ASD was removed (Figure 4a). This was supported by statistically significant quadratic associations (p-values<0.003). Specifically, offspring of old (≥51) and young (<25) fathers had significantly higher ALT scores compared with offspring of fathers aged 25-34. Similar U-shaped associations were observed for the social, communication, and non-social, stereotyped and repetitive behavioral domains in the
Swedish cohort (Figures 4b-d), and for the communication and non-social stereotypes and repetitive behavioral domains in the UK cohort (Figures 4c-d).
Results

Figures 4a-d. Association between paternal age and ALTs

Figure 4a.

Autism spectrum scores

Figure 4b.

Social scores

Adjusted for maternal age, zygosity and SES.

Non-linear (Quadratic) test

Sweden $F = 8.75$ $p = 0.00031$

UK $F = 9.48$ $p = 0.0021$

Sweden $F = 5.02$ $p = 0.0251$

UK $F = 10.6$ $p = 0.3106$

* significant at alpha level 0.05

**significant at alpha level 0.01

†=reference category
Results

Figure 4c.

Communication scores

![Graph for Communication scores](chart_4c)

- Adjusted for maternal age, zygosity and SES
- *significant at alpha level 0.05
- **significant at alpha level 0.01

- Sweden F = 7.15 p = 0.0075
- UK F = 9.72 p = 0.0018

Figure 4d.

Stereotyped and repetitive scores

![Graph for Stereotyped and Repetitive scores](chart_4d)

- Adjusted for maternal age, zygosity and SES
- *significant at alpha level 0.05
- **significant at alpha level 0.01

- Sweden F = 3.08 p = 0.0795
- UK F = 4.74 p = 0.0295
Results

Paper IV: Etiological demarcation between ALTs and ASDs

The final paper in this thesis aims to explore if any demarcation could be discerned between ALTs and ASDs or, consequently, if ASDs could be viewed as the extreme end of a continuum of ALTs.

The genetic and environmental effects for the ALTs and the three cut-offs used in Paper IV (corresponding to the 10th percentile of the diminishing ALTs in the population, being screen-positive for ASDs and meeting research criteria for an ASD, respectively) are shown in Table 18. For the continuous scale, 70% of the phenotypical variation could be explained by genes and 30% by unique environmental factors. For the three cut-offs, the corresponding figures were 54%, 87%, and 72%. Since the CIs largely overlapped, no significant differences with respect to heritability could be discerned over the three cut-offs. Similarly, the unique environmental contributions were largely overlapping (Table 19).

The standardized co-twin mean (which basically can be interpreted as a correlation coefficient between a twin with ASD and the ALT score in his/her co-twin since the standardized population mean is 0, and the proband mean is 1) indicates if ASDs can be best viewed as a continuum of ALTs or as a discrete category. That is, if the co-twin mean is the same as the population mean (0), there is no evidence for a continuum. On the other hand, if the co-twin mean is larger than the population mean then commonalities between ASDs and ALTs are indicated. The co-twin mean for MZ twins with the high cut-off was 0.58, whereas this correlation for DZ twins was 0.24. For the low cut-off, the corresponding figures were 0.66 and 0.21. The extreme-group correlations were consistently higher for boys (Table 19).
### Results

**Table 18.** Estimates of genetic and environmental effects for ALTs and ASDs

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Boys</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>C</td>
</tr>
<tr>
<td><strong>Continuous outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.70</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>(0.68-0.72)</td>
<td>(0.00-0.01)</td>
</tr>
<tr>
<td><strong>Dichotomous outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High cut-off</td>
<td>0.54</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>(0.04-0.92)</td>
<td>(0.00-0.69)</td>
</tr>
<tr>
<td>Low cut-off</td>
<td>0.87</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>(0.68-0.92)</td>
<td>(0.00-0.16)</td>
</tr>
<tr>
<td>10th percentile</td>
<td>0.72</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>(0.52-0.83)</td>
<td>(0.00-0.22)</td>
</tr>
</tbody>
</table>
**Results**

**Table 19. Extreme-group correlations**

<table>
<thead>
<tr>
<th>Extreme group correlations (number of probands)</th>
<th>MZ</th>
<th>DZ</th>
<th>MZ-boys</th>
<th>DZ-boys</th>
</tr>
</thead>
<tbody>
<tr>
<td>High cut-off</td>
<td>0.58 (36)</td>
<td>0.24 (52)</td>
<td>0.66 (30)</td>
<td>0.22 (42)</td>
</tr>
<tr>
<td>Low cut-off</td>
<td>0.66 (103)</td>
<td>0.21 (212)</td>
<td>0.71 (79)</td>
<td>0.19 (150)</td>
</tr>
<tr>
<td>10th percentile</td>
<td>0.63 (331)</td>
<td>0.29 (570)</td>
<td>0.72 (216)</td>
<td>0.18 (369)</td>
</tr>
</tbody>
</table>

In a last step, we calculated to what extent the correlations were affected by genetic and environmental factors. We used the DeFries-Fulker method to estimate the importance of genetic (group heritability) and environmental effects. When the MZ group correlation is more than twice as high as the DZ correlation, the DF-estimates should be restricted to the extreme group correlation. Fifty-eight percent of the correlation between the full variation of ALTs and ASDs (as measured by the high cut-off) was accounted for by genetic effects, and similar, even higher, estimates were found for the low cut-off and the cut-off on the 10th percentile (Table 20). Again, the estimates were higher for boys. No demarcation between ALTs and ASDs could be discerned in these analyses (since both the estimates and CIs were similar), which indicates that ASDs, indeed, is an extreme end of a continuum of ALTs.

**Table 20. Extreme analyses for three cut-offs**

<table>
<thead>
<tr>
<th>DeFries-Fulker group estimates (95% CI)</th>
<th>All (95% CIs)</th>
<th>Boys (95% CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A (95% CIs)</td>
<td>C (95% CIs)</td>
</tr>
<tr>
<td>High cut-off</td>
<td>0.58 (0.42-0.74)</td>
<td>0.00 (- )</td>
</tr>
<tr>
<td>Low cut-off</td>
<td>0.66 (0.56-0.77)</td>
<td>0.00 (- )</td>
</tr>
<tr>
<td>10th percentile</td>
<td>0.63 (0.55-0.71)</td>
<td>0.00 (- )</td>
</tr>
</tbody>
</table>
Summary of findings

1. ALTs are **dimensionally distributed** in the population. Forty-six percent of all participants in the CATSS study had at least one ALT, at least “to some extent” (51% of the boys and 42% of the girls). Ten percent had at least two ALTs. Low-grade ALTs were more common among adults. The three problem domains proposed to constitute the ASDs contributed about equally to the ALTs as to the ASDs. (Paper I and II)

2. The interindividual variation in ALTs is due partly to **genetic effects**, partly to **unique environmental effects**. The overall estimate of heritability for ALTs in the population was 68%, about equally distributed across the ASD triad: 62% for language problems, 55% for social interaction difficulties, and 63% for stereotyped and repetitive behaviors. The heritability estimates for all types of ALTs were consistently higher among boys than girls. (Paper I)

3. ALTs are **relevant for mental health**. Increasing levels of ALTs carry **increased risks** for AD/HD, anxiety disorder, and conduct problems in childhood, and for AD/HD, anxiety disorders, depression, and substance abuse in adulthood. Not only do ALTs converge with these conditions, but **common genetic and environmental background factors** explained between 18% and 52% of the variance. Overall, the co-occurrence of ALTs with other mental health problems and the role of genetic factors behind this were stronger in childhood than in adulthood, while environmental factors were stronger in adulthood. (Paper II)

4. ALTs are influenced by **increasing paternal age**, which is a known risk factor for ASDs. (Paper III)

5. The standardized co-twin mean (which basically can be interpreted as a correlation coefficient) of ALTs in the co-twin of a twin with ASD (defined by two clinical cut-offs, one with high specificity and one with high sensitivity, and one epidemiological cut-off encompassing the 10th percentile of the normal population) were consistently high and predominantly influenced by **genetic factors common to broader and narrow definitions of ASDs**. (Paper IV)
Comments to main findings

Main finding 1 - distribution

**Dimensional distribution**

The studies presented here clearly show that that the distribution of ALTs in the general population is dimensional and continuous with a narrow group consisting of subjects meeting criteria for a research diagnosis of an ASD. These results are in line with those from a total population cohort of 7- and 8-year-olds, where ALTs were present in more than 50% of the cohort\(^\text{172}\), and with the conceptualization of ASD-related traits as dimensions rather than categories proposed by other research groups\(^\text{173}\). In the adult cohort, a noticeably larger proportion of individuals reported one or two ALTs, a finding that is unparalleled since no previous study has investigated ALTs in a general adult population. By just increasing the cut off by one point, the population prevalence of ‘research ASDs’ remained at about 1%, and the highest ALT scores were about as rare in adults as in children. The results should be interpreted in light of the limitations described below, especially concerning the psychometric properties of the methods used. In addition, for both studies, two caveats are warranted. First, this is a phenotypic description of ALTs and must not be simply equated with an etiological path leading to ASDs. Just as for the ASDs, etiological heterogeneity must be the natural assumption for ALTs. Furthermore, it is reasonable to assume that ALTs may be affected by phenomena acting differently in different parts of the distribution. That is, phenomena associated with ALTs may manifest themselves differently in the 5\(^{th}\) percentile of ALTs than in the 30\(^{th}\) percentile. Second, the A-TAC has been developed to capture the autism spectrum disorders, not very narrow, ‘classic autism’ (that includes an abnormal early development and aims to identify a ‘pure, narrow and clearly delineated’ condition). ASD screening may not automatically translate into clinical diagnoses of ASDs, since it is reasonable to assume that groups with ASDs derived systematically from the population are more heterogenous than clinical cases collected in a clinical setting. It is, on the other hand, not obvious which one of these recruitment methods that would provide the most representative, ‘correct’, or valuable study group (or assessments) for scientific studies.

The distribution of ALTs do indeed match a hypothetical distribution of problems arising in the lower-most end of normally distributed abilities for social interaction,

\(^{172}\) Posserud et al. 2006  
\(^{173}\) Constantino & Todd 2003, Happé & Ronald 2008
communication, and behavioral flexibility\textsuperscript{174}. It is, however, still unclear what the other end of such a distribution would represent. Is the opposite of ASDs and ALTs just the absence of autism and ALTs, or is there a corresponding extreme end of well developed abilities (with specific genetic effects), which would be manifested as some sort of hyper-sociability? Personality models have generally included a higher-order trait depicting social relatedness, empathy, and communicability. Considering their prevalence and strong genetic effects, it seems obvious that the ALTs-ASDs exert a strong influence on personality traits related to social relations and communication in the population at large.

\textbf{Gender ratios}

The results of the present studies are consistent with all previous studies that have compared prevalences of ASDs and ALTs between genders in showing higher prevalences for boys\textsuperscript{175}. Even if ALTs in girls are more frequently overlooked, and ASDs are detected later in girls than in boys, it would be rash to refute a true over-representation of ASDs and ALTs among boys as compared to girls\textsuperscript{176}. Still, although boys consistently show higher scores of ALTs and higher prevalences of ASDs, it is probable that gender differences get more pronounced at the extreme end of the ALT-ASD continuum. For instance, in our study there were three boys who met ASD criteria for each girl while the ratio between boys and girls who display one to two ALTs is only 1.3:1 (22.3\% vs 17.3\%). The gender ratio of ALTs thus seems to increase with severity, for mostly unknown reasons (besides the obvious X-linked condition that predominantly affects males). Studies on ASDs in connection with severe learning disabilities, however, have found a less of a gender skew among subjects with delayed general cognitive development, meaning that the most extreme gender skew probably is in the less severe end of the ALT-ASD continuum\textsuperscript{177}. It may be concluded that ALTs are more common in males than in females, but that this difference is much smaller in the general population than in clinical studies.

\textbf{The triad}

The three dimensions of ALTs (corresponding to the triad of restrictions described as characteristic for the ASDs) were about evenly distributed in the population (24\% for language deficits, 24\% for social interaction problems, and 23\% for stereotyped and

\textsuperscript{174} Gillberg 1992
\textsuperscript{175} Gillberg 1995, Kopp 2010, Posserud et al. 2006, Ronald et al. 2008b
\textsuperscript{176} Giarelli et al. 2010, Kopp 2010
\textsuperscript{177} Gillberg 1995
repetitive behaviors). The individual items in each dimension were not, however, evenly distributed. The social dimension, for example, included both the most common item and the two least common ones. The two least common items – “Is he/she uninterested in sharing joy, interests, and activities with others?” and “Does he/she have difficulties expressing emotions and reactions with facial gestures, prosody, or body language?” – are classic ‘core’ features of ASD, but when individuals meeting criteria for ASDs and/or learning disabilities were excluded from the analyses, more than 1% of the population still affirmed these items. Moreover, the prevalence ranking of the 17 different items used to identify ASDs did not differ when individuals with ASDs and/or mental retardation were excluded, indicating that no item was ASD-specific or ASD-weighted as compared to ALTs.

**Main finding 2 - heritability**

**Heritability estimates**

The heritability estimates reported in Paper I for ALTs (68%) are similar to those reported by other research groups using large samples; 76% and 74% . Higher heritability estimates were found for boys (72%) than for girls (59%), which is consistent with other reports showing higher heritability estimates for boys than for girls . It is unclear, however, if there are qualitative differences in ALTs by gender. So far, twin studies have come up with mixed results when looking for sex-specific effects via model-fitting approaches, and the question remains whether the difference between boys and girls reflects a quantitative (different extent of genetic and environmental influences) instead of a qualitative (different genetic or environmental influences) difference.

In Paper IV, the heritability estimate (87%) for the group identified by the screening cut-off for ASDs is in line with the few studies that have actually reported heritability estimates (at 91%) for clinically diagnosed ASDs (or subtypes). The earliest twin studies did not report heritability estimates but concordance rates (i.e. a measure of the presence of ASDs in both twins based on zygosity) which makes comparisons difficult. Nevertheless, the estimate that 87% of the liability for ASDs is explained by genetic factors does not seem at odds with these studies.

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178 Gillberg 1995
179 Ronald et al. 2005, Skuse et al. 2005
180 Constantino & Todd 2005
181 Hallett et al. 2010, Hoekstra et al. 2007a
182 Bailey et al. 1995
183 Folstein & Rutter 1977, Steffenburg et al. 1989
The triad
The heritability estimates for the triad dimensions (63% for language deficits, 51% for social interaction problems, and 59% for stereotyped and repetitive behaviors) were fairly similar, albeit somewhat lower for the social interaction dimension. These results are comparable to those presented by Angelica Ronald and colleagues who studied 'social' (76%) and 'non-social' behaviors (62%) and in a later study examined the triad construct in extreme ends of the population\textsuperscript{184}. Although the heritability estimates are similar for the triad of restrictions in the general population, this should not be taken as an argument for the idea that the \textit{same} genetic factors operate across the triad. On the contrary, general population studies have in fact found quite small phenotypic (symptomatic) and genetic overlaps between the triad dimensions, suggesting that ALTs in the general population are genetically heterogenous\textsuperscript{185}.

Age effects
The differences between the heritability estimates in children and adults for ALTs (70% and 32%) anxiety (66% and 14%) (Paper II), and for the phenotypic correlations between the ALTs and AD/HD (37% vs 21%), and between ALTs and anxiety (33% vs 10%) may reflect age-related effects decreasing the role of hereditary factors for phenotypical expressions during the life-span. For instance, stressful life events have been shown to increase the risk for anxiety disorders, which would deflate the heritability estimate and thus increase the contribution of the unique environment\textsuperscript{186}. Supporting the notion that there really is a difference between the importance of hereditary factors for phenotypic expressions in childhood vs adulthood, the heritability of AD/HD has previously been found to be substantially lower in adult age than in childhood, implying that unique environmental influences acting in concert with the genotype gradually become more important for the phenotypic expression during life\textsuperscript{187}. Conversely, the proportion of unique environmental factors operating across ALTs and AD/HD traits, and between ALTs and anxiety traits, were also higher in adults compared to children. On a speculative note, it may also be argued that children experience a more homogenous environment, where genetics play a larger role, while adults are exposed to more versatile environments, where environmental factors, affecting both ALTs and AD/HD traits and anxiety traits, are more important. To resolve this question,

\textsuperscript{184} Ronald et al. 2005, Ronald et al. 2006b
\textsuperscript{185} Ronald et al. 2006a
\textsuperscript{186} Blazer et al. 1987
\textsuperscript{187} Boomsma et al. 2010
longitudinal studies that include the same measures at each follow-up wave should be collected.

**Main finding 3 – co-existence**

*Overlap*

In Paper I, Table 6, the overlaps between different problem types are given. More often than not, children with ASDs also have other mental health problems. The specific risk estimates for other types of problems were assessed by increasing ALTs and compared between children and adults, showing a consistent pattern of increased risk by each level of ALTs. That is, the risk for AD/HD, anxiety, depression, conduct problems, and substance abuse increased monotonically with the increasing number of ALTs. Even the group with only one or two ALTs had considerably increased risks for all other types of mental health problems as compared to the majority of individuals without any such traits. It has been suggested that sub-threshold ALTs might entail cognitive features useful for careers in, for instance, science or engineering. The results presented here do not contradict such possible advantages but demonstrate that the other side of the coin is that the ALTs carry an increased risk of a number of mental health problems. It is thus important to identify and address ALTs as an indicator of mental health problems, not only in patients but also in ‘sub-threshold’ relatives of persons with ASDs. The precise mechanisms of the interaction between ALTs and other forms of psychopathology call for future studies that will also investigate if there are similar ‘broader phenotype’ interactions in relatives. The finding that genetic influences behind ALTs are also implicated in the pathogenesis of other mental health problems supports this notion. In addition, the presence of ALTs in subgroups of individuals with various forms of psychopathology may influence the response to pharmacological or psychotherapeutic interventions, as shown, for example, in anorexia nervosa, where the presence of ALTs was associated with a poorer psychosocial outcome.

The results are thus consistent with those in previous types of clinical studies showing high levels of ‘co-existence’ between ASDs and other types of mental health problems. It may be argued that the co-existence of clinical diagnoses is due to the fact that the contemporary nosological systems include an ever-increasing number of diagnoses but not sufficiently exclusive diagnostic schemes to demarcate between different types of natural categories. On the other hand, there is no empirical evidence to support that

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188 Baron-Cohen et al. 2001, Focquaert et al. 2007
189 Wentz et al. 2009
there actually is such a category as ‘pure’ or ‘true’ autism (or any other neurodevelopmental condition). A notion of a clearly demarcated condition would have to be supported by the classic validity criteria formulated by Eli Robins and Samuel Guze, requiring clear distinctions between disorder and normality, between one disorder and other types of disorders, and homogeneity in etiology, family aggregation, and long-term prognosis. As the studies presented here show, there is every reason to assume that none of these criteria (except possibly the issue of longitudinal progression) apply to ASDs as compared to ALTs or other mental health problems. Therefore, it seems reasonable to consider hierarchies of mutually excluding, categorical diagnoses as conflicting with scientific evidence. This has important clinical implications as it speaks against the development of sub-specialized services targeting specific mental health problems and, instead, calls for a mental health service that incorporates several medical professions to assess and treat neurodevelopmental and mental problems broadly.

**Common causes**

In Paper II, common underlying genetic and environmental susceptibilities behind ALTs and AD/HD-traits, anxiety traits, depressive traits, conduct problems, and substance abuse were demonstrated. The observed phenotypic correlation between ALTs and traits related to AD/HD and anxiety in children is in line with previous findings of about 0.54 for AD/HD and 0.26 for anxiety. Moreover, our results suggest a modest genetic overlap between ALTs and AD/HD, and between ALTs and anxiety among adults. Epidemiological studies have previously indicated such connections. The correlation between ALTs and symptoms of anxiety and depression in adulthood have not before been put to the test in a genetically sensitive design, and the finding that both conditions were related to ALTs (phenotypical correlations of 0.18 and 0.28, respectively) was not unexpected considering the well-known association between anxiety and depression. Conduct problems and ALTs have previously been linked in clinical studies and in twin studies. The phenotypical correlation between substance abuse and ALTs (0.28) is a
Comments to main findings

A novel finding that needs to be investigated further, but substance abuse and PDD NOS have been shown to co-exist in both clinical psychiatric and forensic settings\(^{198}\).

Taken together, the etiology of ALTs was only partially distinct from that behind AD/HD, anxiety, depression, conduct problems, and substance abuse. The scientific quest for causes behind mental health problems may thus have to be extended beyond categories and be open for the possibility that causes may not only be specifically linked to phenotypical expressions but also generally involved in the complex background to mental dysfunctions and suffering\(^{199}\).

Main finding 4 – paternal age

*Older fathers*

Young and old paternal ages were associated with an increased risk for both ASDs and ALTs. The notion of paternal age as a risk factor for ASDs and ALTs was derived from several studies showing advancing paternal age to increase the risk for schizophrenia and bipolar disorder\(^ {200}\). The explanations for the link between older fathers and increased risk for neurodevelopmental disorders include an increasing rate of de novo germline mutations across the reproductive life-course in men. The hypothesis is that the ongoing spermatogonial stem cell divisions in males result in higher mutation rates and abnormalities in the sperms of older men\(^ {201}\). In addition, age-related epigenetic dysfunctions affecting the male germline may be involved in the increased risk for ASDs and ALTs\(^ {202}\). It is also possible that the accumulated exposure to various environmental toxins over the life-course could result in germline alterations in older men. It is also plausible that problems or peculiarities in social style and perception of self and others (i.e. ALTs) in parents might delay reproduction, and that our findings might reflect a genetic familiarity (i.e. that parental traits are inherited by the offspring) rather than a phenomenon directly associated with increased paternal age. This has, however, been investigated in studies which indicate that ALTs in the parents do not account for the paternal age effect on ASDs\(^ {203}\).

\(^{196}\) Hofvander et al. 2011
\(^{199}\) Anckarsäter 2010
\(^{200}\) Byrne et al. 2003, Frans et al. 2008, Malaspina et al. 2001
\(^{201}\) Buwe et al. 2005, Crow 2000
\(^{202}\) Flanagan et al. 2006
\(^{203}\) Hultman et al. 2010, Puleo et al. 2008
Comments to main findings

Younger fathers
The finding that also younger fathers displayed an increased risk for ASDs was not expected, but Chen and colleagues showed that infants fathered by men younger than 20 years of age had an increased risk of pre-term birth, which may be relevant given the suggested links between pre- and perinatal complications and the risk of developing ASDs\textsuperscript{204}. In addition, young men are more likely to be exposed to certain types of lifestyle risk factors (e.g. drug abuse) that have been linked to de novo mutations in the germline and overall to decreased sperm quality\textsuperscript{205}. Alternatively, the susceptibility for neurodevelopmental disorders might be larger in the offspring of younger parents, who might not form a random sample. That is, in a society where early parenthood is relatively uncommon, younger parents may have elevated rates of psychiatric problems (i.e. AD/HD, ALTs, or social peculiarities). This may gives rise to the possibility of passive gene–environment correlations, where the parental personality influences the early reproduction but also passes on the genetic components for neurodevelopmental disorders.

Main finding 5 – extreme analyses

The connection between ASDs and ALTs
Finally, in Paper IV, the question of whether ALTs share a common etiology with ASDs or whether ALTs are etiologically distinct (i.e. whether they are truly ‘autistic’ or just phenotypically ‘autistic-like’) was empirically addressed. The standardized co-twin mean (which basically can be interpreted as a correlation coefficient between a twin with ASD and the ALT score in the co-twin) indicates if ASDs may be viewed as a continuum of ALTs or as a discrete category. That is, if the co-twin mean is the same as the population mean (0), then there is no evidence for a continuum. On the other hand, if the co-twin mean is larger than zero, then commonalities between ASDs and ALTs are indicated. The mean ALT score in co-twins of children meeting the high ASD cut-off (corresponding to research diagnoses of ASDs) was 0.58 for MZ co-twins and 0.24 for DZ co-twins. In co-twins of children meeting the lower screening cut-off, the corresponding figures were 0.66 and 0.21, and in co-twins of children at the 10\textsuperscript{th} percentile of ALTs in the population, 0.63 and 0.29. Boys had consistently higher extreme-group correlations. The similar co-twin correlations indicated no etiological differences between the three cut-offs. Furthermore, this continuum or ‘link’ was predominantly affected by genes (58\% and 66\% for the clinically validated cut-offs), indicating that genetic factors

\textsuperscript{204} Chen et al. 2008, Hultman et al. 2002
\textsuperscript{205} Robbins et al. 2005
operating behind ASDs also are implicated in the full variation of ALTs. These findings are in line with the quantitative trait locus theory, hypothesizing that many genes, each with a small effect size, influence the whole phenotypic variation\textsuperscript{206}. That is, a phenotypical expression (in this case ASDs) is affected by several genes that also influence quantitatively different phenotypical expressions (i.e. ALTs) but to a lesser extent. The results again question a distinct boundary between pathology and normality and have implications for future versions of diagnostic classification systems. Taken together, the results in Paper IV show that ASDs and ALTs are etiologically linked. This implies that, in addition to research strategies aiming to identify specific, rare causes of autism present in small numbers of affected individuals (such as the different forms of ‘syndromic autism’ reviewed by Catalina Betancur, which, however, seem to be unspecific in relation to mental retardation and general cognitive impairment), genetic research should mainly consider the broad phenotype of socio-communicative dysfunctions in the general population in the search for specific genetic mechanisms behind the ASDs\textsuperscript{207}. It is important to point out that the studies presented here do not allow us to consider subtypes of autism related to specific etiologies, such as intrauterine exposure to environmental toxins (like thalidomide and valproate). There is, however, so far no empirical data to delineate such specific etiologies in subgroups of ASDs from cases due to tail-end ‘exaggerations’ of ALTs.

\textsuperscript{206} Plomin et al. 2008
\textsuperscript{207} Betancur 2011


Comments to main findings

Limitations

Representativeness
It has been suggested that the ASDs are over-represented among twin pairs since the twinning process in itself might be a risk factor for neurodevelopmental disorders, whereby the generalization of twin studies would be limited\textsuperscript{208}. Large epidemiological studies have, however, found no or slight increases in the risk for ASDs among twins and ascribe such potential over-representation to ascertainment biases\textsuperscript{209}. The results from the only study that has investigated if ALTs are over-represented among twins compared to non-twins indicated that male twins do indeed show higher degrees of ALTs than male non-twins on the SRS (no significant differences could be detected between female twins and female non-twins)\textsuperscript{210}. Nevertheless, these results need to be corroborated by other studies that account for age, IQ, SES, and employ other instruments. As the ASD definitions include deviant development of language and communication, it would also seem obvious that having a twin might infer peculiarities, such as shared communicative strategies between the twins, that may play an important part in the development of social interaction and communication and eventually develop differently between MZ than between DZ twins. The results on the global ASD scale and the three other problem domains in the ASDs would hardly be dependent on such features to any considerable extent, however. If findings of increased ALTs among twins are replicated, it will be important to specify these in relation to specific problem areas, to possibly adjust diagnostic criteria to avoid including effects of being a twin among the criteria, and, finally, to review to what extent twin-specific effects might preclude generalizations of twin findings to the general population.

Source of data
The studies rely on different sources of data (parent vs self-ratings), but on no more than one source in each case. Parent, child, and teacher ratings show disagreement when examining the same phenomena in the same individual\textsuperscript{211}. The A-TAC relies solely on parental ratings, which have previously been reported to result in higher heritability than ratings by teachers and children do when examining ALTs\textsuperscript{212}. It would have been

\textsuperscript{208} Betancur et al. 2002, Greenberg et al. 2001
\textsuperscript{210} Ho et al. 2005
\textsuperscript{211} Becker et al. 2004, van der Ende & Verhulst 2005
\textsuperscript{212} Ronald et al. 2008b
optimal to collect data from multiple raters, but this has not been possible for economical and practical reasons.

**Lack of clinical neurodevelopmental diagnoses**
As ASDs are defined as developmental disorders, epidemiological studies without access to developmental clinical assessments are by definition sub-optimal. At the same time, it will probably remain unfeasible to conduct developmental assessments of rare conditions in population-based cohorts.

**Psychometric method problems**
ALTs were assessed by questionnaires validated to predict ASDs, which means that the probability of being assigned a clinical diagnosis of an ASD should increase by each scale step in the questionnaire, something that may not optimally capture ALTs since their exact nature is unknown to us, as is their varying severity, and thereby the best way to measure traits consisting of peculiarities or problems is uncertain. The scales used to measure ALTs are ordinal data, i.e. logically ordered categories describing an increased number of autism-related symptoms that carry an increased liability for autism and ASDs but do not satisfactorily reflect the degree of the examined traits or the severity of the problems they may cause. There is no broad consensus about how to define severity of ALTs or ASDs. Since the scale used for ASDs in adults is not validated at all, there is no data to support that it is reliable over time or even related to clinical diagnoses of ASDs in adults. However, it definitely has construct validity as it is based on established ASD criteria and follows the questions in the validated child instrument. Similar validation problems are, of course, implicated in all conditions addressed in this thesis. The cut-offs used for anxiety and depression have not been formally validated, but the prevalence estimates (4.5% for anxiety and 13.4% for depression) are compatible with previous estimates of the general population prevalence.  

A number of psychometric problems relate to the cut-off values used to categorize the study populations. It may well be argued that, based on the findings of this thesis, all such distinctions are arbitrary. Yet, categories are useful for various scientific and clinical purposes even if they do not represent natural boundaries. To meet the needs for categories, cut-offs based on validations against clinical diagnoses (A-TAC and CAST) or population distribution (STAGE) were used. The validated cut-offs have high sensitivity and specificity, but as the prevalence of ASDs is low, a considerable number of individuals positive for ASDs would not be diagnosed as such in a real-life clinical

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213 Doris et al. 1999, Tyrer & Baldwin 2006
assessment. Because an instrument that can distinguish individuals with ASDs from individuals without ASDs to 98%, and the prevalence, as for ASDs, is 1%, the margin of error in the sensitivity of the instrument will be 2% and with an actual base rate of 1%, half of those diagnosed with an ASD will be wrongly classified. Optimally, all those screen-positive cases should be clinically assessed. Nevertheless, there is no foolproof diagnostic system for ASDs, as even highly structured clinical instruments report less than perfect sensitivities and specificities, and discrepancies on the individual level will probably have to be accepted in scientific studies aiming to capture the interindividual variation in ALTs or liability for ASDs rather than individual characteristics in diagnosed cases\textsuperscript{214}. At the same time, caution is warranted whenever predictions based on systematic ratings with narrow CIs are applied to individual cases, as the CIs rapidly broaden by decreased numbers of subjects assessed, as far as to render predictions or associations more or less meaningless in individual cases\textsuperscript{215}.

**Measurement**

Measurement errors 'load' as environmental factors in standard ACE-models, in most cases as unique environment, but also as shared environment when there is one source of information for both twins, as in the child studies presented here. The differences in heredity estimates between children and adults may thus to some extent be artefactual and due to the different ways of data collection employed. There is also evidence that self-ratings of ALTs show lower heritability estimates than parental ratings\textsuperscript{216}.

\textsuperscript{214} De Bildt et al. 2009
\textsuperscript{215} Cooke & Michie 2010
\textsuperscript{216} Ronald et al. 2008b
Conclusions

This thesis shows a) that ALTs are dimensionally distributed, b) that ALTs are relevant for mental health, c) that both ASDs and ALTs are affected by paternal age, and, finally, d) that ALTs and ASDs are etiologically linked by genetic effects operating across ASDs and ALTs. Taken together, the findings presented in this thesis suggest that ASDs can be viewed as the extreme end of ALTs, and that ALTs are not merely ‘autistic-like’ but ‘shadow’ of ASDs in persons who have sub-threshold problems with social interaction, communication, and behavioral flexibility.

Future directions

Genetic and environmental factors are far from causal

Even if ASDs and ALTs are highly heritable, the actual genetic or environmental etiological factors behind ASDs, ALTs, and the other types of mental health problems associated with them, remain largely unidentified. It is also unclear if these factors are interdependent, i.e. do they interact and, if so, by what modes of interaction (e.g. additive, synthetic, epistatic), and what is the effect of this interaction? In addition, large-scale studies of the genome report several regions as implicated in the etiology of ASDs though they all have very modest effect sizes (i.e. the measure of strength between two variables)\textsuperscript{217}. For syndromic autism, a similar pattern emerges, for instance in Fragile X; the vast majority of individuals with ASDs do not have Fragile X, and most individuals with Fragile X do not have an ASD\textsuperscript{218}. The explanation values for proposed environmental factors are also low; four percent of cases of thalidomide embryopathy display an ASD, and the majority of children exposed to alcohol during gestation do not have an ASD\textsuperscript{219}.

This thesis shows that on the phenotypical level, the risk of having many types of mental problems sharply increases in the extreme end of ALTs (Paper II), while the genetic and environmental liability seems constant, at least from the most narrow definitions of ASDs to the 10\textsuperscript{th} percentile (Paper IV). In addition, at the absolute extreme end of the ASD-ALT continuum, the genes that broadly affect the full variation of problems may also be influenced by rare mutations entailing general cognitive impairment rather than ASDs specifically, as all the genes and loci are implicated also in learning disabilities\textsuperscript{220}.

\textsuperscript{217} Glessner et al. 2009, Pinto et al. 2010, Weiss 2009
\textsuperscript{218} Bailey et al. 1993, Turk 1992
\textsuperscript{219} Aronson et al. 1997, Strömland et al. 1994
\textsuperscript{220} Betancur 2011
On a speculative note it may be argued that ALTs in themselves are susceptibilities for other mental problems. That is, the presence of ALTs may lower a ‘threshold’ for other neurodevelopmental and mental problems to be expressed phenotypically, and that this threshold gets lower for each increase of ALTs. Neurophysiological correlates affecting both ALTs and ASDs should, reasonably, be involved in this process\(^\text{221}\), and the findings from the studies on the broader autism phenotype briefly reviewed in the introduction may provide anecdotal evidence for this notion. This may also be relevant for the transition of ALTs into full ASDs. As seen in Paper I, it is more common to have a total of three ALT points spread out across the triad than to have three points within the same domain. It may very well be that the presence of a problem in one of the domains in the triad also decreases the ‘threshold’ for problems in the two other domains. Such effects could partly explain the sharply increasing phenotypical problem load (at least when measured by the number of symptoms) in the extreme end of the distribution. It is also plausible that the genetic underpinnings for ALTs are a prerequisite or a facilitation for ASDs with learning disabilities, and that the general intellectual disability is caused by rare effects.

**ALTs provide a new approach to the genetic etiology of ASDs**

Taken together, the scientific evidence available today cannot single out one causal factor selectively responsible for an ASD (with the possible exception of herpes encephalitis, although it is doubtful if a viral infection affecting large parts of the central nervous system should be viewed as an ASD instead of as a condition artefactually diagnosed as an ASD by descriptive diagnostic criteria)\(^\text{222}\). It may be more fruitful for future research to focus on phenomena that in themselves are not sufficient to cause an ASD but may contribute to the susceptibility for ASDs. For instance, as described before, common genetic variants previously linked to ASDs have also been connected to communication deficits in the normal population (i.e. ALTs), and a specific mutation causing language impairment has been linked to ASDs\(^\text{223}\). This notion is further supported by the fact that the different domains of the triad are genetically heterogeneous in the general population\(^\text{224}\) but possibly converge in the extreme end\(^\text{225}\).

A study using a quantitative measure for ALTs showed that it was possible to use this

\(^{221}\) Belmonte et al. 2010

\(^{222}\) Ghaziuddin et al. 2002


\(^{224}\) Ronald et al. 2006a

\(^{225}\) Ronald et al. 2006b
strategy to identify genetic susceptibilities for ASDs and ALTs. In the light of these findings, it would seem more promising to include the whole variation of ALTs (from those showing no ALTs to individuals diagnosed with an ASD) in future whole genome analyses instead of just probands, as this approach would give greater statistical power to identify genetic variants and open up for mapping not only ALTs but also the quantitative susceptibility for overlapping problems, for instance ALTs and AD/HD, and describe the contribution of actual genetic factors behind disorders.

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226 Duvall et al. 2007
227 Almasy & Blangero 1998
228 Plomin et al. 2009
References


References


References


References


References


References


References


Appendix

Appendix I

Table 21. Model-fitting in CATSS, proposed online material

Univariate analyses (CATSS)

<table>
<thead>
<tr>
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<th>ALTs</th>
<th>AD/HD</th>
<th>Anxiety</th>
<th>Conduct problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>$h^2$</td>
<td>0.70 (0.66-0.73)</td>
<td>0.66 (0.62-0.70)</td>
<td>0.58 (0.52-0.62)</td>
<td>0.64 (0.53-0.69)</td>
</tr>
<tr>
<td>$c^2$</td>
<td>0.00 (0.00-0.03)</td>
<td>0.00 (0.00-0.04)</td>
<td>0.00 (0.00-0.05)</td>
<td>0.01 (0.00-0.13)</td>
</tr>
<tr>
<td>$e^2$</td>
<td>0.30 (0.27-0.33)</td>
<td>0.34 (0.30-0.38)</td>
<td>0.42 (0.38-0.47)</td>
<td>0.35 (0.31-0.39)</td>
</tr>
</tbody>
</table>

Bivariate analysis (CATSS)

<table>
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<th>ALTs - AD/HD</th>
<th>ALT - Anxiety</th>
<th>ALT - Conduct problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>-2LL</td>
<td>DF</td>
<td>AIC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saturated</td>
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<td>12324</td>
<td>6681.4</td>
</tr>
<tr>
<td>ACE</td>
<td>31347.1</td>
<td>12339</td>
<td>6669.1</td>
</tr>
</tbody>
</table>

Note: -2LL = loglikelihood fit statistics, DF = degrees of freedom, AIC= Akaike’s information criteria, $\Delta \chi^2 = \text{difference chi-squared}$, $h^2 / c^2 / e^2 = \text{variance explained by genetic /shared /non-shared influences}$, $rg = \text{additive genetic correlation}$, $rc = \text{shared environment correlation}$ and $re = \text{non-shared environment correlation}$. The phenotypical correlation is obtained by: $\sqrt{h^2} * \sqrt{h^2} * r_g + \sqrt{c^2} * \sqrt{c^2} * r_c + \sqrt{e^2} * \sqrt{e^2} * r_e$. 
### Appendix

#### Appendix II

**Table 22.** Model-fitting in STAGE, proposed online material

<table>
<thead>
<tr>
<th></th>
<th>ALTs – AD/HD</th>
<th>ALT – Anxiety</th>
<th>ALT – Depressive traits</th>
<th>ALT – Substance abuse</th>
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</thead>
<tbody>
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<td>DF</td>
<td>AIC</td>
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<td>14843</td>
<td>9905.4</td>
<td>42483.4</td>
</tr>
</tbody>
</table>

### Univariate analyses STAGE

<table>
<thead>
<tr>
<th></th>
<th>ALTs</th>
<th>AD/HD</th>
<th>Anxiety</th>
<th>Depressive traits</th>
<th>Substance abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>h²</td>
<td>0.32 (0.30-0.36)</td>
<td>0.38 (0.26-0.44)</td>
<td>0.13 (0.03-0.17)</td>
<td>0.35 (0.27-0.39)</td>
<td>0.36 (0.00-0.78)</td>
</tr>
<tr>
<td>c²</td>
<td>0.00 (0.00-0.05)</td>
<td>0.02 (0.00-0.12)</td>
<td>0.00 (0.00-0.08)</td>
<td>0.00 (0.00-0.07)</td>
<td>0.29 (0.00-0.66)</td>
</tr>
<tr>
<td>e²</td>
<td>0.68 (0.64-0.71)</td>
<td>0.69 (0.56-0.63)</td>
<td>0.87 (0.83-0.91)</td>
<td>0.65 (0.61-0.68)</td>
<td>0.35 (0.22-0.50)</td>
</tr>
</tbody>
</table>

### Bivariate analyses (STAGE)

<table>
<thead>
<tr>
<th></th>
<th>ALTs – AD/HD</th>
<th>ALT – Anxiety</th>
<th>ALT – Depressive traits</th>
<th>ALT (6 levels)</th>
<th>Substance abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>h²</td>
<td>0.32 (0.25-0.36)</td>
<td>0.38 (0.26-0.44)</td>
<td>0.13 (0.03-0.16)</td>
<td>0.39 (0.26-0.45)</td>
<td>0.38 (0.00-0.78)</td>
</tr>
<tr>
<td>c²</td>
<td>0.00 (0.00-0.06)</td>
<td>0.03 (0.00-0.13)</td>
<td>0.00 (0.00-0.07)</td>
<td>0.00 (0.00-0.00)</td>
<td>0.26 (0.00-0.64)</td>
</tr>
<tr>
<td>e²</td>
<td>0.68 (0.64-0.71)</td>
<td>0.59 (0.56-0.63)</td>
<td>0.87 (0.84-0.91)</td>
<td>0.61 (0.55-0.66)</td>
<td>0.35 (0.22-0.49)</td>
</tr>
</tbody>
</table>

Note: -2LL = log likelihood fit statistics, DF = degrees of freedom, AIC= Akaike’s information criteria, Δχ² = difference chi-squared, *h², c², e²* = variance explained by genetic /shared /non-shared influences, rg = additive genetic correlation, re = shared environment correlation and re = non-shared environment correlation. The phenotypical correlation is obtained by: \( r_{ph} = \sqrt{h^2_{g} + c} * \sqrt{h^2_{c} + e} + \sqrt{c} * \sqrt{c} + r_e + \sqrt{e} * \sqrt{e} + r_e \)