

Asperger syndrome and schizophrenia

Psychiatric and social cognitive aspects

Tove Lugnegård

Gillberg Neuropsychiatry Centre,
Institute of Neuroscience and Physiology
Sahlgrenska Academy at University of Gothenburg



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tove.lugnegard@liv.se

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Tove Lugnegård

Gillberg Neuropsychiatry Centre, Institute of Neuroscience and Physiology,
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ABSTRACT

Background: Asperger syndrome (AS) and schizophrenia are psychiatric disorders often implying low global social functioning and a life-long course. Both disorders are of neurodevelopmental origin and genetic factors are prominent. Diagnostic criteria concerning age of onset, life course and the presence of psychotic symptoms differ markedly across the two disorders. However, considerable similarities regarding social cognitive and neurocognitive deficits as well as developmental delays have been noted. The boundaries between AS and schizophrenia are still not clear, and particularly not between the broader concepts of autism spectrum and schizophrenia spectrum. This thesis aims to explore similarities and differences between AS and schizophrenia by using a cross-sectional approach. Psychiatric comorbidity in young adults with AS was studied, as well as occurrence of personality disorders according to DSM-IV. Social cognitive ability and self-report of autistic traits were compared across a group with AS, a group with schizophrenia and a non-clinical comparison group. **Method:** Fifty-four individuals (26 men, 28 women) with a clinical diagnosis of AS were given the Structured Clinical Interview for DSM-IV Axis I Disorders and the Structured Clinical Interview for DSM-IV Axis II Disorders. The clinical AS diagnosis was confirmed by performing the Diagnostic Interview for Social and Communication Disorders with a parent. The same AS study group, another group of 36 individuals (22 men, 14 women) with schizophrenic psychosis (schizophrenia, schizoaffective disorder, schizofreniform psychosis, psychotic disorder NOS) and a non-clinical comparison group (19 men, 30 women) were compared regarding self-report of autistic traits measured by the Autism-Spectrum Quotient (AQ) and as regards social cognition, as indexed by the Animations Task and the Reading the Mind in the Eyes Test. **Results:** Of the individuals with AS, 70% had experienced at least one episode of major depression and 50% had suffered from recurrent depressive episodes. Anxiety disorders were present in about 50%. No one fulfilled criteria for schizophrenia, and other psychotic disorders and substance-induced disorders were uncommon. Approximately half of the group fulfilled diagnostic criteria for a personality disorder, all within cluster A or cluster C according to the DSM-IV. Comparison on social cognitive ability across AS, schizophrenic psychosis and the non-clinical sample, demonstrated significant impairments in the two clinical groups, the schizophrenia group being the most impaired. Both clinical groups demonstrated significantly higher total AQ scores than the non-clinical group. The difference across the AS and schizophrenia groups was small, but significant, with the AS group demonstrating higher scores. **Conclusions:** The phenotypes of AS and schizophrenia show considerable overlap regarding both social cognitive impairments and self-report of autistic traits. Nevertheless, among young adults with a clinical diagnosis of AS, schizophrenia does not appear to be overrepresented. However, other psychiatric disorders, particularly related to mood and anxiety, are common in AS, and about half meet criteria for personality disorders. Future research on genetic susceptibility and the etiology of neurodevelopmental disorders will benefit from approaches based on more refined endophenotypes as well as including several diagnostic domains, rather than being based solely on established diagnostic criteria.

Keywords: Asperger syndrome, autism spectrum, schizophrenia, Autism-Spectrum Quotient, Animations Task, Reading the Mind in the Eyes Test, mood disorder, personality disorder

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SAMMANFATTNING PÅ SVENSKA

Schizofreni och Aspergers syndrom är kroniska psykiska funktionshinder som ofta medför allvarlig funktionsnedsättning och försämrad livskvalitet. Diagnostiska kriterier skiljer sig avseende debutålder, förlopp och akuta symptom, men likheter är beskrivna när det gäller utvecklingsrelaterade svårigheter i barndomen och social kognition. Förhållandet mellan schizofreni och Aspergers syndrom är fortfarande delvis oklart.

Femtiofyra vuxna med kliniskt fastställd diagnos Aspergers syndrom undersöktes avseende psykiatrisk samsjuklighet och avseende kriterier för personlighetsstörningsdiagnos. Gruppen jämfördes sedan med 36 vuxna med schizofreni samt en frisk jämförelsegrupp avseende autistiska drag och social kognition.

Av personerna med Aspergers syndrom hade 70% haft minst en egentlig depression, 50% hade haft recidiverande depressioner och ungefär 50% hade någon ångestdiagnos. Psykosdiagnoser var sällsynta. Ungefär hälften (relativt sett flera män än kvinnor) uppfyllde kriterier för någon personlighetsstörningsdiagnos. Vid jämförelse mellan Aspergers syndrom, schizofreni och friska personer, uppvisade de bägge patientgrupperna betydligt mer omfattande autistiska drag jämfört med den friska gruppen. Skillnaden mellan Aspergers syndrom och schizofreni var liten, men signifikant. Gruppen med Aspergers syndrom uppvisade en något högre nivå av autistiska drag. Vid jämförelse avseende social kognition uppvisade bägge patientgrupperna signifikant sämre förmåga jämfört med friska, men gruppen med schizofreni var mera avvikande än gruppen med Aspergers syndrom.

Fenotypen för Aspergers syndrom och schizofreni uppvisar en betydande överlappning. Samtidigt ses ingen ökad schizofreniförekomst bland unga vuxna med Aspergers syndrom. Unga vuxna med Aspergers syndrom har däremot en mycket hög risk för ångest och depressionstillstånd. Män med Aspergers syndrom uppfyller mycket ofta kriterier för personlighetsstörning i unga vuxna år. Vid fortsatt forskning om genetisk sårbarhet och orsaker till utvecklingsrelaterade funktionshinder, är det viktigt att genomföra studier som baseras på endofenotyper och andra väldefinierade mått snarare än enbart diagnoskriterier i DSM och ICD.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. Lugnegård, T., Unenge Hallerbäck, M., Gillberg, C. (2011). Psychiatric comorbidity in young adults with a clinical diagnosis of Asperger syndrome. *Research in Developmental Disabilities* 32, 1910-1917.
- II. Lugnegård, T., Unenge Hallerbäck, M., Gillberg, C. (2011). Personality disorders and autism spectrum disorders: what are the connections? *Comprehensive Psychiatry* (in press)
- III. Lugnegård, T., Unenge Hallerbäck, M., Gillberg, C. (2012). Self-report of autistic traits in schizophrenia: a comparative study using the Autism-Spectrum Quotient (AQ). (submitted)
- IV. Lugnegård, T., Unenge Hallerbäck, M., Hjärthag, F., Gillberg, C. (2012). Social cognition impairments in Asperger syndrome and schizophrenia. (submitted)

CONTENT

| | |
|--|----|
| ABBREVIATIONS | IV |
| 1 INTRODUCTION..... | 1 |
| 1.1 Asperger syndrome/AS and Autism spectrum disorder/ASD..... | 1 |
| 1.2 Schizophrenia..... | 3 |
| 1.3 History..... | 6 |
| 1.4 Psychiatric phenotype | 8 |
| 1.5 Neurocognitive impairments..... | 14 |
| 1.6 Social cognitive impairments..... | 14 |
| 1.7 Genetic overlap | 15 |
| 2 AIMS | 17 |
| 3 METHODS | 18 |
| 3.1 Participants..... | 18 |
| 3.2 Measurements | 24 |
| 3.3 Ethics..... | 28 |
| 3.4 Statistical analyses | 28 |
| 4 RESULTS | 29 |
| 4.1 Psychiatric comorbidity in AS (I) | 29 |
| 4.2 DSM-IV PD diagnostic criteria met in AS group (II)..... | 31 |
| 4.3 Comparison of self-reported autistic traits in AS, SP, and NCC (III). 32 | |
| 4.4 Comparison of social cognition ability in AS, SP, and NCC (IV)..... | 34 |
| 4.5 DISCO-11 assessment (I-IV)..... | 37 |
| 4.6 WAIS-III assessment (I-IV)..... | 37 |
| 5 DISCUSSION | 39 |
| 6 CONCLUSIONS | 53 |
| 7 IMPLICATIONS FOR CLINICAL PRACTICE AND RESEARCH..... | 54 |
| ACKNOWLEDGEMENTS | 57 |
| REFERENCES..... | 59 |

ABBREVIATIONS

| | |
|-----------|---|
| AD | Autistic Disorder |
| ADHD | Attention-Deficit/ Hyperactivity Disorder |
| AS | Asperger Syndrome |
| ASD | Autism Spectrum Disorder |
| AQ | Autism-Spectrum Quotient |
| CDD | Childhood Disintegrative Disorder |
| DAH | Department of Adult Habilitation |
| DISCO-11 | Diagnostic Interview for Social and Communication Disorders, 11 th version |
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders, 4 th edition |
| DSM-IV-TR | Diagnostic and Statistical Manual of Mental Disorders, 4 th edition, Text Revision |
| ICD-10 | International Classification of Diseases, 10 th edition |
| NCC | Non-clinical comparison group |
| NCCA | Neuropsychiatric Clinic for Children and Adolescents |
| PD | Personality Disorder |
| PDD | Pervasive Developmental Disorder |
| PDD-NOS | Pervasive Developmental Disorder, Not Otherwise Specified |
| SCID-I | Structured Clinical Interview for DSM-IV Axis I Disorders |
| SCID-II | Structured Clinical Interview for DSM-IV Axis II Disorders |
| SP | Schizophrenic Psychosis |
| ToM | Theory of Mind |
| WAIS-III | Wechsler Adult Intelligence Scale, third edition |

1 INTRODUCTION

Asperger syndrome (AS) and schizophrenia are operationalised diagnoses that are separated in current diagnostic manuals according to age of onset, symptom profile and outcome (WHO 2004; APA 2000). Nevertheless, both disorders have a neurodevelopmental origin and major features in common (Fatemi & Folsom 2009; Coleman & Gillberg 2011; Cheung, Yu, Fung et al. 2010). AS is a pervasive (often lifelong) developmental disorder included within the category of autism spectrum disorders (ASD) and it is usually diagnosed in childhood. Schizophrenia is a broad clinical syndrome, with diagnostic criteria based on psychotic symptoms and functional deterioration, and though onset frequently occurs around the age of 20 years, precursors such as developmental deviations have often been present from an early age (Coleman & Gillberg 1996; APA 2000; Niemi, Suvisaari, Tuulio-Henriksson et al. 2003; Tandon, Keshavan & Nasrallah 2008). In both schizophrenia and ASD, neurocognitive deficits as well as deficits in social cognition and social functioning are marked (Abdi & Sharma 2004; Pinkham, Hopfinger, Pelphey et al. 2008). The boundaries and possible overlap between AS/ASD and schizophrenia are still not clear, and particularly not between the broader concepts of autism spectrum and schizophrenia spectrum. Moreover, current research indicating shared genetic vulnerability (Burbach & van der Zwaag 2009; Owen, O'Donovan, Thapar et al. 2011; Coleman & Gillberg 2011) between the two spectra makes this issue even more pertinent.

1.1 Asperger syndrome/AS and Autism spectrum disorder/ASD

ASD, also classified as pervasive developmental disorders (PDD) among axis-I disorders in the DSM-IV, are relatively common social communication disorders that affect about 0.6-1% of the general population (Baird, Simonoff, Pickles et al. 2006; Fernell & Gillberg 2010; Nygren, Cederlund, Sandberg et al 2011). ASD/PDD under the DSM-IV share a core triad of abnormalities: 1) qualitative impairments in reciprocal social interactions, 2) qualitative impairments in verbal and non-verbal communication, and 3) restricted social imagination with repetitive and stereotyped patterns of interests and behaviour. The DSM-IV includes autistic disorder (AD) (pervasive deficits in all three domains), AS (pervasive deficits in social interaction and behaviours in the presence of superficially normal expressive verbal development) and pervasive developmental disorder not otherwise specified (PDD-NOS) (not meeting full criteria for either AD or AS, but with pervasive deficits in social

interaction), and the extremely rare variant referred to as childhood disintegrative disorder (CDD) (with onset of symptoms after a few years of normal development) (APA 2000). An AD diagnosis requires a delay in development obvious before the age of three, although for AS and PDD-NOS, no specific age criteria are stipulated. The boundaries within the ASD/PDD spectrum are not clear and have been an issue for debate (Miller & Ozonoff 1997 ; Howlin 2003). As a consequence, major modifications are suggested for the DSM-V, which, in principle, involve fusion of AD, AS, PDD-NOS, and CDD into one integrated category, namely ASD (APA 2011). Even though PDD is the concept used in the current edition of DSM, ASD is more commonly used, particularly in clinical practice. Therefore, the term ASD will be used here when referring to the whole spectrum. The outcome of ASD is very variable with “classic” cases of AD (usually associated with moderate-major cognitive general impairment and poor expressive language skills) having an extremely restricted psychosocial outcome in adult life, and AS cases (with often excellent expressive language skills) having, sometimes, a much better prognosis for adult life functioning. DSM-IV criteria for AS are presented in Table 1.

After the inclusion of AS in DSM-IV in 1994, and with better knowledge and awareness about ASD among professionals and the general population, the recognition and clinical diagnosis of individuals with ASD including AS have increased considerably in recent years (APA 1994; Baird et al. 2006; Fernell & Gillberg 2010; Nygren et al 2011). In Sweden, diagnostic assessment of children with ASD and other neurodevelopmental problems has been more easily available in child psychiatric health care since the beginning of the 1990s. In adult psychiatric health care, however, diagnostic evaluation of developmental disorders has not come to the forefront until the last five to ten years.

Table 1. Diagnostic criteria for Asperger's Disorder (DSM-IV-TR)

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| <p>A. Qualitative impairment in social interaction, as manifested by at least two of the following:</p> <ol style="list-style-type: none"> 1) marked impairment in the use of multiple nonverbal behavior such as eye-to-eye gaze, facial expression, body posture, and gestures to regulate social interaction 2) failure to develop peer relationships appropriate to developmental level 3) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest to other people) 4) lack of social or emotional reciprocity <p>B. Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:</p> <ol style="list-style-type: none"> 1) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus 2) <input type="checkbox"/>pparently inflexible adherence to specific, nonfunctional routines or rituals 3) stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements) 4) persistent preoccupation with parts of objects <p>C. The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning.</p> <p>D. There is no clinically significant general delay in language (e.g. single words used by age 2 years, communicative phrases used by age 3 years).</p> <p>E. Ther 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.</p> <p>F. Criteria are not met for another specific Pervasive Developmental Disorder or Schizophrenia.</p> |
|--|

1.2 Schizophrenia

Schizophrenia is described to occur in all populations with prevalence in the range of 0.1-0.5% and incidence rates in the range of 0.16 - 0.42 per 1,000. Life-time risk is stated to be approximately 1% (Jablensky 2000). Although frequently described as such, schizophrenia is not considered to be a single

disease, but rather to represents a broad clinical heterogeneous syndrome of probably different etiologies (Murray, O'Callaghan, Castle et al. 1992; Coleman & Gillberg 1996; Carpenter 2006; Jablensky 2006; Keshavan, Nasrallah & Tandon 2011). In DSM-IV and ICD-10, the emphasis is put on the presence of positive symptoms (delusions, hallucinations, thought disorder) although no single symptom is stated as pathognomonic. Additional criteria include so called negative, or deficit, symptoms (e. g. avolition, flat affect, anhedonia) as well as functional deterioration (APA 1994; APA 2000; WHO 2004). (See Table 2). Although neurocognitive impairment is regarded as a major characteristic of schizophrenia, such features are not within the diagnostic schemes. Cognitive deficits include dysfunction in attention, memory and executive functions, as well as impairments in social cognition (Rund 1998; Green, Kern, Braff et al. 2000; Sprong, Schothorst, Vos et al. 2007).

The onset of psychosis regularly occurs in late adolescence or early adulthood (Fatemi & Folsom 2009). However, precursors of the disorder are known to be present already in childhood in a substantial proportion of patients. Children who, in their late teens or adulthood, develop schizophrenia have been described as slightly different from their age peers with regard to motor performance, cognitive development, activity control and social interaction. Premorbid impairments have been widely investigated in cohort studies, conscript studies and high-risk studies (Jones, Rodgers, Murray et al. 1994; Done, Crow, Johnstone et al. 1994; Malmberg, Lewis, David et al. 1998; Niemi et al. 2003). Despite extensive study of these predisposition phenomena, the nature of the neurodevelopmental deviations is still not clearly understood.

Schizoaffective disorder is a diagnosis closely related to schizophrenia, with identical criteria for positive psychotic symptoms, however with the addition of mood symptoms of such extent that criteria for major depressive, manic or mixed episode is fulfilled during a substantial proportion of the illness episode, but separated from bipolar disorder by the presence of positive psychotic symptoms even in euthymic periods. Schizophreniform disorder is a diagnosis applied when all criteria for schizophrenia is fulfilled apart from the duration criteria of six months, instead symptoms must have been present for at least one month (APA 2000). In clinical studies on schizophrenia, patients diagnosed with schizoaffective disorder or schizophreniform disorder are generally included.

Table 2. Diagnostic criteria for Schizophrenia (DSM-IV-TR)

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| <p>A. <i>Characteristic symptoms:</i> Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):</p> <ol style="list-style-type: none"> 1) Delusions 2) Hallucinations 3) Disorganized speech 4) Grossly disorganized or catatonic behavior 5) Negative symptoms, i.e., affective flattening, alogia, or avolition <p>Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.</p> <p>B. <i>Social/occupational dysfunction:</i> For a significant portion of the time since the onset of the disturbance, one or major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).</p> <p>C. <i>Duration:</i> Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e. active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in attenuated form (e.g., odd beliefs, unusual perceptual experiences).</p> <p>D. <i>Schizoaffective and Mood Disorder exclusion:</i> Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either (1) no Major Depressive, Manic, or Mixed Episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during the active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.</p> <p>E. <i>Substance/general medical condition exclusion:</i> The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.</p> <p>F. <i>Relationship to a Pervasive Developmental Disorder:</i> If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).</p> |
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1.3 History

Neither schizophrenia, nor autism (or AS) constitutes a unitary disease entity. In contrast, both concepts are heterogeneous and may include a substantial diversity of symptoms, deficits, courses and etiologies. Historically, both schizophrenia and autism have gone through various diagnostic drifts: sometimes approaching each other, sometimes separating from each other. Furthermore, the term “autism” in itself has given rise to some confusion: either referring to a pathological introversion/egocentric thinking (a symptom), or to a syndrome (defined group of symptoms).

The concept of AS was first described in 1944 by Hans Asperger, although he applied the name “autistic psychopathy” for his delineation of a group of boys with social interaction impairments, special interests and odd behaviours (Asperger 1944). At the same time, the concept of (early infantile) autism as a syndrome was introduced by Kanner, describing a group of children with severe abnormalities in social interaction (Kanner 1943). Prior to Asperger’s and Kanner’s descriptions of what is now recognized as parts of an autism spectrum, similar children were diagnosed with, “schizoid personality” or “childhood schizophrenia” (Bender 1947; Wolff 1996). For several decades the terms “childhood schizophrenia” and “infantile autism” were used interchangeably. It was not until the beginning of the 1970s that a clear separation between the concepts was drawn by Israel Kolvin and Michael Rutter (Rutter 1972; Kolvin, Ounsted, Humphrey et al. 1971). “Childhood schizophrenia” almost ceased to exist as an independent diagnosis, instead adult criteria for schizophrenia were applied for children, whereas “infantile autism” became the term used for the developmental disorder presenting at an early age. The term “pervasive developmental disorder” (PDD) was introduced in the DSM-III (APA 1980) as a general category including infantile autism as a major subgroup. The high-functioning end of the autism spectrum became resurrected through Lorna Wing’s seminal article from 1981 (Wing 1981), where the term AS was launched. Since then, the concept of what constitutes autism has expanded from a rare disorder, implying profound lack of social interest, often in combination with intellectual developmental disorder/mental retardation, to a broader range of functional impairment in social communication. The proportion of individuals with ASD who also have intellectual disability have consequently dropped from 80% to less than 35% in some studies (Fombonne 2009; Fernell & Gillberg 2010; Nygren et al. 2011) and prevalence rates have increased markedly (Coleman & Gillberg 2011).

The evolution of the concept of schizophrenia has been in progress since the late 19th century. Emil Kraepelin's dementia praecox patients had an early onset of illness and a progressively deteriorating course with no return to premorbid levels of function (Berrios, Luque, & Villagran 2003). These features contrasted with the later onset, episodic nature and relatively intact thinking in manic-depressive psychoses. Even now, this separation is referred to as the "Kraepelinian dichotomy". Eugen Bleuler replaced dementia praecox with the term schizophrenia. He described four fundamental symptoms: ambivalence, disturbance of affect, disturbance of association and a preference for fantasy over reality (Bleuler 1920). Bleuler was also the one to coin the term autism for the egocentric thinking he believed to be the core of schizophrenia (Bleuler 1911). Psychotic features (delusions and hallucinations) emphasized by today's criteria were not crucial for Bleuler's diagnosis of schizophrenia. However, in the 1950s, Kurt Schneider introduced the concept of "first-rank symptoms" (audible thoughts, voices commenting on the patient's actions, voices discussing the patient, thought withdrawal, thought broadcast, experiences of influences of the body and delusional perception), meaning psychotic symptoms of special importance in the diagnosis of schizophrenia (Schneider 1950). First-rank symptoms heavily influenced the development of DSM-III criteria (APA 1980) and continued to influence DSM-IV and ICD-10 respectively (APA 1994; WHO 2004). In spite of clarified operational criteria, the emphasis on first-rank symptoms in the last decades has occurred on the expense of analysis of premorbid difficulties, course and outcome (Parnas 2011; Keshavan, Nasrallah & Tandon 2011).

Thus, since the early 1970s, there has been a notion that the autism spectrum and the schizophrenia spectrum are clearly separated. Undoubtedly, this separation has been emphasized by the current DSM criteria. For instance, in DSM-IV, co-existent diagnoses of Asperger syndrome and schizophrenia were not possible according to an exclusion criterion (APA 1994), however modified in the text revised version (APA 2000). In the last five years, mainly due to genetic and neuroimaging findings together with broadening of the autism spectrum, this notion of clear separation is being questioned (Rapoport, Chavez, Greenstein et al. 2009; Craddock & Owen 2010; King & Lord 2011).

1.4 Psychiatric phenotype

1.4.1 Psychiatric comorbidity in ASD

It is still an open question whether ASD in young children infers an increased risk for the later development of schizophrenia and other psychotic disorders; different investigations point in opposite directions. A retrospective chart review (Volkmar & Cohen 1991), a few follow-up studies (Rumsey, Rapoport & Sceery 1985; Howlin, Goode, Hutton et al. 2004; Cederlund, Hagberg, Billstedt et al 2008) and a few cross-sectional studies (Ghaziuddin, Tsai & Ghaziuddin 1992; Leyfer, Folstein, Bacalman et al. 2006) all demonstrated no or very few cases of schizophrenia in ASD samples. In contrast, other clinically based studies have reported prevalence rates of psychotic disorders including schizophrenia in the range of 12-20% (Tantam 1991; Stahlberg, Soderstrom, Rastam et al. 2004; Hofvander, Delorme, Chaste et al. 2009). Additionally, several question-provoking case series on the topic have been published over the years, illustrating the presence of concomitant schizophrenia and ASD (Petty, Ornitz, Michelman et al. 1984; Clarke, Littlejohns, Corbett et al. 1989; Konstantareas & Hewitt 2001).

When it comes to comorbidity of mood disorders and anxiety disorders in ASD, previous findings are not as diverging as for psychotic disorders, although studies on adults are still scarce. There is growing evidence that people with ASD are at high risk of associated depression and anxiety (Wing 1981; Ghaziuddin 2002; Sverd 2003; Stewart, Barnard, Pearson et al. 2006; Skokauskas & Gallagher 2010). Current depression was suggested to be present in a large minority of adults with AS/AD using the self-report Beck Depression Inventory (Hill, Berthoz, & Frith 2004; Cederlund, Hagberg & Gillberg 2010). By using Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), Hofvander et al showed that about 50% in their ASD study group had a lifetime diagnosis of mood disorder (Hofvander et al. 2009). Moderately high rates of mood and anxiety disorders assessed with SCID-I have also been reported in an investigation on insomnia in 20 individuals with AS (Tani, Lindberg, Wendt et al. 2003). Another group found depressive symptoms in about 40% of their clinically referred group of 46 cases with ASD, using a psychiatric history interview similar to the SCID-I (Sterling, Dawson, Estes et al. 2008).

1.4.2 Personality disorder/PD

Personality disorders are classified on a separate axis, axis II, in the DSM-IV (as were both personality disorders and PDDs in the DSM-III-R). A personality disorder (PD) is an “enduring pattern of inner experience and

behaviour that deviates markedly from the expectations of the individual's culture, is pervasive and inflexible, has an onset in adolescence or early adulthood, is stable over time, and leads to distress or impairment" (APA 2000). General criteria for PDs are presented in Table 3. PDs are typically not diagnosed in children and adolescents and criteria are developed for assessments in adulthood, even though no specific age criteria exist (with the exception of antisocial PD, which cannot be diagnosed in individuals under age 18 years). Nevertheless, several researchers have applied PD criteria to children and adolescents (Nagy & Szatmari 1986; Diforio, Walker & Kestler 2000; Neumann & Walker 2003; Asarnow 2005). Currently, ten separate PDs are defined, grouped into three clusters A-C, based on descriptive similarities. (See Table 4.) The validity of the actual PD classification has been questioned over time (Shedler & Westen 2007), one reason being the major overlaps between different PDs. Another weakness is the categorical approach on a truly dimensional field. These shortcomings will be taken into account in the DSM-V, and thus important changes are being suggested, e. g. five PD types as a replacement for ten PDs as well as an inclusion of a dimensional rating (APA 2011).

Table 3. General diagnostic criteria for a personality disorder (DSM-IV-TR)

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| <p>A. An enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual's culture. This pattern is manifested in two (or more) of the following areas:</p> <ol style="list-style-type: none"> 1) cognition (i. e. ways of perceiving and interpreting self, other people, and events) 2) affectivity (i.e. the range, intensity, lability, and appropriateness of emotional response) 3) interpersonal functioning 4) impulse control <p>B. The enduring pattern is inflexible and pervasive across a broad range of personal and social situations.</p> <p>C. The enduring pattern leads to clinically significant distress and or impairment in social, occupational, or other important areas of functioning</p> <p>D. The pattern is stable and of long duration, and its onset can be traced back at least to adolescence or early adulthood.</p> <p>E. The enduring pattern is not better accounted for as a manifestation or consequence of another mental disorder.</p> <p>F. The enduring pattern is not due to the direct physiological effects of a substance (e.g. a drug abuse, a medication) or a general medical condition (e.g., head trauma).</p> |
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Table 4. Clusters and personality disorders (PD) according to DSM-IV-TR

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|-------------------------|
| A. Cluster A |
| Paranoid PD |
| Schizoid PD |
| Schizotypal PD |
| B. Cluster B |
| Antisocial PD |
| Histrionic PD |
| Borderline PD |
| Narcissistic PD |
| C. Cluster C |
| Avoidant PD |
| Obsessive-compulsive PD |
| Dependent PD |

The relationship between DSM-IV personality disorders and PDD/ASD is not clear. Even though now classified as an axis-I disorder, the basic characteristics of a PDD/ASD (“pervasive impairment”, “abnormal development”) are in fact equal to those for axis-II disorders (“the pattern is stable and of long duration, and its onset can be traced back at least to adolescence or early adulthood”). Strictly applied, an exclusion criterion in the general PD criteria states that “the enduring pattern is not better accounted for as a manifestation or consequence of any other mental disorder” which implies that a PDD/ASD diagnosis has precedence before an axis-II disorder in the DSM hierarchical system. Previous research on similarities and overlap is limited, although one focus has been on distinguishing between PDD/ASD and schizoid/schizotypal PD (Rutter 1987; Tantam 1988; Baltaxe, Russell, D’Angiola et al. 1995). The DSM-IV-TR criterion A for schizoid PD delineates a pattern well compatible with PDD/ASD criteria and in the text manual on differential diagnosis, it is emphasized that differentiating between schizoid PD and PDD may involve great difficulty. The risk for misdiagnosis is emphasized by an exclusion criterion B, which implies that a PDD must be excluded before establishing a diagnosis of schizoid PD or schizotypal PD. Moreover, the text manual implies that when differentiating between schizoid/schizotypal PD and PDD; social interaction, stereotyped behaviours and interests are more severely impaired in PDD than in schizoid/schizotypal PD. When Sula Wolff started her research on developmentally impaired children in the 1960s, she

classified the group that she was particularly interested in as schizoid/schizotypal (Wolff & Chick 1980). Her follow-up studies offer colourful clinical descriptions of severely impaired children who also, in many cases, proved to have a negative outcome (Wolff, Townshend, McGuire et al. 1991). In the 1990s, Sula Wolff revised her previous classification and considered her study group as belonging to the autism spectrum (Wolff 1991). Additionally, a chart review by Nagy and Szatmari of children with schizotypal PD is still of interest: the authors emphasize their findings regarding overlap between PDD/ASD and schizotypal PD, point out limitations of the DSM classification system and question the term “schizotypal” as being useful (Nagy & Szatmari 1986). Another approach when investigating schizotypal personality traits has been to compare them to autistic features in non-clinical samples, results showing a substantial degree of overlap (Hurst, Nelson-Gray, Mitchell et al. 2007; Russell-Smith, Maybery & Bayliss 2011). In another recent study, children and adolescents diagnosed with schizotypal PD were found to have high rates of autistic features (Esterberg, Trotman, Brasfield et al. 2008).

Regarding the relationship between PD and schizophrenia, PDs within cluster A have a close connection to schizophrenia. In fact, criteria for schizotypal PD were empirically derived based on the clinical picture observed in relatives of patients with schizophrenia (Kendler 1985; Siever, Silverman, Horvath et al. 1990). In ICD-10, the term used is “schizotypy”, classified not as in DSM-IV as one of the PDs, but as a separate entity within the group of schizophrenic disorders. However, phenomenologically the concepts could be regarded as almost identical. Schizotypal PD is a heterogeneous condition and biological studies find evidence for at least two types of schizotypal PD/schizotypy. “Negative schizotypy” implies negative/deficit symptoms, neuropsychological impairments and eye-tracking abnormalities, and is particularly seen among relatives of patients with schizophrenia. “Positive schizotypy” implies mild positive symptoms like magical ideation and unusual perceptual experiences and is usually not related to a family history of schizophrenia (Kendler & Walsh 1995; Tsuang, Stone, Tarbox et al. 2002; Kwapil, Barrantes-Vidal & Silvia 2008). The term “schizophrenia spectrum” usually refers to schizophrenic disorder/schizophrenia, schizotypal PD and schizotypy.

The relationship between schizoid PD, also within cluster A, and schizophrenia is described to be less strong than for schizotypal PD (Kendler, McGuire, Gruenberg et al. 1993; Kendler, Neale & Walsh 1995). This is somewhat contradictory to the facts that (1) criteria for schizoid PD and schizotypal PD show a substantial overlap, and (2) the above delineated

concept “negative schizotypy” and schizoid PD are almost one and the same. Criterion A of schizotypal PD includes characteristics virtually identical to those of schizoid PD, but with the addition of psychotic-like symptoms (e. g. “ideas of reference”, “magical thinking”). Both for schizoid PD and for schizotypal PD, there is a specific exclusion criterion B (apart from the general PD exclusion criterion E) stipulating the necessity to rule out a diagnosis of schizophrenia. An additional closely related nosological concept is “schizotaxia”, a term established with a view to delineating the genetic predisposition to schizophrenia (Meehl 1962). The concept has not entered DSM or ICD, (Faraone, Green, Seidman et al. 2001; Tsuang, Stone & Faraone 2002), but represents a constellation of clinical and neurobiological features including negative symptoms (e. g. avolition, flat affect, anhedonia, low social interest) and cognitive deficits affecting verbal memory, attention and executive functions. The concept of schizotaxia is described to be broader than schizotypal PD and more similar to “negative schizotypy”.

In summary, even though (1) the connection between schizophrenia and schizotypal PD/schizotypy has been clearly demonstrated, and (2) the criteria overlap between schizoid/schizotypal PD and ASD is prominent, there has simultaneously been a notion that schizophrenia and ASD are unrelated to each other (Volkmar & Cohen 1991; Crespi & Badcock 2008) which is now being questioned (Esterberg et al. 2008; Rapoport et al. 2009; Craddock & Owen 2010; King & Lord 2011). Since the DSM hierarchical system does not “allow” comorbid diagnoses of PDD/ASD and PD, according to the general exclusion criterion described above (Table 3.), when investigating the issue of whether or not the two conditions are related and when applying the “PD map system” (=PD criteria) on individuals with an already diagnosed PDD/ASD, the exclusionary criterion must be disregarded in order to make such a study possible.

1.4.3 Autistic traits

It is now generally accepted that traits (or features) of autism are quite common in the general population without a diagnosis of ASD (Gillberg, Gillberg & Steffenburg 1992; Constantino & Todd 2005; Posserud, Lundervold & Gillberg 2006; Hoekstra, Bartels, Verweij et al. 2007). These traits include difficulties in communication and social interaction, preference for routines and decreased flexibility, however an exact definition is not stated. Autistic traits as a continuum allow a quantitative approach to ASD which complements categorical diagnostics. The “broader autism phenotype” is a term used for the presence of autistic traits that are not severe enough to fulfill criteria for an ASD diagnosis. The broader autism phenotype is

considered to be related to genetic liability to ASD (Bishop, Maybery, Maley et al. 2004; Ingersoll 2010; Wheelwright, Auyeung, Allison et al. 2010; Lundstrom, Chang, Kerekes et al. 2011). This quantitative approach has led to the development of the Autism-Spectrum Quotient (AQ) (Baron-Cohen, Wheelwright, Skinner et al. 2001), an instrument now frequently used for measuring autistic traits in different populations (Carroll & Yung 2006; Wakabayashi, Baron-Cohen, Wheelwright et al. 2006; Hoekstra, Bartels, Cath et al. 2008; Lepage, Lortie, Taschereau-Dumouchel et al. 2009). The AQ is a 50-item, self-administered questionnaire, which was originally developed as a screening instrument for ASD among adults with intelligence within the normal range, and has been applied as such in several studies (Woodbury-Smith, Robinson, Wheelwright et al. 2005; Brugha, McManus, Bankart et al. 2011). Additionally, it has been used in evaluation against other personality measures (Austin 2005; Kunihira, Senju, Dairoku et al. 2006; Wakabayashi, Baron-Cohen & Wheelwright 2006). As already mentioned, the above described issue on overlap between schizoid/schizotypal PD and ASD, has been addressed on the level of personality *traits* (schizotypal traits versus autistic traits) by use of AQ (Hurst et al. 2007; Claridge & McDonald 2009; Russell-Smith, Maybery & Bayliss 2011). Taken together, the AQ has become a widely used measure in the field of autism spectrum research as well as in research on personality traits.

To date, only a few studies using the AQ have included psychiatric patients with other diagnoses than ASD. Patients with obsessive-compulsive disorder and patients with social anxiety disorder have been demonstrated to have intermediate AQ scores compared to patients with ASD and controls, although sample sizes have been small (Cath, Ran, Smit et al. 2008). In another study, individuals diagnosed with attention-deficit/hyperactivity disorder (ADHD) had significantly lower AQ scores compared to individuals with ASD. However it was concluded that the instrument was of limited use in differentiating between the two conditions (Sizoo, van den Brink, van Eenige et al. 2009). Three previous studies have applied the AQ on patients with schizophrenia. One of these reported higher AQ scores for schizophrenia patients compared to non-clinical control subjects, although the study did not include an ASD comparison group (Koelkebeck, Pedersen, Suslow et al. 2010). In a Japanese study, an ASD group (including both AS and AD) and a schizophrenia group were compared to each other, indicating significantly higher scores on AQ for the ASD group (Naito, Matsui, Maeda et al. 2010). In two separate papers, Spek and Wouters reported results on AQ for 21 men with schizophrenia, 21 men with AD and 21 non-clinical comparison men (Spek & Wouters 2010; Wouters & Spek 2011), finding both clinical groups

showing higher levels of autistic traits compared to the non-clinical group; those with AD had higher scores than those with schizophrenia.

1.5 Neurocognitive impairments

Although not within the diagnostic criteria for either concept, deficits in neurocognition, in particular executive functions, have been shown to be prominent in both schizophrenia and ASD (Szoke, Trandafir, Dupont et al. 2008; Bora, Yucel & Pantelis 2009; Pisula 2010). A few comparative studies on neurocognitive abilities have been undertaken (Goldstein, Minshew, Allen et al. 2002; Bolte, Rudolf & Poustka 2002), but they have been too few and too small for firm conclusions to be drawn. The extensive research on neurocognition within each domain indicates a great deal of heterogeneity, both concerning neuropsychological patterns and courses. Consequently, a “specific” neurocognitive profile has not been possible to identify.

1.6 Social cognitive impairments

Impairments in the area of social cognition are characteristic of both ASD and schizophrenia (Abdi & Sharma 2004; Sasson, Pinkham, Carpenter et al. 2011). Although related to neurocognition, social cognition is considered a separate cognitive domain (Sergi, Rassovsky, Widmark et al. 2007; Pickup 2008). Social cognition can be defined as “the mental operations underlying social interactions, which includes the human ability to perceive the intentions and dispositions of others and the cognitive processes that subserve behaviour in response to others”. It is a central human cognitive ability, essential for understanding social information (Brothers 1990; Frith & Frith 2007). Social cognition is an umbrella concept including functions such as theory of mind, attributional style, and social perception. Theory of mind (ToM) is a social cognitive faculty - sometimes equated with empathy - that involves the ability to attribute independent mental states to self and others in order to explain and predict behaviour. Attributional style is described as an individual’s characteristic way of explaining events (Pinkham, Penn, Perkins et al. 2003; Penn, Sanna & Roberts 2008). Social perception comprises abilities crucial for social cognition such as emotion perception, including facial affect recognition, and social cue recognition. Certainly, these different components affect each other: an excellent social perception (to perceive another person’s facial expression) may facilitate theory of mind ability (to put the perception in a context and make expectations out of it) although this connection does not mean that the concepts are equivalent.

Extensive research on different aspects of social cognition disabilities in ASD, in particular ToM and social perception, has shown predominantly reduced performance (Klin 2000; Tager-Flusberg 2007; Pisula 2010; Pelphrey, Morris, McCarthy et al. 2007), even though real life impairments can be difficult to fully capture in experimental tasks. In the last decade, there has been an increasing focus on social cognitive deficits also in schizophrenia and closely related disorders. Numerous studies have shown that people with schizophrenia perform poorly on tests of social cognition, both those that are considered to reflect ToM and social perception (Couture, Penn & Roberts 2006; Sprong et al. 2007; Green, Penn, Bentall et al. 2008). It has been shown that social cognitive impairment is a major factor contributing to low functional outcome among patients with schizophrenia (Bell, Tsang, Greig et al. 2009; Fett, Viechtbauer, Dominguez et al. 2011; Couture, Granholm & Fish 2011). Moreover, in schizotypy as well, some findings demonstrate that social cognitive impairments are prominent (Langdon & Coltheart 1999; Schiffman, Lam, Jiwatram et al. 2004).

Although social cognition is of great current research interest in both ASD and schizophrenia, only a few prior studies have made direct comparisons between the two conditions. One recent study comparing ToM in the two disorders, demonstrated worse performance in individuals with AS. However, schizophrenia patients with a high level of negative symptoms showed as marked ToM impairments as the AS group (Ozguven, Oner, Baskak et al. 2010). A few small-scale studies on adults have revealed no differences between schizophrenia and “high-functioning” ASD on social cognition tasks (Craig, Hatton, Craig et al. 2004; Murphy 2006; Couture, Penn, Losh et al. 2010). One study on children showed poor ToM abilities in both ASD and schizophrenia (Pilowsky, Yirmiya, Arbelle et al. 2000). In contrast, a study on facial affect recognition in children and young adults, those with ASD performed significantly worse than those with schizophrenia (Bolte & Poustka 2003). A small comparative study indicated a shared abnormality between the two disorders in utilizing facial information (Sasson, Tsuchiya, Hurley et al. 2007). Neural activation during social cognitive demands was compared in an fMRI study, showing a similar pattern between ASD and paranoid schizophrenia, but not between ASD and non-paranoid schizophrenia (Pinkham et al. 2008).

1.7 Genetic overlap

Both ASD and schizophrenia demonstrate considerable heritability (Freitag 2007; Tandon, Keshavan & Nasrallah 2008; Bourgeron 2009), and genetic

research has been in focus for both domains since many years. Recent studies demonstrate clear genetic overlaps between the two domains, and challenge the previous view of genes specific to a particular syndrome (Fatemi 2010; Owen et al. 2011). Two large case-control studies have shown that parental schizophrenia is a risk factor for ASD ((Larsson, Eaton, Madsen et al. 2005; Daniels, Forssen, Hultman et al. 2008). Findings suggest several genomic factors associated with both autism and schizophrenia, examples of genes in focus for both domains are the SHANK3 gene and CNTNAP2 gene (Rapoport et al. 2009; Burbach & van der Zwaag 2009). Additionally, several copy number variants (CNV) have been shown to be of interest (Cook & Scherer 2008; McCarthy, Makarov, Kirov et al. 2009).

2 AIMS

The main aim of the present thesis was to examine similarities and differences between AS and schizophrenia in young adults using a cross-sectional approach. More specifically, the aims were:

- 1) to investigate psychiatric comorbidity in adults with AS, in particular the occurrence of psychotic disorders,
- 2) to estimate the rate at which individuals with AS meet full DSM-IV diagnostic criteria for personality disorders, in particular in relation to the schizophrenia spectrum,
- 3) to compare self-reported autistic traits across AS, schizophrenia, and “normality”,
- 4) to compare social cognition abilities across AS, schizophrenia, and “normality”.

3 METHODS

3.1 Participants

An overview of all participants in the four substudies of the present thesis is given in Table 5. All four substudies (I-IV) included one group with clinically diagnosed AS. Studies III and IV also included one group with schizophrenic psychosis (SP) and one non-clinical comparison group (NCC). The number of cases included in each substudy varied somewhat owing to withdrawal before completing all assessments. Eligibility and attrition will be described separately for each of the clinical groups. The original intention was to include 30 men and 30 women in each diagnostic group (AS and SP), however, due to resource and time constraints, this objective was not fully achieved. A diagnosis of intellectual disability (intellectual developmental disorder/mental retardation) was considered an exclusion criterion for all study groups (AS, SP and NCC).

Table 5. Overview of all participants in AS, SP and NCC groups

| | <i>AS study group</i> | <i>SP study group</i> | <i>NCC study group</i> |
|-------------------|-----------------------|-----------------------|------------------------|
| Total | 55 | 37 | 50 |
| Male: Female | 27: 28 | 23: 14 | 19: 31 |
| Mean age (SD) | 27.2 (4.1) | 28.9 (4.3) | 28.8 (9.3) |
| Included in study | I-IV | III, IV | III, IV |

3.1.1 Asperger syndrome/AS (I-IV)

Recruitment sources

The 55 participants (27 men, 28 women) with AS were recruited from two different sources: (1) current or previous patients at the Department of Adult Habilitation (DAH) in Karlstad, Värmland county, which is an out-patient clinic for individuals aged 19 years and older with a diagnosis of ASD, (2) previous patients at the Neuropsychiatric Clinic for Children and Adolescents (NCCA) in Karlstad, which is an outpatient clinic for individuals under age 19 years for assessment of ASD and other neurodevelopmental problems. Both the DAH and NCCA are regional centres within the public health services, free of charge and with a catchment area that includes the whole county of Värmland (population c. 280 000). DAH has a broad range of professional support: some patients have major needs and long-term treatment contacts, whereas others come for a single visit for general

information. Its focus is on neurodevelopmental disorders and not on psychiatric treatment. In the county, there exists no other clinic for adults with ASD, and the majority of adults who have ever been given a clinical diagnosis of AS in the area are known at DAH. Moreover, most children and adolescents diagnosed with AS in the county are evaluated at NCCA. Thus, when intending to systematically reach clinically diagnosed individuals regardless of age at AS diagnosis, the two clinics are the most adequate to approach in this particular geographic area.

Eligibility and attrition

At DAH and NCCA, all patients with a registered clinical diagnosis of AS, born between 1972 and 1986, and still living in the county of Värmland at the end of 2005, were considered eligible for the study (n=155). Recruitment and assessment of participants was done in order of age, starting with the oldest individuals. Eligible individuals were sent or given a participation inquiry. Additional oral information about the study was provided for those who requested it. If no response had been received after 4-6 weeks, a reminder was sent.

Forty-eight of the 155 eligible individuals (31%) did not respond at all, 46 (30%) actively declined participation and 61 (39%) agreed to participate. After complete description of the study to the participant, written informed consent was obtained. Six of the 61 individuals left the study before any assessment was completed, leaving 55 (35% of the total eligible group, 51% of those who responded) for in-depth assessment. There were no significant differences as regards age at diagnosis of AS or age at being approached for participation in the study across those who did not respond, those who refused to participate, and the group that participated in the final study. However, the three groups differed as regards gender, more males failing to respond to the participation inquiry. The three subgroups of eligible individuals also differed in respect of recruitment source: a larger proportion of the non-responders had attended only the NCCA.

One man did not complete full assessment for study I. Another man was not assessed for study II, III or IV due to withdrawal. (This means that for studies I and II, a total of 54 individuals with AS were included in the analyses). Data essential for study III was missing for two men. (This means that for study III, a total of 51 individuals with AS were included in the analyses). One woman withdrew before assessment for study III and IV was accomplished. (This means that for study IV, a total of 53 individuals with AS were included in the analyses).

Characteristics

Fifty-five individuals with AS participated in at least one of the four studies: 27 men (mean age 26.8 years) and 28 women (mean age 27.5 years). Mean age at original AS diagnosis was 19.0 years (SD 7.6). Seven individuals (13%) had received their AS diagnosis when they were 10 years or younger, 19 (35%) between the ages of 11 and 18 years, and 29 (53%) when they were 19 years or older. Four participants (7%) were previous patients at NCCA and never known at DAH, 14 (25%) were known at both NCCA and DAH, and 37 participants (67%), were current or previous patients at DAH, never known at NCCA. Demographic characteristics of the AS study group are presented in Table 6.

Table 6. Demographic characteristics of the AS study group

| Characteristic | Total (n=55) | | Women (n=28) | | Men (n=27) | |
|--|---------------------|-----------|---------------------|-----------|-------------------|-----------|
| | Mean | SD | Mean | SD | Mean | SD |
| Age (years) | 27.2 | 4.1 | 27.5 | 4.3 | 26.8 | 3.8 |
| Age at AS diagnosis | n | % | n | % | n | % |
| ≤10 years | 7 | 13 | 2 | 7 | 5 | 19 |
| 11-18 years | 19 | 35 | 12 | 43 | 7 | 26 |
| >18 years | 29 | 53 | 14 | 50 | 15 | 56 |
| Maximum educational level | | | | | | |
| Special school | 3 | 5 | 1 | 4 | 2 | 7 |
| Compulsory school (regular program) | 4 | 7 | 3 | 11 | 1 | 4 |
| High school studies without exam | 18 | 33 | 9 | 32 | 9 | 33 |
| High school final exam | 23 | 42 | 12 | 43 | 11 | 41 |
| University (with or without degree) | 7 | 13 | 3 | 11 | 4 | 15 |
| Source of income | | | | | | |
| Dependent on social services | 7 | 13 | 5 | 18 | 2 | 7 |
| Disability pension | 32 | 58 | 16 | 57 | 16 | 59 |
| Combination disab pension/social service | 3 | 5 | 2 | 7 | 1 | 4 |
| Combination disab pension/employment | 4 | 7 | 1 | 4 | 3 | 11 |
| Study grant | 2 | 4 | 1 | 4 | 1 | 4 |
| Supported employment | 4 | 7 | 1 | 4 | 3 | 11 |
| Regular employment | 3 | 5 | 2 | 7 | 1 | 4 |
| Daily occupation | | | | | | |
| No daily occupation | 22 | 40 | 15 | 54 | 7 | 26 |
| Sheltered occupational activity | 15 | 27 | 6 | 21 | 9 | 33 |
| Employment (supported or regular) | 11 | 20 | 4 | 14 | 7 | 26 |
| Studies (different levels) | 7 | 13 | 3 | 11 | 4 | 15 |

3.1.2 Schizophrenic psychosis/SP (III, IV)

Recruitment sources

The 37 individuals, 23 men (mean age 28.9), 14 women (mean age 28.9), with a clinical diagnosis of schizophrenic psychosis (SP) (schizophrenia, schizoaffective disorder or schizophreniform disorder) were recruited from the only psychiatric outpatient clinic in the county of Värmland (n=33) or one of the psychiatric outpatient clinics in Gothenburg (n=4). In Värmland, all adult psychiatric services were in the public domain at the time of the studies, and organized at the county level into one clinic. In order to reach a sufficient number of study participants, the original intention was to also recruit patients from an outpatient clinic (public domain) for patients with psychosis in the city of Gothenburg. Due to practical circumstances, only four patients were included from this clinic.

Eligibility and attrition

At the psychiatric clinic in Värmland, all patients with a registered clinical diagnosis of SP, born between 1972 and 1986, and still living in the county of Värmland at the end of 2005, were considered eligible for the study (n=84). Staffs at the various departments of the clinic were asked to inform patients about the study, and to provide a participation inquiry. Patients who did not have an ongoing contact at the clinic were sent a participation inquiry by mail. Additional oral information about the study was provided for those who requested it. If no response had been received after 4-6 weeks, a reminder was sent. Individuals with current severe psychotic symptoms requiring hospitalisation were approached when symptoms were considered less florid. After complete description of the study to the participant, written informed consent was obtained.

Thirty men from Värmland (52% of the whole eligible group) accepted to participate, but two of them withdrew before the first assessment. Seventeen women from Värmland (65% of all eligible women) accepted to participate. Two of them changed their mind before entering the study. One woman was excluded because the diagnosis had never been confirmed by a psychiatrist. Thus, 42 patients (28 men, 14 women) from Värmland with a clinical diagnosis of schizophrenic psychosis were originally included. From the Gothenburg outpatient clinic, four patients (one man, three women) with SP were recruited.

Thus, a total of 46 patients with a clinical diagnosis of SP were originally included in the study. However, after administering the Structured Clinical Interview for DSM-IV diagnosis (SCID-I) (First and Gibbon, 2004), five

patients were excluded since a diagnosis of SP could not be confirmed. Two patients (one man, one woman) did not fulfil criteria for any psychotic disorder, two men were shown to have bipolar I disorder, and one man met criteria for substance-induced psychotic disorder instead. A diagnosis of SP was verified in 36 of the remaining 41 patients. Five patients met criteria for psychotic disorder NOS instead; all five of these had a history of several, schizophrenia-like psychotic episodes requiring inpatient treatment, however a distinction between schizoaffective disorder and schizophrenia was not possible due to uncertain information on mood symptoms, neither was a distinction between schizophrenia and schizophreniform disorder possible due to uncertain information on the duration of episodes. On the basis of the SCID-I-based symptom information, and because their original clinical diagnosis had been a SP diagnosis, these five patients with psychotic disorder NOS were still retained for participation in the study and are referred to as a part of the SP study group. Unfortunately, four patients (two men, two women) withdrew before assessment necessary for study III and IV was completed. One man did not complete assessment required for study IV and missing data excluded one woman from study III. Consequently, out of the remaining 37 individuals constituting the SP group, 36 (23 men, 13 women) participated in study III and 36 (22 men, 14 women) participated in study IV, out of whom 35 individuals took part in both studies.

Additionally, in order to estimate whether the recruited sample was as complete and representative as possible, the number of eligible patients from Värmland (n=84) was compared to results from a nation-wide Swedish study using register data. In that study, performed by Hultman *et al* as part of the International Schizophrenia Consortium study (ISC, 2008), cases were identified via the Swedish Hospital Discharge Register, which contains a register of all individuals hospitalized in Sweden since 1973. Each record contains the main discharge diagnosis, as well as secondary diagnoses. Patients with a discharge diagnosis of schizophrenia who had at least two admissions were included. From the county of Värmland a total of 80 individuals (50 men and 30 women) born in our target years 1972-1986 met these criteria. In contrast to our study, intellectual disability was not an exclusion criterion. Numbers found in the register study are not widely discrepant from those found by us, providing support for the notion that our eligible group of participants is as close to a representative sample of individuals with a clinical diagnosis of schizophrenic psychosis, as would be possible to identify and contact in a general population setting. Based on these numbers, the prevalence of schizophrenic psychosis in Värmland for persons born in 1972 to 1986 was 0.2%.

Characteristics

Demographic characteristics of the 37 individuals in the SP group in any of the studies III or IV are shown in Table 7. SCID-I-based diagnoses for the SP group are shown in Table 8.

Table 7. Demographic characteristics of the SP study group

| <i>Characteristic</i> | <i>Total (n=37)</i> | | <i>Women (n=14)</i> | | <i>Men (n=23)</i> | |
|--|---------------------|-----------|---------------------|-----------|-------------------|-----------|
| | Mean | SD | Mean | SD | Mean | SD |
| Age (years) | 28.9 | 4.3 | 28.9 | 4.7 | 28.9 | 4.1 |
| Age at onset of psychosis (years) | 22.0 | 4.1 | 22.9 | 4.8 | 21.6 | 3.5 |
| Maximum educational level | n | % | n | % | n | % |
| Special school | - | - | - | - | - | - |
| Compulsory school (regular program) | - | - | - | - | - | - |
| High school studies without exam | 13 | 35 | 5 | 36 | 8 | 35 |
| High school final exam | 18 | 49 | 6 | 43 | 12 | 52 |
| University (with or without degree) | 6 | 16 | 3 | 21 | 3 | 13 |
| Source of income | | | | | | |
| Dependent on social services | 3 | 8 | 1 | 7 | 2 | 9 |
| Disability pension | 30 | 81 | 11 | 79 | 19 | 83 |
| Combination disab pension/social service | - | - | - | - | - | - |
| Combination disab pension/employment | 1 | 3 | - | - | 1 | 4 |
| Study grant | 1 | 3 | - | - | 1 | 4 |
| Supported employment | - | - | - | - | - | - |
| Regular employment | 2 | 5 | 2 | 14 | - | - |
| Daily occupation | | | | | | |
| No daily occupation | 25 | 68 | 8 | 57 | 17 | 74 |
| Sheltered occupational activity | 8 | 22 | 4 | 29 | 4 | 17 |
| Employment (supported or regular) | 3 | 8 | 2 | 14 | 1 | 4 |
| Studies (different levels) | 1 | 3 | - | - | 1 | 4 |

Table 8. SCID-I diagnoses of the SP study group

| <i>SCID-diagnosis</i> | <i>Total (n=37)</i> | | <i>Women (n=14)</i> | | <i>Men (n=23)</i> | |
|--------------------------------------|---------------------|----------|---------------------|----------|-------------------|----------|
| | n | % | n | % | n | % |
| Schizophrenia, paranoid type | 17 | 46 | 7 | 50 | 10 | 43 |
| Schizophrenia, undifferentiated type | 6 | 16 | 1 | 7 | 5 | 22 |
| Schizoaffective disorder | 6 | 16 | 4 | 29 | 2 | 9 |
| Schizophreniform disorder | 3 | 8 | - | - | 3 | 13 |
| Psychotic disorder NOS | 5 | 8 | 2 | 14 | 3 | 13 |

3.1.3 Non-clinical comparison/NCC (III, IV)

Recruitment source

The 50 individuals, 19 men (mean age 25.8), 31 women (mean age 30.7) in the NCC group were recruited from among students at Karlstad University, studying on different programmes (e. g. nursing, teaching, engineering). Recruitment was done by information on general notice boards. Participation was voluntary and did not influence any course credit. Data essential for study III was missing for one woman.

Characteristics

Participants in the NCC group were evaluated with a short questionnaire including educational data and data on occurrence of ASD, ADHD or psychosis. No participant in the NCC group had a reported history of any of these diagnoses.

3.2 Measurements

3.2.1 Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (I-IV)

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First & Gibbon 2004) is a semi-structured interview, widely used in research and in clinical practice for systematic assessment of axis-I psychiatric morbidity according to DSM-IV. The SCID-I was performed in (1) the AS group so as to investigate concomitant psychiatric morbidity (study I-II), and in (2) the SP group so as to confirm clinical diagnosis (see 3.1.2) (study III-IV).

3.2.2 Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) (II)

The Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) (First & Gibbon 2004) is a semi-structured interview for systematic assessment of personality disorders according to DSM-IV. It was performed to investigate the occurrence of concomitant personality disorders in the AS group. In order to make the present issues possible to investigate, exclusion criteria for pervasive developmental disorder (PDD) were disregarded. (Criterion E in general diagnostic criteria for personality disorders in DSM-IV-TR, and criterion B for schizoid PD and schizotypal PD respectively.)

3.2.3 Diagnostic Interview for Social and Communication Disorders, 11th version (DISCO-11) (I-IV)

The DISCO-11 is a 2-4 hour semi-structured interview intended for use with a person (usually a parent) who knew the individual with a suspected ASD from early childhood (Wing, Leekam, Libby et al. 2002). The DISCO-11 covers a wide range of developmental domains, and with excellent psychometric properties including validity for clinical PDD/ASD diagnoses. Algorithms, based on DSM-IV criteria as well as ICD-10 criteria, are designed for the different diagnostic categories. The Swedish translation of DISCO-11 (Nygren, Hagberg, Billstedt et al. 2009) was used in the present study. It was performed in (1) the AS group with a view to confirming the clinical diagnosis, and in (2) the SP group as part of a separate study by Hallerbäck with a view to investigate the presence of an ASD (Hallerbäck, Lugnegård & Gillberg *submitted for publication*).

3.2.4 Autism-Spectrum Quotient (AQ) (II, III)

The Autism-Spectrum Quotient (AQ) is a self-administered questionnaire developed in the UK for the explicit purpose of measuring autistic traits in adults of normal intelligence (Baron-Cohen, Wheelwright, Skinner et al. 2001). It consists of five subscales, each comprising 10 items, covering five different domains: “Social skill”, “Attention switching”, “Attention to detail”, “Communication” and “Imagination”. Each AQ item is a brief statement followed by four possible ratings: “definitely agree”, “slightly agree”, “slightly disagree” or “definitely disagree”. In order to avoid response bias, approximately half the items are worded to produce a “disagree” response and half an “agree” response. According to the original scoring procedure, each item scores one point if the respondent endorses the feature either mildly or strongly (“0 or 1 response”), yielding a range of scores from 0 to 50 (the higher the more autistic traits). Subsequent studies, however, have predominantly applied a scoring procedure taking the full 1-4 Likert scale into account, which renders a range of scores from 50 to 200 (yet again, the higher score, the more autistic traits). For the sake of clarity, our results are reported according to both scoring procedures for the total AQ score. Results on subscales are reported according to full 1-4 Likert scoring procedure.

3.2.5 Vocabulary subtest of Wechsler Adult Intelligence Scale, Third Edition (III, IV)

Verbal ability was measured using the subtest Vocabulary of the Swedish version of the Wechsler Adult Intelligence Scale, Third Edition, (WAIS-III) (Wechsler 1997) in the three groups.

3.2.6 Animations Task (IV)

The Animations Task by Frith, Castelli and Happé consists of 12 (3x4) computer-presented animations, lasting 34-45 s each, where a big red triangle and a small blue triangle move around the screen (Abell, Happe, & Frith 2000; Castelli, Happe, Frith et al. 2000). (See Fig.1.) There are three types of animations: random movements, goal-directed movements (GD) and animations where the triangles are moving as if they know what the other triangle is thinking or feeling (Theory of Mind, ToM). The participants were informed that they would be shown a series of animations and that they would be asked to provide a description of how they perceived the movements after each animation. Three practice animations were shown to begin with, in order to familiarize the participant with the task. Then the 12 animations were presented in a mixed order. After each animation, the participant was given the neutral question “What was happening in this animation?” On no occasion was feedback given on the content of the responses, but participants were generally praised for their descriptions. Responses were recorded, transcribed and later scored according to a scoring manual. Scoring procedure was based on work by Castelli et al (Castelli, Frith, Happe et al. 2002). Each description was rated according to 1) Appropriateness and to 2) Intentionality.

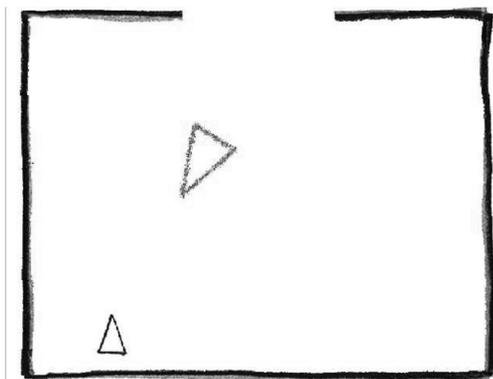


Figure 1. Still from the Animations Task.

The *Appropriateness score* range is 0-3 for each animation (there are four animations of each of the three types (random, GD and ToM), so the maximum total score is 12 for each type of animation) according to how accurately the description captures the events in the animation, as intended by the underlying script: 0=no answer or “I don’t know”; 1=inappropriate answer with reference to the wrong type of interaction between the triangles or focuses only on a minor aspect of the animation; 2=partial description of the sequence, description is related to the sequence but imprecise or incomplete; 3=a spot-on description of the story of the actions presented.

The *Intentionality score* range is 0-5 for each animation (maximum total score 20 for each of the three types (random, GD and ToM) of animation) and reflects the degree to which the participant describes complex, intentional mental states. On this score the *verbs* of the narrative are in focus. The verbs are rated independently of whether they correctly match the underlying script: 0=non-deliberate action (e.g. ”bouncing off”, “moving around”); 1=deliberate solitary action (e.g. “swimming”, “ice-skating”); 2=deliberate action with somebody else (e.g. “dancing”, “following”); 3=deliberate action in response to others actions (e.g. “the big one is preventing the little one to get out”) ; 4=deliberate action with reference to mental states (e.g. “being happy”, “they are arguing”); 5=deliberate action with explicit goal of effecting other’s mental state (e.g. “surprising”, “persuading” or “teasing”). Thus, a particular description can be rated low on Intentionality and high on Appropriateness and vice versa. The scoring procedure was blinded: no personal data on participants were included in the transcripts, and group affiliation could not be revealed in any other way.

3.2.7 Reading the Mind in the Eyes Test (IV)

A Swedish version of the Reading the Mind in the Eyes Test (Eyes Test) was used. It is a translation and abbreviation of the Baron-Cohen child version (Baron-Cohen, Wheelwright, Hill et al. 2001; Baron-Cohen, Wheelwright, Spong et al. 2001) consisting of 24 black and white photographs of the eye region illustrating complex mental states. The participant is asked to choose which of four words best describes what the person in the photograph is feeling or thinking. Responses are scored 1 or 0 for correctness, meaning that the maximum score on the Swedish version of the Eyes Test is 24. This abbreviated Swedish version has previously been tested on 158 students, and the test-retest reliability has been examined, showing limits of agreement (Bland-Altman plot) of +/-4 points (Hallerbäck, Lugnegård, Hjärthag et al. 2009).

3.3 Ethics

All participants provided informed consent and were seen personally in an out-patient setting. The study was approved by the Medical Ethical Review Board at Uppsala.

3.4 Statistical analyses

The PASW Statistics 18.0 was used for all analyses. All statistical tests were two-tailed. The significance level was set at 0.05. Analysis of Covariance (ANOVA) and chi square test were used for analyzing group differences in demographic characteristics. Chi square tests were further used when comparing categorical variables in study II. In study III and study IV, scores for the applied measurements were (1) not continuous variables, but on an ordinal level and (2) could not be assumed to be normally distributed; therefore, non-parametric statistical tests were used. Kruskal-Wallis tests were first performed as omnibus testing of overall group differences. For *post hoc* between-group comparisons the Mann-Whitney U-test was applied. Holm-Bonferroni correction for multiple comparisons (Holm 1979; Pett 1997) was performed whenever appropriate. In study IV, associations between social cognition measures and verbal ability were evaluated with Spearman's correlation coefficients.

4 RESULTS

4.1 Psychiatric comorbidity in AS (I)

Thirty-eight of the 54 participants in the AS group (70%) had experienced at least one episode of major depression, and 27 of these (50% of the total group) had had recurrent major depressions. Five participants (9% of the total group) met criteria for bipolar II disorder, whereas none met criteria for bipolar I disorder. Thirty individuals (56%) met criteria for at least one anxiety disorder, and 11 of these fulfilled diagnostic criteria for two or more anxiety disorder diagnoses. Twelve (22%) had social anxiety disorder, 12 (22%) had generalized anxiety disorder, seven (13%) had panic disorder, eight (15%) had agoraphobia and four participants (7%) had obsessive-compulsive disorder. Two individuals met criteria for psychosis: one for brief psychotic disorder and one for psychotic disorder NOS. Seven participants (13%) had experienced recurrent (primarily auditory) hallucinations without other signs of psychosis. No participant met criteria for schizophrenia, schizoaffective disorder or substance induced psychotic disorder. Two participants (4%) had bulimia nervosa, and none had anorexia nervosa. Six participants (11%) had had a previous substance dependence disorder (one woman and one man with a combination of alcohol and drug dependence, two men with alcohol dependence and two men with drug dependence). Sixteen participants (30%) had been given a diagnosis of AD/HD before the study. One individual (2%) had been diagnosed with Tourette syndrome. No gender differences were seen in terms of psychiatric comorbidity. The distribution of diagnoses is shown in Table 9.

Table 9. Psychiatric comorbidity in 54 young adults with AS

| <i>Disorders based on SCID-I</i> | <i>Total (n=54)</i> | | <i>Women (n=28)</i> | | <i>Men (n=26)</i> | |
|---------------------------------------|---------------------|----------|---------------------|----------|-------------------|----------|
| | n | % | n | % | n | % |
| Mood disorders | | | | | | |
| Life-time major depression | 38 | 70 | 20 | 71 | 18 | 69 |
| Depression, single episode | 11 | 20 | 7 | 25 | 4 | 15 |
| Depression, recurrent episodes | 27 | 50 | 13 | 46 | 14 | 54 |
| Bipolar I disorder | - | - | - | - | - | - |
| Bipolar II disorder | 5 | 9 | 3 | 11 | 2 | 8 |
| Anxiety disorders | | | | | | |
| Any anxiety disorder | 30 | 56 | 16 | 57 | 14 | 54 |
| Generalized anxiety disorder | 12 | 22 | 7 | 25 | 5 | 19 |
| Social anxiety disorder | 12 | 22 | 5 | 18 | 7 | 27 |
| Panic disorder | 7 | 13 | 5 | 18 | 2 | 8 |
| Agoraphobia | 8 | 15 | 4 | 14 | 4 | 15 |
| Obsessive-compulsive disorder | 4 | 7 | 1 | 4 | 3 | 12 |
| Life-time psychotic disorders | | | | | | |
| Brief psychotic disorder | 1 | 2 | 1 | 4 | - | - |
| Psychotic disorder NOS | 1 | 2 | - | - | 1 | 4 |
| Schizophrenic disorder | - | - | - | - | - | - |
| Schizoaffective disorder | - | - | - | - | - | - |
| Substance-induced psychosis | - | - | - | - | - | - |
| Recurrent hallucinations | 7 | 13 | 4 | 14 | 3 | 11 |
| Life-time eating disorders | | | | | | |
| Anorexia nervosa | - | - | - | - | - | - |
| Bulimia nervosa | 2 | 4 | 2 | 7 | - | - |
| Life-time substance dependence | | | | | | |
| Any substance dependence | 6 | 7 | 1 | 4 | 5 | 19 |
| Alcohol dependence | 4 | 7 | 1 | 4 | 3 | 12 |
| Drug dependence | 4 | 7 | 1 | 4 | 3 | 12 |
| Other disorders | | | | | | |
| ADHD | 16 | 30 | 8 | 29 | 8 | 31 |
| Tourette syndrome | 1 | 2 | - | - | 1 | 4 |

4.2 DSM–IV PD diagnostic criteria met in AS group (II)

Twenty-eight (19 women, 9 men) of the 54 participants (52%) did not meet criteria for any axis-II disorder. Twenty-six participants (48%) (9 women and 17 men) did meet criteria for at least one axis-II disorder, 5 of whom (3 women and 2 men) met criteria for at least two axis-II-disorders. There was a significant difference across genders, men with AS meeting PD-criteria much more often than women with AS (65% versus 32%, $p < 0.05$, Chi-square with Yates's correction).

Fourteen participants (26% of the whole AS group) (5 women and 9 men) met criteria for schizoid PD, 7 (13%) (3 women and 4 men) met criteria for avoidant PD, and 10 (19%) (3 women and 7 men) met criteria for obsessive-compulsive PD. One individual (a woman) met criteria for schizotypal PD. None met criteria for paranoid PD, antisocial PD, histrionic PD, borderline PD, narcissistic PD or dependent PD respectively. For distribution of axis-II diagnoses, see Table 10, and for overlap of axis-II diagnoses, see Table 11.

Table 10. Axis-II diagnoses in 54 young adults with AS

| <i>Axis-II diagnosis</i> | <i>Total (n=54)</i> | | <i>Women (n=28)</i> | | <i>Men (n=26)</i> | |
|--------------------------|---------------------|----------|---------------------|----------|-------------------|----------|
| | <i>n</i> | <i>%</i> | <i>n</i> | <i>%</i> | <i>n</i> | <i>%</i> |
| <i>Cluster A</i> | | | | | | |
| Paranoid PD | - | - | - | - | - | - |
| Schizoid PD | 14 | 26 | 5 | 18 | 9 | 36 |
| Schizotypal PD | 1 | 2 | 1 | 4 | - | - |
| <i>Cluster B</i> | | | | | | |
| Antisocial PD | - | - | - | - | - | - |
| Histrionic PD | - | - | - | - | - | - |
| Borderline PD | - | - | - | - | - | - |
| Narcissistic PD | - | - | - | - | - | - |
| <i>Cluster C</i> | | | | | | |
| Avoidant PD | 7 | 13 | 3 | 11 | 4 | 16 |
| Obsessive-compulsive PD | 10 | 19 | 3 | 11 | 7 | 27 |
| Dependent PD | - | - | - | - | - | - |

Table 11. Overlap of diagnoses in 5 individuals with more than one axis-II-diagnosis

| | Case no | | | | |
|-------------------------|----------|----------|----------|------------|-----------|
| | 1 (male) | 2 (male) | 3 (male) | 4 (female) | 5(female) |
| Schizoid PD | | X | X | | X |
| Schizotypal PD | | | | | X |
| Avoidant PD | X | | | X | |
| Obsessive-compulsive PD | X | X | X | X | X |

4.3 Comparison of self-reported autistic traits in AS, SP, and NCC (III)

Self-report of autistic traits was measured by the AQ. The distribution of AQ total scores is shown in Fig. 2.

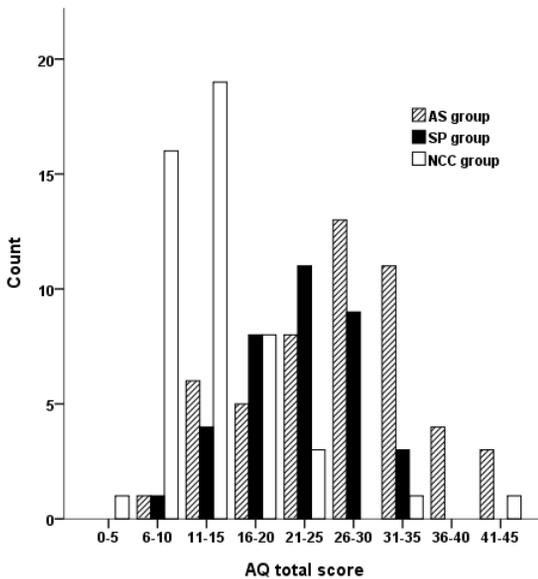


Figure 2. Distribution of AQ scores in AS, SP and NCC groups (maximum total score =50)

Median scores for AQ total - with a maximum of 50 (dichotomous scoring, range 0-50) as well as for AQ total with a maximum of 200 (using the full 1-4 Likert scale, range 50-200) are presented in Table 12. Irrespective of

scoring procedure, both the AS and the SP groups showed significantly higher scores than the NCC group. The AS group showed a higher median score than the SP group. Results on the AQ subscales scores are shown in Table 12. There were significant overall group differences for all subscales scores. *Post hoc* analyses showed that the SP group had significantly higher scores than the NCC group on all subscales, except “Attention to detail” where no difference was seen. There were no differences between the SP group and the AS group on the majority of subscales, with the exception of “Attention switching” where the AS group showed significantly higher scores. The AS group showed significantly higher scores on all subscales compared to the NCC group.

Table 12. Median scores on AQ total score and subscales

| | AS | SP | NCC | Statistical analysis | | | | | | | |
|---------------------------------|--------------|--------------|--------------|----------------------|-----------------------|-----------------------|-----------------------|------------------------|-----------------------|------------------------|-----------------------|
| | <i>n</i> =51 | <i>n</i> =36 | <i>n</i> =49 | Overall ^c | | AS vs SP ^d | | SP vs NCC ^d | | AS vs NCC ^d | |
| | Median | Median | Median | <i>H</i> | <i>p</i> ^e | <i>U</i> | <i>p</i> ^e | <i>U</i> | <i>p</i> ^e | <i>U</i> | <i>p</i> ^e |
| AQ, max 50 ^a | 28 | 23 | 12 | 57.9 | <.001 | 648 | .020 | 228 | <.001 | 265 | <.001 |
| AQ, max 200 ^b | 129 | 122 | 99 | 49.0 | <.001 | 657 | .024 | 287 | <.001 | 341 | <.001 |
| Subscale ^{b, c} | | | | | | | | | | | |
| Social skill | 26.0 | 24.0 | 17.0 | 38.4 | <.001 | 662 | NS | 401 | <.001 | 373 | <.001 |
| Attention switch | 30.0 | 26.0 | 21.0 | 55.2 | <.001 | 556 | .03 | 280 | <.001 | 261 | <.001 |
| Attention to detail | 27.0 | 24.5 | 24.5 | 8.8 | .012 | 686 | NS | 855 | NS | 776 | .014 |
| Communication | 22.0 | 22.0 | 17.0 | 35.4 | <.001 | 842 | NS | 319 | <.001 | 456 | <.001 |
| Imagination | 24.0 | 24.0 | 19.0 | 24.7 | <.001 | 758 | NS | 855 | <.001 | 597 | <.001 |

^a Dichotomous scoring “0 or 1”; range for total score is 0-50

^b Scoring based on the full Likert scale, 1-4: range for total score is 50-200, for subscale 10-40

^c Kruskal-Wallis test for overall group differences

^d *Post hoc* Mann-Whitney U test

^e Holm-Bonferroni corrected for multiple comparisons

NS=not significant

Additional analysis of AQ scores were performed in the AS group (presented in study II), comparing AQ scores between individuals with and without full criteria for a PD. Individuals with AS meeting PD criteria demonstrated significantly higher AQ total scores compared to individuals with AS not fulfilling PD criteria (median 31.0 vs. median 22.0; $U=134$, $p=.001$).

4.4 Comparison of social cognition ability in AS, SP, and NCC (IV)

Social cognition ability was measured with the Animations Task and the Eyes Test. Median scores and statistical analyses for the total study group are shown in Table 13.

Table 13. Median scores on social cognition measurements

| | AS | SP | NCC | Statistical analysis | | | | | | | |
|-------------------------|--------------|--------------|--------------|----------------------|-----------------------|-----------------------|-----------------------|------------------------|-----------------------|------------------------|-----------------------|
| | <i>n</i> =53 | <i>n</i> =36 | <i>n</i> =50 | Overall ^a | | AS vs SP ^b | | SP vs NCC ^b | | AS vs NCC ^b | |
| | Median | Median | Median | <i>H</i> | <i>p</i> | <i>U</i> | <i>p</i> ^c | <i>U</i> | <i>p</i> ^c | <i>U</i> | <i>p</i> ^c |
| Eyes Test (0-24) | 18.0 | 18.0 | 19.0 | 7.9 | .019 | 779 | NS | 592 | .02 | 1082 | NS |
| Animations Task | Median | Median | Median | <i>H</i> | <i>p</i> ^c | <i>U</i> | <i>p</i> ^c | <i>U</i> | <i>p</i> ^c | <i>U</i> | <i>p</i> ^c |
| RandomApp (0-12) | 11.5 | 11.0 | 11.0 | 0.9 | NS | - | - | - | - | - | - |
| RandomInt (0-20) | 2.0 | 3.0 | 1.0 | 0.8 | NS | - | - | - | - | - | - |
| GD App (0-12) | 10.0 | 9.0 | 10.0 | 7.3 | NS | - | - | - | - | - | - |
| GD Int (0-20) | 9.0 | 10.0 | 11.0 | 8.3 | NS | - | - | - | - | - | - |
| ToM App (0-12) | 8.0 | 6.0 | 10.0 | 33.6 | <.001 | 537 | .002 | 260 | <.001 | 899 | .008 |
| ToM Int (0-20) | 15.0 | 12.0 | 16.0 | 26.6 | <.001 | 578 | .003 | 324 | <.001 | 1001 | .028 |

^a Kruskal-Wallis test for overall group differences.

^b *Post hoc* Mann-Whitney U test.

^c Holm-Bonferroni corrected for multiple comparisons.

NS=not significant.

For the Random animations as well as for the Goal-directed animations, there were no group differences either on Appropriateness score or on Intentionality score. The distributions of ToM Appropriateness scores for the three groups are presented in Fig. 3. There was a significant difference between groups, $H(2) = 33.6$, $p < .001$. *Post hoc* tests showed that the SP group had lower scores than the AS group, which, in turn, had lower scores than the NCC group.

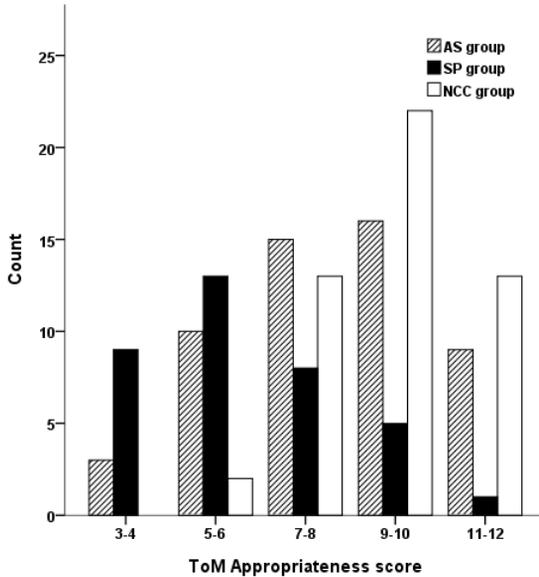


Figure 3. Distribution of scores on Appropriateness in the four ToM animations in AS, SP and NCC groups (maximum total score=12)

The distributions of ToM Intentionality scores for the three groups are presented in Fig. 4. (Intentionality score, 0-5 for each animation, is a measure of verbs used by the participant: the more advanced interaction described, the higher score.) There was a significant group difference, $H(2)=26.6$, $p<.001$. *Post hoc* analysis showed that the SP group had lower scores compared to the AS group, which, in turn, had lower scores than the NCC group.

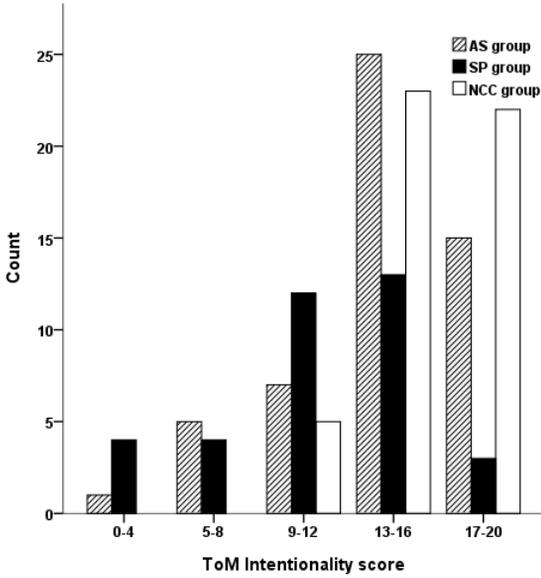


Figure 4. Distribution of scores on Intentionality in the four ToM animations in AS, SP and NCC groups (maximum total score=20)

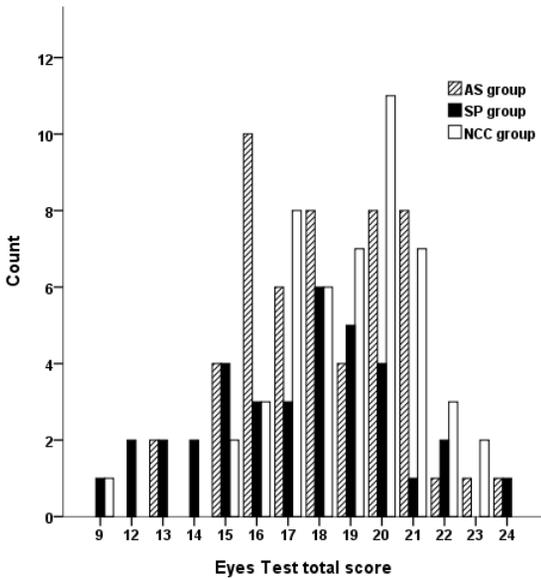


Figure 5. Distribution of scores on the Eyes Test in AS, SP and NCC groups (maximum total score=24)

The distributions of Eyes Test scores are shown in Fig. 5. The overall test revealed a significant group difference, $H(2)=7.9$, $p=.019$, on the Eyes Test. *Post hoc* tests showed a significant difference between the SP group and the NCC group, although no other comparisons showed any significant differences.

4.5 DISCO-11 assessment (I-IV)

In the AS group, DISCO-11 interview with a parent/both parents was completed for 45 (out of 55) participants. Four participants did not agree to parental interview, parents of three participants did not accept to take part and another three have not been possible to assess due to practical circumstances. The diagnosis of AS was confirmed in all of the 45 DISCO-11-assessed cases. However, 20 of these 45 had some ($n=12$) or considerable ($n=8$) symptoms before age 3 years, and were discussed for a diagnosis of AD. However, given that symptom criteria for AS were met in all cases, the clinical AS diagnosis was considered to be confirmed in these cases also.

In the SP group, DISCO-11 interview with a parent/both parents was completed for 27 (out of 37) participants. Two participants did not agree to parental interview, parents of seven participants did not accept to take part and parents of one participant have not been possible to assess due to practical circumstances. Out of the 27 assessed within the SP group, 11 (41 % of the DISCO-assessed, 30 % of the total group) met diagnostic criteria for a childhood ASD diagnosis. Results of the DISCO-11-assessments are described in detail elsewhere (Hallerbäck, Lugnegård & Gillberg *submitted for publication*).

4.6 Vocabulary subtest of WAIS-III (III, IV)

Results on verbal ability as measured by Vocabulary subtest of WAIS-III are shown in Table 14. Due to early withdrawal or unwillingness to perform the subtest, data were missing for six individuals in the AS group and five individuals in the SP group.

Table 14. Results on WAIS-III Vocabulary subtest for the three study groups

| | <i>AS group</i> (<i>n=55</i>) ^a | | <i>SP group</i> (<i>n=37</i>) ^a | | <i>NCC group</i> (<i>n=50</i>) | | <i>Statistics</i> | <i>p</i> |
|-------------------------------------|---|-----|---|-----|-------------------------------------|-----|-------------------|----------|
| | Mean | SD | Mean | SD | Mean | SD | | |
| Vocabulary subtest, scaled score | 10.4 | 2.3 | 9.4 | 2.2 | 9.9 | 2.1 | <i>F=2.176</i> | .118 |

^a Data missing for six participants in the AS group and for five participants in the SP group.

ToM Appropriateness scores as well as ToM Intentionality scores of the Animations Task correlated weakly with the WAIS-III Vocabulary subtest ($r=.20$, $p=.02$ for both measures). Similarly, for the Eyes Test, a weak correlation ($r=.20$, $p=.019$) with WAIS-III Vocabulary subtest was seen (study IV).

5 DISCUSSION

General findings

In study I, it was shown that individuals with AS have a high rate of comorbid psychiatric disorders, mainly mood and anxiety disorders whereas a low rate of psychotic disorders was present. In study II, it was demonstrated that DSM-IV-TR criteria for PDs within cluster A and cluster C were met for about half of the AS study group. In the two comparative studies (III and IV), it was shown that individuals with AS and individuals with SP share a substantial amount of clinical features, both regarding autistic traits and social cognitive impairments. The groups are more similar to each other than what is generally assumed or suggested in the all-dominant diagnostic manuals, in many research papers and in everyday clinical practice.

Limitations

Two limitations of the study are the relatively small sample sizes and the low participation rate out of the total eligible individuals in the two clinical groups. The original objective was to include 30 men and 30 women from each diagnostic group, which was not achieved. In contrast, some basic facts are known about non-participants (sex, age, age at diagnosis for the AS group and recruitment source). One can assume that individuals declining participation may have more severe symptoms compared to study participants, which may have led to an underestimation of psychiatric comorbidity (including psychotic disorders) in the AS group and a bias towards individuals with higher functioning in social cognition and neurocognition in both the AS group and the SP group. However, voluntary participation and informed consent are fundamental principles in clinical research, even in observational studies, and there is no alternative way to address these questions. Another uncertainty is the fact that the non-clinical comparison group was not examined concerning psychiatric symptoms, but only asked (in a questionnaire) whether they had been treated for psychotic disorder or had a diagnosis of ASD or AD/HD.

Unfortunately, there are no “golden standard” measures for social cognitive abilities. The intention was to select instruments with low demands on verbal memory and that captured different aspects of social cognition. Although both the Animations Task and the Eyes Test are relatively easy to carry out, they both have their shortcomings. The Animations Task is recently developed, has a complicated scoring system, has only been used in small studies and there is a lack of population based data. The Eyes Test, on the other hand, is straight-forward to score and frequently used in studies,

however the validity as well as test-retest reliability has been questioned (Spek, Scholte, & Van Berckelaer-Onnes 2010; Hallerbäck et al. 2009). A more advantageous approach would have been to include additional social cognitive measures, however at the expense of time and financial resources. Like other measures in the field of social cognition, data are on an ordinal level, which limits the statistical analyses to non-parametric tests.

The AQ is the most frequently used dimensional instrument for measuring autistic traits in adults. Unfortunately though, the Swedish translation of AQ has not been validated in any population based study. Furthermore, it would have been valuable to apply alternative measures of autistic traits simultaneously, as well as a dimensional measure for schizotypal traits. Finally, a further limitation of study II is the absence of a “blinded” procedure of the SCID-II-interview. The interviewer was aware of the AS diagnoses in the study group and, consequently, a totally “neutral”, unbiased position was not possible to expect. This may have led to an underestimation of the number of PD criteria being met. Moreover, the SCID-II-interview requires a certain level of self-reflection, which may be impaired in individuals with AS.

Psychiatric comorbidity in AS

A strikingly high rate of lifetime major depression was found in young adults with AS. Despite the relatively young mean age of the individuals in the sample (27 years), a full 70% of the group had experienced at least one major episode of depression. Half of all participants in the study had already suffered recurrent depressive episodes, and this group is clearly at risk for long-standing psychiatric illness (Jonsson, Bohman, von Knorring, et al. 2011). The results are in line with earlier assumptions on depression rates in adults with ASD and normal intellectual ability (Skokauskas & Gallagher 2010). Although the limited number of prior investigations have shown a similar occurrence of mood disorder, some patient populations have probably been more biased towards psychiatric illness (Hofvander et al. 2009), and others may have been skewed in the opposite direction due to recruitment procedure (Hill, Berthoz & Frith 2004) or exclusion criteria (Sterling et al. 2008).

Very high rates of anxiety disorders were also found, the most prevalent being generalized anxiety disorder and social anxiety disorder. No previous studies with a focus on occurrence of anxiety disorders in adults with AS have been published, but rates varying from 30% to 65 % have been reported as associated findings (Tani et al. 2003; Sterling et al. 2008; Hofvander et al. 2009). About a fifth of the participants in the present study met criteria for

social anxiety disorder. Even though impairment in social interaction-communication is among the core symptoms in AS, there is considerable variation in the way in which this core difficulty affects social behaviour. Some people with AS are uninterested in and indifferent to other people's opinions, but there are also those who are socially interested but yet unconcerned about how they are seen by others ("active but odd") (Wing 1997). For some individuals with AS, their reduced ability in interpreting social cues leads to a major concern about what impression they make on others and even a disabling fear for social situations, thus fulfilling criteria for social anxiety disorder. OCD is controversial as a co-morbid diagnosis in AS given that rituals and rigid adherence to routines are among the criteria for a diagnosis of AS. DSM-IV criteria for OCD include egodystonicity, whereas many individuals with AS experience their rituals as egosyntonic. Nevertheless, several researchers have pointed out the fact that OCD including egodystonicity may well occur in individuals with AS (Bejerot, Nylander & Lindstrom 2001; Cath et al. 2008). In the present study, participants who were markedly distressed by their compulsive rituals and/or obsessive thoughts received a diagnosis of OCD. In contrast, participants with egosyntonic ritual behaviours, presenting no subjective suffering, were not given an OCD diagnosis. This, along with differences in study populations, is a probable explanation for the present finding (7%) compared to prior studies, in which OCD occurrence has varied between 20-35% (Russell, Mataix-Cols, Anson et al. 2005; Sterling et al. 2008; Hofvander et al. 2009).

Interestingly, a low rate of psychotic disorders was found. No individual in the AS group met criteria for SP, and only one met criteria for brief psychotic disorder and another one for psychotic disorder NOS. However, 13% of the AS group reported recurrent auditory hallucinations, without fulfilling any other criteria for a psychotic disorder. (In the general population, such psychotic symptoms are estimated to be present in approximately 5%, although prevalence may be influenced by socio-economic factors and the occurrence of substance use (van Os, Linscott, Myin-Germeys et al. 2009)). Even though hallucinations had been present for several years, none of these individuals had sought treatment for this reason, probably because the symptoms had not caused major distress.

AS and risk for psychosis

The low rate of psychotic disorder in the AS group of the present study is in remarkable contrast to the results of the DISCO assessment in the SP group. Eleven out of 27 DISCO-assessed participants with SP fulfilled criteria for a childhood ASD diagnosis, whereas no individual in the AS group met criteria

for schizophrenia and only one individual for psychotic disorder NOS. Previous studies on comorbidity of psychosis in ASD show very diverging results. Undoubtedly, selection bias may be one important explanation for this variation. Patients suffering from severe psychosis are less likely to participate in longitudinal follow-up studies (Howlin 1997; Howlin et al. 2004; Cederlund et al. 2008). On the other hand, in studies based on clinically referred adults there is a risk for bias towards increased psychiatric illness (Stahlberg et al. 2004; Hofvander et al. 2009). Inclusion criteria for ASD may also influence psychosis prevalence of the study population. Some studies include patients with learning disability, for whom making the diagnosis of concomitant schizophrenia can be extremely difficult or not even possible, particularly in individuals with no or very little spoken language (Volkmar & Cohen 1991). The inclusion or exclusion of PDD-NOS is another factor possibly affecting the occurrence of psychosis, since PDD-NOS is a more unspecific concept compared to AD and AS (Towbin 1997), and some findings indicate that psychosis risk may be particularly elevated in PDD-NOS (Jansen, Gispens-de Wied, van der Gaag et al. 2003). Moreover, when comparing studies on comorbidity of psychosis in ASD, it is crucial to consider the age range of the study sample, as psychosis very often has its onset between ages 18 and 25 years. In studies based on children and adolescents, a low psychosis rate may be due to the fact that the study population has not yet passed the critical age period (Ghaziuddin, Tsai & Ghaziuddin 1992; Leyfer et al. 2006). These explanations for diverging results *between* studies are partly relevant for the present study. The age range in the AS group was 22-37 years, thus, many but not all had passed the critical period. Selection bias (severely ill patients declining study participation) may have led to a false low rate of SP in the AS group. Through clinical records, the existence of several cases with a diagnosis of schizophrenia among the non-participants of the eligible AS group is known to the research group. However, the extent of such bias has been difficult to estimate. In fact, the contradictory findings in our study are just in line with the diverging results of previous research. There is a pattern that the rate of psychotic disorders is *low* in ASD study groups based on (1) cases diagnosed at young age, (2) mainly including AD and (3) including cases with learning disability, but also a pattern that the rate of psychotic disorders is *high* in ASD study groups based on (1) cases diagnosed as adults, (2) the whole spectrum, including PDD-NOS and (3) cases without learning disability. Although speculative, this general pattern may not only be due to shortcomings of study designs and biases, but may reveal something about the risk for developing a psychotic disorder. For schizophrenia and related psychotic disorders, the diathesis-stress model is a well accepted model to describe the interaction between factors that may lead to psychotic illness

(Walker & Diforio 1997). The model proposes that stress (external/environmental factors) acts upon a preexisting vulnerability of the individual to trigger the onset or worsening of psychosis. Interpretation of previous study results may not have taken the diathesis-stress model into full account. If the preexisting vulnerability is obvious, such as in severe ASD diagnosed at an early age, a major adaptation of the environment, including lowering of demands, usually takes place. Even though the vulnerability is massive for the individual, the environmental stress is usually reduced since the vulnerability is observable. However, if the preexisting vulnerability (e.g. social perception deficits, neurocognitive deficits) is *not* readily observable to the environment (family, school, peers), the demands upon the person will not be reduced and stress factors risk becoming harmful. In other words: an obvious preexisting vulnerability is a problem in itself (leading to a need of extra support), but a hidden preexisting vulnerability can be even more hazardous to the development of psychiatric illness, despite the fact that the “total” vulnerability is lower. This “model of hidden vulnerability” (Gillberg 1983) could be a partial explanation for our diverging results: the SP group shows high occurrence of developmental impairments although not previously identified (“hidden vulnerability”), whereas the AS group is having difficulties in the same range although identified (“observable vulnerability”). A similar reasoning, but rarely studied in comparative studies, is the issue of environmental attribution effects towards an individual with some sort of impairment. One research group recently demonstrated that parents of adults with autism exhibit very low rates of the negative component of “expressed emotion” (EE, a measure of attribution towards a person) compared to parents of adults with schizophrenia (Wasserman, de Mamani & Mundy 2010). Other results indirectly supporting this vulnerability model come from a different perspective, namely from studies on young people at high risk for psychosis (e.g. prodromal syndrome/psychosis proneness). Recent reports emphasize the role of prior (and not recognized) social interaction difficulties in the risk for psychosis development (Addington & Addington 2008; Cornblatt, Carrión, Addington et al 2011).

Furthermore, the “model of hidden vulnerability” may also be pertinent for the development of mood and anxiety disorders in ASD. Early recognition of ASD is generally seen as important in order to understand the child’s difficulties, adjustment of the child’s total situation and to support development in all domains, everything with a view to improving outcome. In the light of the diathesis-stress model, such early interventions may decrease the risk for secondary psychiatric morbidity. Yet again, the interpretation of data is complicated by the fact that individuals who are

recognized at a young age are usually those with core difficulties that are more severe and more obvious. On the one hand, severe core difficulties may involve a high risk for psychiatric comorbidity *per se*. On the other hand, severe core difficulties increase the chance of an early diagnosis and consequent reduction of environmental stress. More subtle core difficulties are likely to lead to delayed or failed recognition. Referral for diagnostic evaluation may not even be thought of until secondary problems have become unmanageable. In support of this reasoning, a recent study indicates that individuals with ASD with more subtle social impairments are actually more likely to develop depressive symptoms (Sterling et al. 2008). In conclusion, further understanding of the interaction of core vulnerability, age of recognition and environmental factors on the risk for general psychiatric morbidity is needed. Additionally, the nature of vulnerability and its relation to specific psychiatric symptoms (e. g. positive psychotic symptoms) needs to be better understood. Most important, we need research on what interventions/preventions would be most beneficial.

Personality disorders and AS

When applying the PD criteria (by disregarding the exclusion criterion) to individuals with AS, approximately half of the group met criteria for a PD according to DSM-IV-TR. Among the men, about two thirds, and among the women, one third met such criteria. All PDs were within cluster A or cluster C, not one individual in the AS study group met criteria for PD within cluster B. The substantial overlap with schizoid PD (26% of the whole AS group) is not surprising given the resemblance of diagnostic criteria for the two conditions (described in section 1.4.2). The text manual in DSM-IV-TR implies that when differentiating between schizoid PD and PDD; social interaction, stereotyped behaviours and interests are more severely impaired in PDD than in schizoid PD. This is in contrast with our results demonstrating that individuals with AS also meeting schizoid PD criteria showed *more marked* autistic features according to AQ compared to those not meeting such criteria. Individuals with AS may show more subtle social interaction and communication problems than those delineated by schizoid PD criteria. Most likely however, a substantial subgroup of people with PDD/ASD have clear “schizoid traits” which involves a pattern of social disinterest/social detachment and mainly corresponds to the “loners” originally described by Sula Wolff (Wolff 1995) and included in Lorna Wing’s classification (Wing 1997). The existence of “pure” schizoid PD without an underlying PDD/ASD is, in fact, questionable, although cannot be ruled out based on the present findings. Schizotypal PD includes characteristics identical with those for schizoid PD in combination with psychotic-like symptoms. Just as in the case of schizoid PD, there is an

exclusion criterion B, which emphasizes that a PDD must be ruled out before assigning a diagnosis of schizotypal PD. There is considerable criterion overlap between PDD/ASD and schizotypal PD, however the overlap is mainly due to criteria shared with schizoid PD. Criteria unique to schizotypal PD are those related to psychotic-like experiences and magic thinking, which may well be present in people with PDD/ASD, although not among the core features. In the present study, only one individual met criteria for schizotypal PD. The low rate may be due to (1) the relatively young age (schizotypal PD is believed to become more apparent with increasing age), (2) high tolerability for “odd speech” (which is relatively common in AS) by the interviewer or (3) a true low incidence. Interestingly, recurrent auditory hallucinations, clearly part of schizotypal criteria, were experienced by 7 out of 54 participants (13%) which may argue for underestimation of schizotypal PD in the present study.

PDs within cluster B are based on criteria which do not include any core features of ASD. However, the finding that no one met criteria for a cluster B PD is somewhat surprising. Possibly, selection bias may have led to false low rates. Most likely, individuals with marked personality traits within cluster B, as well as those with clear paranoid traits in cluster A, do not accept participation in a clinical study, and this could be one explanation for the negative findings in this respect.

Within cluster C, criteria for both avoidant PD and obsessive-compulsive PD were met by a sizeable proportion of individuals in the AS group. Criteria for avoidant PD do not necessarily entail the core features of PDD/ASD. When markedly avoidant behaviour is present in individuals with PDD/ASD, it could rather be seen as a consequence of the PDD/ASD. For some individuals with AS, their disability in interpreting social cues leads to a major concern about what impression they make on others and even a disabling fear for social situations, thus increasing the risk for avoidant behaviour. Moreover, elevated sensitivity to stressful environments due to visual and auditory perceptual difficulties may well contribute to avoidant behaviour. Nevertheless, avoidant PD can clearly be present without the core difficulties of a PDD/ASD. Criteria for obsessive-compulsive PD show marked overlap with PDD criteria, particularly those that concern restricted behavioural patterns (criterion B for AS and criterion A.3 for AD). The major difference across the two categories is as regards age criteria: for obsessive-compulsive PD the onset of the behaviour has to be at least “early adulthood” whereas for PDD, a childhood onset is stipulated. In the text manual, differential diagnostic difficulties are not mentioned, and in contrast to schizoid PD and schizotypal PD, there is no exclusion criterion for PDD. As

already highlighted by others, there is a clear risk for misdiagnosis if PDD/ASD is not considered in patients with obvious obsessive-compulsive traits (Bejerot, Nylander & Lindstrom 2001; Fitzgerald 2002; Bejerot 2007).

When studying the concept of PD in relation to the concept of PDD/ASD, the impact of approach may clearly influence results and interpretations. Some researchers in the PD field have taken an interest in looking for autistic features in patients with PD (Rydén, Rydén & Hetta 2008; Esterberg et al. 2008). In the study by Esterberg on children with schizotypal PD, participants were recruited by newspaper announcements, aimed at parents of children with adjustment problems that consisted of a “lay description of key diagnostic criteria in schizotypal PD”. Possibly, in a different clinical setting with a clear focus on PDD/ASD, the identical description may have been used in order to recruit children with probable PDD/ASD, and a diagnosis of schizotypal PD would not even have been considered. Other researchers (like those involved in the present study) do the opposite: investigation of presence of PD in patients with PDD/ASD (Anckarsater, Stahlberg, Larson et al. 2006; Barneveld, Pieterse, de Sonnevile et al. 2011), which in turn may risk that PD traits are underestimated due to the investigator’s alternative frame of reference. As referred to above, some researchers take a “neutral” approach and focus on comparisons between personality traits (instead of categorical diagnosis of PD) in non-clinical populations (Hurst et al. 2007; Claridge & McDonald 2009; Russell-Smith, Maybery & Bayliss 2011). Findings from these studies, with the clear advantage of reduced bias compared to categorical classification, show that schizotypal personality traits and autistic traits show a high correlation, possibly indicating a considerable degree of overlap.

Another inconsistency that complicates the comparison of the PD concept to the PDD/ASD concept is the age dependent diagnostic criteria. PDDs are, by definition, present from a very early age, even though sometimes not recognized until adulthood. PDs are usually not diagnosed before the age of 18. This separation is undoubtedly reinforced by the clear age dependency of current criteria in DSM-IV. PD criteria are delineated for adults, however traits of a PD are supposed to have been present at least since adolescence (or early adulthood). In contrast, criteria for PDD are clearly developed for children, and not always easy to apply for adults. Major changes in the DSM-V regarding both PD and PDD/ASD are suggested: for PD, five instead of 10 categories as well as a dimensional measure, and for PDD/ASD, focus on “in or out of” ASD rather than differentiating “within” ASD, as well as criteria more applicable to adolescents/adults (APA 2011). These coming

modifications will possibly improve diagnostic practice within each domain, even though they do not automatically lead to clarification between domains.

Autistic traits

The issue of autistic traits is closely related to the issue of PD, since “traits” (regardless of being labeled “autistic”, “schizotypal”, or “prodromal”) represent a dimensional approach of personality. In the present study, both individuals with SP and individuals with AS demonstrated high levels of autistic traits, as measured by the self-report questionnaire AQ. Both clinical groups showed significantly higher scores on AQ total score compared to a non-psychiatric sample. The AS group scored significantly higher than the group with SP, although the overlap was substantial and within-group heterogeneity was considerable for both conditions. Results for the SP group were closer to results for the AS group, than to results of the NCC group. The findings support previous results showing that individuals with AS score high on AQ compared to healthy comparisons (Baron-Cohen, Wheelwright, Skinner et al. 2001; Kurita, Koyama & Osada 2005; Wheelwright, Baron-Cohen, Goldenfeld et al. 2006). Similarly, the results are in line with prior studies that have applied AQ on patients with schizophrenia, showing high levels of autistic traits in this group compared to healthy comparisons (Koelkebeck et al. 2010; Wouters & Spek 2011). Apart from the present investigation, two more studies have made direct AQ comparisons across schizophrenia and ASD (Naito et al. 2010; Spek & Wouters 2010). These two studies also demonstrated significantly higher scores for the ASD group compared to the schizophrenia group, although both concluded that the use of AQ as a differential diagnostic tool is limited. They reported somewhat higher mean AQ for their ASD groups compared to our result, which is not surprising since their ASD study populations, in contrast to ours, included persons with AD, which is usually more clinically impairing than AS. Regarding the level of scores for the different schizophrenia study populations, our patient group showed total scores in line with those in the study by Naito et al, and slightly higher compared to the schizophrenia group in the study by Spek et al.

Why do persons with schizophrenia show high levels of self-reported autistic traits? One interpretation is that many individuals with schizophrenia have “true” autistic features, almost to the same extent as individuals with an ASD diagnosis, or at least to the same degree as those with “broader autism phenotype”. Another interpretation would be to question the validity of AQ, and to say that the AQ is not as a specific measure of “true” autistic traits as has been proposed, but rather a more unspecific evaluation of social skills and social interest, no matter what underlies the behavioural picture. A

problem is that the definition of “autistic traits” is still unclear, despite the abundance of studies using the term. A straight-forward definition would be: “autistic traits are personal traits and preferences measured by the self-report instrument AQ”. A more complex definition is: “autistic traits are personal traits and preferences predominantly occurring in people with ASD and their relatives”. The latter definition makes demands on knowledge that is not yet unequivocal, and also implies a risk for circular reasoning (e. g. “ASD is diagnosed by the presence of autistic traits and autistic traits is defined by the presence of ASD”). In fact, what definition is really applied is only rarely spelled out in an explicit manner. Irrespective of interpretation of the present results, when using the AQ for screening purposes, either in psychiatric patient populations or in large community population studies, it is essential to take into account that individuals with originally “non-ASD” psychiatric diagnoses may present with high scores. This has been demonstrated not only for schizophrenia, but also for obsessive-compulsive disorder and ADHD (Cath et al. 2008; Sizoo et al. 2009). In spite of the fact that the AQ has been shown to discriminate between individuals with ASD and healthy comparison subjects, focusing solely on confirming or rejecting an ASD diagnosis following an AQ screening, may lead to overlooking relevant diagnostic information. Thus, diagnostic assessment subsequent to AQ screening needs to include “the big picture”, and vary according to the clinical or research issues at hand. Moreover, the high correlation between AQ and measures on schizotypal traits needs further clarifying (Sugihara, Tsuchiya & Takei 2008; Barneveld et al. 2011).

Social cognitive impairments

Deficits in social cognition are among the core features of ASD. These deficits are not specific to ASD. Individuals with SP may have as marked impairments, or even worse. Both the AS and SP groups included here clearly deviated from a community sample on implicit ToM, as measured by the Animations Task. The results are in line with those of prior studies where traditional ToM instruments have been used, such as the Hints task (Craig et al. 2004) or variants of false belief tasks (Murphy 2006; Ozguven, Oner, Baskak et al. 2010), also demonstrating convergence in ToM deficits across the two groups. There was no difference between patient groups and comparison group on the “mechanical” animations (random and goal directed movements) which is in line with some previous results (Abell, Happé & Frith 2000; Castelli et al. 2002; Horan, Nuechterlein, Wynn et al. 2009). However, other studies have reported poor results on GD animations (Russell, Reynaud, Herba et al. 2006; Koelkebeck et al. 2010) and random animations (Russell et al. 2006) for patients with schizophrenia

In contrast to the majority of reported investigations, only minor group differences were seen on the Eyes Test. There was a considerable spread of scores in all three groups. The only significant difference was between the SP group and the NCC group, which was a consequence of NCC women scoring significantly higher on this task. The Eyes Test has been used in several studies on ASD and schizophrenia, including in three head-to-head comparative studies. In one of these, a battery of social perception tasks was used, including the Eyes Test. Individuals with AS and individuals with schizophrenia performed worse than a non-clinical group on all tasks apart from the Eyes Test where no significant group differences were seen (Couture et al. 2010). In another study individuals with AS and schizophrenia both scored worse than healthy controls, but they did not differ from each other (Craig et al. 2004). Yet another study demonstrated no difference between AS and schizophrenia on the Eyes Test, although both groups scored worse than a comparison group with personality disorder (Murphy 2006). Our results may be a consequence of a ceiling effect, due to the use of the child version of the Eyes Test. Another possible explanation for contradictory findings may be major differences in neurocognitive abilities between study samples, since, in some of the previous studies, neurocognitive measures have not been included (Couture, Penn, Addington et al. 2008; Kettle, O'Brien-Simpson & Allen 2008). Moreover, small study samples increase the risk for random errors. To be sure, widespread within-group score heterogeneity is seen on the Eyes Test, which results in a substantial overlap between groups and small effect sizes.

The question of impact of general cognitive abilities on performance on social cognitive tasks is of great interest. Even though neurocognition and social cognition are clearly shown to be separate domains, qualities such as attention, vigilance and memory are necessary (but not sufficient) bases for social cognitive processes. Different social cognition measures differ markedly in terms of neurocognitive demands. Furthermore, in explicit ToM tasks with a “0 or 1 response”, abstract reasoning may compensate for low functioning of implicit ToM. Neither the Animations Task, nor the Eyes Test requires verbal memory or abstract reasoning. Both the Animations Task and the Eyes Test were only weakly correlated with verbal ability, indexed by WAIS-III Vocabulary, which is in line with results by Bell et al who reported a moderate correlation between WAIS-III Vocabulary subtest and a modified version of the Animations task in individuals with schizophrenia (Bell, Fiszdon, Greig et al. 2010).

Same spectrum, two separate spectra or more spectra?

Even though on the face of it representing two different syndromes, AS and schizophrenia share a substantial amount of clinical features. The evident difference is the presence of positive psychotic symptoms (delusions and hallucinations) in schizophrenia - which is not characteristic of AS. However, the groups are more similar to each other than what is commonly assumed in diagnostic manual schemes, research papers and clinical practice. ASD as well as schizophrenia are both heterogeneous concepts, including a variety of symptoms, courses and etiologies. The question as to whether ASD and schizophrenia are on separate spectra or contained within one and the same spectrum, has been posed by other researchers (Hurst et al. 2007; Esterberg et al. 2008; Rapoport et al. 2009; Russell-Smith, Maybery & Bayliss 2011; King & Lord 2011; Sheitman, Kraus, Bodfish et al. 2004). One interpretation of our findings is that the two domains may include subgroups that are more closely related to each other, genetically and etiologically, than to its original overall domain. Currently proposed subgroups in the schizophrenia domain, such as “deficit schizophrenia”(Kirkpatrick, Buchanan, Ross et al. 2001; Cohen, Brown & Minor 2010), and previously “simple schizophrenia”(Kendler, McGuire, Gruenberg et al. 1994), share major features with ASD; however it has not been studied if patients classified as “deficit schizophrenia” have the same developmental trajectory as individuals with ASD. Another proposed subgroup of interest within the ASD domain is “multiple complex developmental disorder”, characterized by severe affect dysregulation in addition to social impairment and shown to have increased risk for psychosis (Sprong, Becker, Schothorst et al. 2008). In contrast, there are other subgroups in each concept that clearly differ from one another: for instance those in the schizophrenia domain with severe psychosis but without any prior developmental impairment compared to “classic” autism according to Kanner’s original description.

A further complicating aspect, are the continuously ongoing diagnostic drifts and trends over time (Coleman & Gillberg 1996). Undoubtedly, diagnostic drifts *within* a spectrum affect *other* spectra, and this may occur either intentionally (like the result of the studies by Kolvin and Rutter in the 1970s or at revisions of DSM) or rather unintentionally. When AS was not defined as a separate construct, and autism spectrum was limited to the severe picture according to Kanner, the schizophrenia concept was still broad. A diagnosis of schizophrenia was likely to be established for an adult patient with low functioning, difficulties in social interaction and odd behaviour, irrespective of positive psychotic symptoms. Today, the most probable diagnosis for the same picture would be AS or another ASD diagnosis. Misdiagnoses in this field have been frequently reported the last fifteen years, not surprising, since

we are in the middle of an ongoing diagnostic drift (Taiminen 1994; Perlman 2000; Nylander & Gillberg 2001; Raja & Azzoni 2009). Moreover, some would claim that the schizophrenia concept has drifted not only from broad to narrow in the context of premorbid (“trait”) features, but also from specific to unspecific in the context of positive psychotic symptoms (“state” features) (Fischer & Carpenter 2009; Parnas 2011).

Other spectra “at drift”, and currently broadening, are bipolar disorder and ADHD, clearly affecting each other as well as closely related domains such as the autism spectrum and the schizophrenia spectrum (Rydén, Thase, Straht et al. 2009). An ongoing issue is the relationship between bipolar disorder and schizophrenia, including questioning “the Kraepelinian dichotomy” (Craddock & Owen 2005; Fischer & Carpenter 2009). The connection between bipolar spectrum and ASD is not well studied (Raja & Azzoni 2008), although considerable co-existence of ADHD and ASD is now well described (Rommelse, Franke, Geurts et al. 2010; Lundstrom et al. 2011). In summary, co-existence of disorders and sharing of symptoms across disorders seem to be the rule rather than the exception in the field of neurodevelopmental disorders (Gillberg 2010). Impairments involve neurocognition, social cognition and affective regulation, possibly leading to a diversity of psychiatric symptoms such as mood changes, anxiety and psychosis. The mixture of impairments, as well as the impact of compensatory factors, is unique to each person. The choice of “label” for the individual patient is only partly due to the clinical picture. Instead, the actual reference frame of the clinician or researcher is fundamental for what “label” is applied: “you find what you look for”. ASD experts look for ASD patients, experts on prodromal syndrome see prodromal patients and schizotypal/schizotaxia researchers recognize schizotypy etc (Tsuang et al. 2002; Tessner, Mittal & Walker 2011; Cornblatt et al 2011). A main reason for this phenomenon is evident: it is easy to recognize a concept within one’s own expert field. But, other incentives (consciously or unconsciously) may also be present, such as aims to obtain sufficiently sized study groups for research. Furthermore, as an expert in a specific field, there is a risk to view alternative concepts as less valuable, less stringent and more diffuse than one’s “own” domain, or to presume the alternative concept to be narrower than what is done by its proponents. For instance, if experts in the field of prodromal syndrome argue that there are no patients with autism within their study group, a reason for this may be their use of very narrow criteria for autism. On the contrary, an autism expert may not be familiar with the criteria for schizotypy or for prodromal syndrome, or perhaps consider them irrelevant or not valid for patients with ASD.

In psychiatric daily practice, we are forced into categorical concepts due to practical circumstances. The use of the term “spectrum” is very valuable in the sense of implying a dimensional quality. However, even the current spectra (such as “autism spectrum”, “schizophrenia spectrum”, “bipolar spectrum”) are highly influenced by our categorical concepts. Alternative dimensions would be, for instance, “pervasive deficits in reciprocal social interaction”, “mood swings” and “reality distortion”. Such dimensions, more closely associated to the fundamental characteristics of the individual, would possibly facilitate understanding of the individual patient as well as psychiatric research.

6 CONCLUSIONS

The overall purpose of the present study was to explore similarities and differences between the autism spectrum and the schizophrenia spectrum. This was done in a cross-sectional way by studying two diagnostic concepts within each spectrum - AS and schizophrenia - and by using two different approaches: (1) investigation of concomitant psychiatric comorbidity and overlap with PD in a group with AS and (2) direct comparison regarding autistic features and social cognition between AS and schizophrenia. Results concerning PD criteria in AS and direct comparison of autistic features, indicated that the two spectra overlap on a behavioural level. Social cognitive impairments were shown to be at least as prominent in schizophrenia as in AS, which is in line with previous research. In contrast to this plausible overlap between spectra, the presence of schizophrenia and other psychotic disorders in the AS study group was remarkably low. A further important finding, though not related to the issue of overlap, was the noticeably high rate of mood and anxiety disorders in AS.

The present study only highlights a phenotypic overlap, although it cannot answer the question of the relation between the two spectra. Certainly, further research is needed, combining current methods on biological markers and endophenotypes with study designs that go across existing diagnostic domains. In the important field of research on prevention/early intervention of psychosis in young people, including both nosological perspectives would hopefully reveal new insights on vulnerability.

7 IMPLICATIONS FOR CLINICAL PRACTICE AND RESEARCH

According to the study results, some implications for clinical practice are apparent. Young adults with AS are at elevated risk for mood and anxiety disorders. Preparedness for offering psychiatric treatment to this group is essential, and a high level of alertness for additional psychiatric disorders is needed whenever an assessment for a neurodevelopmental disorder is made. Furthermore, in adult psychiatry, it is crucial to consider an ASD diagnosis in patients with PD diagnoses or with marked personality traits within cluster A or cluster C. Clinical awareness, a careful developmental history and genuine knowledge about PDD/ASD are essential. For the individual patient, a “re-definition” from PD to ASD will often provide a basis for a better understanding of the core problems faced by the individual with social communication impairment. The behavioural overlaps between AS and schizophrenia implies that differential diagnostics sometimes may be challenging. Yet again, a thorough developmental history will give helpful information as well as a genuine understanding of perceptual, communicative and cognitive features of the individual.

Even now, a hundred years after Kraepelin and Bleuler, psychiatric research as well as clinical practice is based on concepts with unclear and fluctuating boundaries (Coleman & Gillberg 1996; Kendler 2006; Coleman & Gillberg 2011) The diagnostic concepts are helpful to a considerable extent: for communication purposes, and sometimes to choose treatment or to predict outcome. Although well-intentioned, the effort to define well-characterized disorders based on operational criteria creates artificial borders with weak biological underpinnings. Moreover, when applying these concepts as they were discrete disease entities (which they are not), they risk becoming obstacles instead of tools. The diagnostic concepts have such strong influence, so that even imagining a clinical study not based on DSM- or ICD diagnoses is a real challenge. So, what could be done instead? All research groups in the different fields of neurodevelopmental disorders need to take a meta-perspective and to take into account the presence of overlapping “neighbour” concepts. Several researchers already do, applying novel approaches (Sasson et al. 2007; Esterberg et al. 2008; Sprong et al. 2008; Toal, Bloemen, Deeley et al. 2009; Barneveld et al. 2011). Surprisingly though, many are still stuck within their own domain, without reflecting on possible overlaps or unclear boundaries. It has long been known that “within-syndrome” heterogeneity is substantial for neurodevelopmental disorders.

“Cross-syndrome” similarities, the focus of this thesis, have also been repeatedly demonstrated (Levy & Ebstein 2009; Gillberg 2010). Future research would benefit from both “cross-syndrome” similarities and “within-syndrome” heterogeneity approaches. One way to address the issue has been attempts to define more homogeneous subgroups (e.g. “deficit schizophrenia”, “multiple complex developmental disorder”). However, when a new diagnostic subgroup is defined, its validity and boundaries are usually investigated solely within its own original domain and not in relation to other domains. Consequently, the “cross-syndrome” approach is missing. Instead, validation of new diagnostic subgroups requires much more extensive comparisons *across* domains than what is generally done. What is more, dimensional measures have clear advantages compared to categorical classifications irrespective of whether “within-syndrome” or “cross-syndrome” issues are investigated. Examples of phenotypes possible to examine by dimensional measures are personality traits, different aspects of social cognition, positive psychotic symptoms, mood swings etc. Elaboration of such dimensional measures is an essential research task. Yet again, when validating a dimensional measure, there is a need to include populations from several diagnostic domains. Increased focus on refined endophenotypes (e. g. neuroimaging markers, neurophysiological markers), in combination with a “cross-syndrome” approach is another possible way forward. The current notion of “lumping” diagnostic concepts into larger domains, like the suggested changes in DSM-V on ASD and PD may superficially look like a step backwards. However, if research on these “lumped” concepts will be combined with valid dimensional measures, biological markers and genetics, psychiatric research will, hopefully, advance more rapidly.

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