Autism and early development in adults with schizophrenia

Methodological and clinical aspects

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Gothenburg 2012

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ISBN 978-91-628-8405-5 http://hdl.handle.net/2077/28249

Printed in Gothenburg, Sweden 2012
Ineko AB

The story of autism and Asperger's syndrome attests the truth of three wise sayings. There is nothing new under the sun. Nothing exists until it has a name. Nature never draws a line without smudging it.

Lorna Wing, 2005

To Per-Olof, Sofia and Rickard

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ABSTRACT

Background: Typical symptoms of schizophrenia usually appear in young adult life, but problems with social interaction, activity control, motor performance, and cognition have often been noted in childhood. This thesis explores similarities and differences regarding early development between individuals with clinical diagnoses of schizophrenia and Asperger syndrome (a clinical variant of autism spectrum disorder/ASD). **Methods:** A Swedish version of the "Reading the Mind in the Eyes Test", was completed by 158 university students with a view to assessing the psychometric properties of this instrument before applying it in a clinical research setting. Fifty-eight of these students completed the test twice, three weeks apart. The Bland Altman test-retest reliability method was used. For the other three substudies 46 individuals (29 men, 17 women) with a clinical diagnosis of schizophrenic psychosis (SP) and 54 (26 men, 28 women) with a clinical diagnosis of Asperger syndrome (AS) were included. In 70% of those with SP and 83% of those with AS, collateral information was provided by parents. The Diagnostic Interview for Social and COmmunication disorders – eleventh version (DISCO-11) was used when interviewing these relatives. This instrument covers childhood development, adaptive functioning, and symptoms of ASD. There is a strict algorithm for ASD diagnosis. The clinical schizophrenia diagnoses were confirmed or rejected using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). The rate of clinically diagnosed ADHD (and its relation to nicotine use) in adults with SP and with AS was examined. **Results:** Test-retest findings on the Reading the Mind in the Eyes test showed that score variation in the range of ±4 (out of 24 possible) is to be expected for the same individual. Thirteen of the 32 cases with SP examined had a DISCO-algorithm diagnosis of ASD. Focusing only on those for whom schizophrenic psychosis was confirmed by SCID and for whom a DISCO-interview was obtained, 52% met criteria for an ASD diagnosis. The deficits in quality of friendship and social interaction as well as restricted interests were similar/identical to those found in individuals with AS. These deficits were present prior to the psychosis according to the parental interviews. Ten per cent of the schizophrenia group and 30% of the AS group had a clinical ADHD diagnosis. Nicotine use was common in individuals with schizophrenia, and in the Asperger syndrome group with co-existing ADHD. **Conclusions:** The Reading the Mind in the Eyes test had poor psychometric properties and was not considered appropriate as a reliable measure of core ASD social interaction problems. Half the cases with SCID-I-verified schizophrenic psychosis had ASD according to results of parental interview. The findings suggest the need to revisit the DSM dichotomy between ASD and schizophrenia. Furthermore, ADHD was not uncommon in schizophrenia and quite common in AS, underscoring the need for a full appraisal of childhood onset neurodevelopmental disorders (including ADHD), whenever diagnoses of schizophrenia or ASD are considered in clinical practice. The WRAADDS used as a self-rating scale for ADHD held promise for clinical use.

Keywords: schizophrenia, Asperger syndrome, autism spectrum disorder, ADHD, Reading the Mind in the Eyes test, DISCO-11, SCID-I, nicotine, early development, WRAADDRS, SNAP
ISBN: 978-91-628-8405-5 http://hdl.handle.net/2077/28249

SAMMANFATTNING PÅ SVENSKA

Schizofreni debuterar oftast i ung vuxen ålder men det är vanligt att personer som drabbas av schizofreni har varit annorlunda redan som barn. De har ofta haft svårigheter med socialt samspel, koncentration, språk och motorik. Numera är det vanligt att barn som har motsvarande svårigheter remitteras för utredning och ställningstagande till eventuell neuropsykiatrisk diagnos. De svårigheter som har beskrivits föregå schizofreni liknar det vi idag beskriver som autismspektrumtillstånd (AST). Om det är helt olika tillstånd, hur kan man i så fall skilja dem åt? Om de inte kan skiljas åt, innebär det att vuxna med diagnos schizofreni egentligen istället har AST eller har de båda tillstånden? Denna avhandling avser att undersöka detta.

I studien har 46 unga vuxna med klinisk diagnos schizofren psykos (schizofreni, schizoaffektivt syndrom eller schizofreniformt syndrom) och 54 unga vuxna med Aspergers syndrom (en form av AST) deltagit. Alla har intervjuats med en strukturerad intervju, ”Structured Clinical Interview for DSM-IV Axis I Disorders” (SCID-I) för att kartlägga aktuell och tidigare psykiatrisk ohälsa i syfte att på ett standardiserat sätt värdera eventuell psykiatrisk diagnos. Därutöver har föräldrar till 32 av deltagarna med schizofren psykos och 46 av deltagarna med Aspergers syndrom intervjuats med en semistrukturerad intervjumetod, ”Diagnostic Interview for Social and COmmunication disorders” – elfte versionen (DISCO-11). Föräldraintervjun kartlägger olika utvecklingsområden med särskilt fokus på utvecklingsavvikelser och beteenden typiska för AST.

Alla deltagare har i samband med SCID-intervjun tillfrågats om de ha utretts för ADHD. Deltagarna, samt deras föräldrar, har fyllt i frågeformulär som avser att mäta förekomst av ADHD symptom. De olika frågeformulären har analyserats avseende hur väl de korresponderar till klinisk ADHD diagnos. Andelen som använder nikotin regelbundet i de olika diagnosgrupperna har analyserats.

Dessutom har psykometriska egenskaper hos en svensk version av ett relativt nyutvecklat testinstrument, ”Reading the Mind in the Eyes”, undersökts. Trots att ”Reading the Mind in the Eyes testet har använts internationellt i ett stort antal studier och även används kliniskt på vissa håll så saknas tidigare studier av test-retest reliabilitet, dvs analys av hur testresultaten för en och samma individ stämmer överens om man gör testet två gånger. I denna delstudie deltog 158 studenter från Karlstad universitet, 58 av dem genomförde testet två gånger med cirka tre veckors mellanrum.

Av föräldraintervjuerna framkom att 13 av 32 deltagare med klinisk schizofren psykos-diagnos har haft symptom under barndomen som vid AST. Enligt föräldraintervjuerna har de haft svårigheter med kamratrelationer och begränsade intressen på motsvarande sätt som de med Aspergers syndrom. Patientintervjuerna verifierar den kliniska diagnosen för en majoritet (12 av 13) av dem. Deras symptombeskrivningar stämmer med diagnoserna schizofreni, schizoaffektivt syndrom respektive schizofreniformt syndrom också enligt SCID I. De har således både AST och schizofren psykos, inte antingen eller.

Studien visar dessutom att det inte är ovanligt att personer med schizofreni respektive Aspergers syndrom dessutom har ADHD. Att rökning är vanligt vid schizofreni är känt sedan tidigare och bekräftas av denna studie. Vid Aspergers syndrom har rökning tidigare beskrivits vara ganska ovanligt men vi visar att det är vanligt i den undergrupp som förutom Aspergers syndrom även har ADHD. En självskattningsskala för ADHD hos vuxna (WRAADDS) föreföll väl användbar för kliniskt bruk och bör bli föremål för fördjupad forskning.

Det är anmärkningsvärt att testinstrumentet ”Reading the Mind in the Eyes” fått en sådan spridning trots att så lite har beskrivits avseende testets grundläggande psykometriska egenskaper. För att kunna värdera ett enskilt resultat på ett test måste man veta hur reliabelt, tillförlitligt, ett testresultat är. Denna studie visar att resultaten för en och samma individ varierar relativt mycket mellan två testtillfällen med vår version av testet. Hur mycket testresultaten för originalversionen, eller andra översättningar av testinstrumentet, varierar för en och samma individ vid två separata testtillfällen, är än så länge inte känt.

LIST OF PAPERS

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

I. Maria Unenge Hallerbäck, Tove Lugnegård, Fredrik Hjärthag, Christopher Gillberg. The Reading the Mind in the Eyes Test: test-retest reliability of a Swedish version. Cognitive Neuropsychiatry 2009;14: 127-143

II. Maria Unenge Hallerbäck, Tove Lugnegård, Christopher Gillberg. Is autism spectrum disorder common in schizophrenia? Psychiatry Research 2012 (in press) Doi:10.1016/j.psychres.2012.01.016

III. Maria Unenge Hallerbäck, Tove Lugnegård, Christopher Gillberg. Childhood impairments in social interaction: a controlled study of young adults with schizophrenic psychosis or Asperger syndrome**.** (submitted)

IV. Maria Unenge Hallerbäck, Tove Lugnegård, Christopher Gillberg. ADHD in schizophrenia and Asperger syndrome: a controlled study. Journal of Attention Disorders 2012 (in press)

CONTENT

ABBREVIATIONS

ADHD	Attention-Deficit/Hyperactivity Disorder
ARMS	At Risk Mental State
AS	Asperger Syndrome
ASD	Autism Spectrum Disorder
AUC	Area Under the Curve (ROC curve statistical analysis)
CAP	Child and Adolescent Psychiatry
COS	Childhood Onset Schizophrenia
DISCO	Diagnostic Interview for Social and COmmunication Disorders
DSM-III	Diagnostic and Statistical Manual of Mental Disorders. Third Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition. Text Revision.
ESSENCE	Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations
fMRI	Functional Magnetic Resonance Imaging
ICD-10	International Classification of Diseases. Tenth Edition
IP	Infantile Psychosis
IQ	Intelligence Quotient
LOP	Late Onset Psychosis

MCDD	Multiple Complex Developmental Disorder
PDD-NOS	Pervasive Developmental Disorder Not Otherwise Specified
ROC	Receiver Operating Characteristic
SNAP	Swanson, Nolan And Pelham questionnaire
SP	Schizophrenic psychosis
SSD	Schizophrenia Spectrum Disorder
WRAADDS	Wender Reimherr Adult Attention Deficit Diagnostic Rating Scale

DEFINITIONS IN BRIEF

Schizophrenic psychosis	Schizophrenia, schizoaffective disorder, and schizophreniform disorder
Schizophrenia spectrum disorder	Schizophrenia, schizoaffective disorder, schizophreniform disorder, schizoid, and schizotypal personality disorder
Autism spectrum disorders	Autistic disorder/childhood autism, Asperger´s disorder/Asperger syndrome, and pervasive developmental disorder not otherwise specified/atypical autism (possibly also “broader autism phenotype”)
Pervasive developmental disorders	Same as autism spectrum disorders (plus, in DSM-IV and ICD-10, Rett syndrome)

1 INTRODUCTION

The relationship between schizophrenia and the syndrome of (childhood) autism has been intensely discussed for relatively brief periods of time over the past seventy years. For almost forty years now they have been regarded as more or less discrete conditions with no or minimal overlap (Figure 1). The definitions of both disorders (and their "spectrum disorders") have evolved and changed over time. The history of the diagnoses, some important classifications and research findings will be presented in the following text.

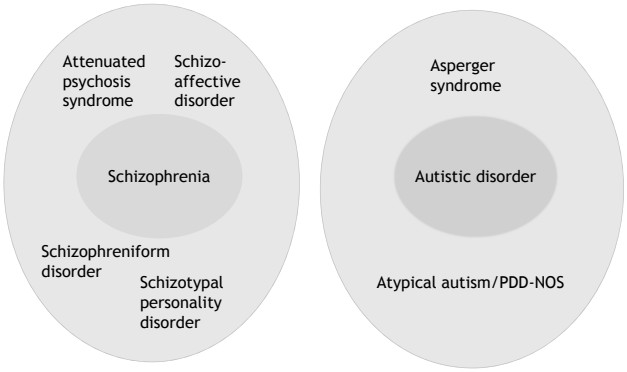

Figure 1. Schizophrenia spectrum disorder and autism spectrum disorder

1.1 Schizophrenia spectrum disorder

Schizophrenia is now conceded as a neurodevelopmental disorder (Rapoport et al., 2005). The aetiology is unknown but genes are of major importance and the heritability is high.

1.1.1 Former classifications of schizophrenia

In the late 19th century the mental hospitals were harbouring people with a wide variety of mental disorders. Emil Kraepelin (1856-1926) found himself "bewildered" by the "wide differences in terminology and conceptions" of

the mental disorders that faced him (Decker 2007¸ Moskowitz & Heim 2011). He attempted to bring some order in the terminology. He strongly emphasized a somatic/biological etiology of mental disorders. He shared his interest in biological systems of classifications with his brother Karl Kraepelin, a renowned biologist. Kraepelin used special diagnostic cards (Zählkarten) on which important features of the clinical picture were noted (Weber & Engstrom 1997). By sorting the cards and analyzing the information he found resemblances as well as distinguishing characteristics. Kraepelin conceptualized dementia praecox and manic-depressive psychosis as two distinct diseases. This dichotomy continues today in the nosological classes of schizophrenia and bipolar disorder (Fischer & Carpenter 2009). Kraepelin noted that age of onset, family history and premorbid personality distinguished dementia praecox from manic-depressive psychosis. Furthermore, dementia praecox had, according to Kraepelin, a chronic deteriorating course whereas manic-depressive psychosis had a cyclical less devastating course (Kendler 1986).

Eugene Bleuler (1857-1939) acknowledged Kraepelin's classification "as vast advance from all earlier attempts to define this disease-group" but he found the name "dementia praecox" awkward. He argued that all cases do not go on to complete deterioration. The "course is at times chronic, at times marked by intermittent attacks, and which can stop or retrograde at any stage, but does not permit a full *restitution ad integrum."* (Bleuler 1911/1950). In the introduction of his monograph "Dementia praecox or the group of schizophrenias" he writes:

"Thus we are left with no alternative but to give the disease a new name, less apt to be misunderstood. I am well aware of the disadvantages of the proposed name but I know of no better one. It is really quite impossible to find a perfect name for a concept which is still developing and changing. I call dementia praecox "schizophrenia" because (as I hope to demonstrate) the "splitting" of the different psychic functions is one of its most important characteristics. For the sake of convenience, I use the word in the singular although it is apparent that the group includes several diseases"

Bleuler (1911) distinguished between fundamental symptoms, specific to schizophrenia, and accessory (non-specific) symptoms such as hallucinations, delusions, memory disturbances and catatonic symptoms. One key fundamental symptom ("egocentric thinking") was defined as autism from the Greek word autos (self). Bleuler described a variety of clinical manifestations of schizophrenic autism: detachment from reality associated with rich fantasy life, poor ability to enter into contact with

others, withdrawal, rigid attitudes and behaviours, private hierarchy of values and goals, inappropriate expression and behaviour, idiosyncratic logic and thinking, a propensity to delusion formation and the typical egocentric thinking. Egocentric thinking, interestingly, is currently, by many authorities, considered to be the key feature of the syndrome often referred to as "childhood autism" (Gillberg 1992).

Bleuler proposed and practiced a critically mediating link between two basic psychiatric positions which stood at two controversially opposite poles in the beginning of the 20th century; the psychoanalytic depth psychological school on the one hand and the academic psychiatry, which was principally oriented towards a descriptive somatic approach on the other (Hoff 2001). In the preface to his monograph he appraises both Kraepelin and Freud (Bleuler 1911/1950). Bleuler was convinced that the brain function played a decisive role in the aetiology and pathogenesis of schizophrenia. However, he always insisted that it was of great importance to understand the clinical picture of each individual. (Hoff 2001). In 1904 Bleuler wrote to inform Sigmund Freud that he and his staff, most notably his chief assistant, C. G. Jung, had been making use of psychoanalytic ideas at Burghölzli (the hospital near Zurich where Bleuler was director) (Yorke 2001). Bleuler later became a charter member of the "International Psychoanalytic Association" and was editor of the first "Jahrbuch für psychoanalytische und psychopathologische Forschung". Bleuler resigned from the "International Psychoanalytic Society" in 1910 because of his discontent with the authoritarian style of leadership (Hoff 2001). In a critical review of Freud's analysis of a patient with psychosis Bleuler raised serious objections against the libido-based theory as an explanation for the psychosis. It is apparent that Bleuler distanced himself from the psychoanalytic movement, but if he also distanced himself from Freud's theories in general is debated (Dalzell 2007; Moskowitz 2011)

For many decades, the psychoanalytic theory influenced many clinicians, and a psychiatric diagnosis was regarded as largely irrelevant for making psychotherapy treatment decisions (Andreasen 2007). The life history of the individual was the most significant element in the aetiology of the disease, as Adolf Meyer (1866-1950), an influential leader of the specialty, declared. (Grob 1985; Aboraya, Rankin, France et al. 2006). In this era, theories like the double-bind hypothesis, marital schism and marital skew, and the schizophrenogenic mother as causes of schizophrenia evolved (Adityanjee, Aderibigbe, Theodoridis et al.1999).

The first version of the Diagnostic and Statistical Manual of Mental Disorders (DSM) was published by the American Psychiatric Association in 1952. It reflected the predominant psychodynamic psychiatry, although biological perspectives and the concepts from Kraepelin's system of classification were included (Gillberg 2011).

Kurt Schneider defined schizophrenia according to first and second rank symptoms (Schneider 1950). Partly reversing the relationship between the two groups as compared with Bleuler, he listed first rank symptoms as: delusion of control, thought broadcasting, thought withdrawal, thought insertion, hearing one's thoughts spoken aloud, auditory hallucinations that comment on one's behaviour, and auditory hallucinations in which two voices carry on a conversation. The second rank symptoms included other forms of hallucinations, depressive or euphoric mood changes, emotional blunting, perplexity, and sudden delusional ideas (Mellor 1970). The Schneider criteria have been criticized for not being specific to schizophrenia but also present in other forms of psychosis (Carpenter & Strauss 1974; Peralta & Cuesta 1999; Carpenter 2006). Nevertheless, they were largely incorporated into both the DSM-III and DSM-IV criteria for schizophrenia and have had a tremendous impact on our present concept of schizophrenia.

The diagnosis schizophrenia became more widely used in the United States during the 1950s-60s. There was a marked difference in how the diagnosis schizophrenia was used in the United States as compared to in Europe. (Spizer & Fleiss 1974; El Missisry, Aboraya, Manseur et al. 2011).

The emergence of neuroleptic drugs changed the treatment of psychosis. Patients could leave the mental hospitals due to reduction of the major symptoms of the illness (Insel 2010). The psychopharmacology discovery process required comparison across studies. In this process, a diagnostic approach with agreed-upon definitions was essential. Whereas Bleuler referred to the group of schizophrenias, there was now a search for "true" schizophrenia and the concept of nuclear schizophrenia was established based on definitions from Langfeldt and Schneider (Carpenter 2006).

One large and remarkable study was conducted by the WHO; the International Pilot Study of Schizophrenia (IPSS), collected data in nine nations beginning in 1968 (Sartorius, Shapiro, Kimura et al. 1972; Sartorius, Sharp & Jablensky 1974). The nations involved were: Colombia, Czechoslovakia, Denmark, India, Nigeria, China, The Soviet Union, the United Kingdom, and the United States. The aims of the IPSS were to answer certain methodological questions and to provide information about

the nature and distribution of schizophrenia. In total 1200 persons, aged 15-44 years, were included, 82 % of them were traced and re-interviewed two years later. The IPSS demonstrated that it was possible; using standardized reliable methods of assessment, to identify schizophrenic patients in centers in nine countries of the world who are similar with regard to their clinical picture at the time of a psychotic episode.

The DSM-III, published in 1980, was a total revision from the DSM- II, which had been published in 1968. In the work with DSM-III, the members of the committee, under the Chair of Bob Spritzer, had high goals. They wanted to improve communication between clinicians, to provide reliable diagnoses that would be useful in research, to enhance teaching (to train psychiatry students in clinical interviewing and differential diagnosis), and to realign American psychiatry with the rest of the world. They wanted the DSM-III to be devoid of theories about aetiology, since the aetiologies for most psychiatric disorders are unknown. They were aware that the increased simplicity and clarity could lead to misuses. Therefore the introduction included caveats about: the problems of using the manual to set policies, the risk that DSM would be taken as the ultimate authority on diagnosis, the lack of adequate validation for the criteria, and the importance of going beyond DSM criteria in history taking (Andreasen 2007).

In DSM-III, schizophrenia was defined exclusively by psychotic symptoms with associated duration and impaired function. There was an emphasis on reality distortion pathology as opposed to the wider concept where schizophrenia was defined as existing in a wider context within a certain type of personality (Carpenter 2006; Andreasen 2007; Parnas 2011).

1.1.2 Current classification of schizophrenia

According to the classifications in DSM-IV-TR, schizophrenia is a disorder that lasts for at least six months and includes at least one month of active-phase symptoms (i.e., two or more of the following: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour, negative symptoms). Schizophrenia is divided into five subtypes; paranoid, disorganized, catatonic, undifferentiated and residual type. The paranoid type is characterized by the presence of prominent delusions or auditory hallucinations in the context of a relative preservation of cognitive function and affect. The essential features of the disorganized type are disorganized speech, disorganized behaviour, and flat or inappropriate affect. This subtype is usually associated with “poor premorbid personality”, early and insidious onset, and a continuous course without significant remission.

Historically this type was termed *hebephrenic*. The essential feature of the catatonic type is marked psychomotor disturbances that may involve motoric immobility, excessive motor activity, extreme negativism, mutism, peculiarities of voluntary movement, echolalia or echopraxia. In the undifferentiated type criteria for schizophrenia are met but not the specific criteria for paranoid, disorganized or catatonic. Finally in the residual type there has been at least one episode of schizophrenia and there is continuing evidence of the disturbance, as indicated by presence of negative symptoms or two or more attenuated positive symptoms. The subtypes of schizophrenia are probably not to be included in the DSM 5, according to the recommendation from the DSM 5 work group (www.dsm5.org).

Schizophreniform disorder is identical to schizophrenia except for two differences: the total duration of the illness (including prodromal, active and residual phases) is at least one month but less than six months; second, impaired social or occupational functioning during some part of the illness is not required (although it may occur).

Schizoaffective disorder is characterized by an uninterrupted period of illness during which, at some time, criteria for major depressive, manic, or mixed episode are fulfilled concurrent with schizophrenia (i.e., two or more of the following: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour, negative symptoms) (APA 2000).

There are certain personality disorders that are connected to schizophrenia, particularly schizoid and schizotypal personality disorder. The essential features of schizoid personality disorder are, according to DSM-IV-TR, a pervasive pattern of detachment from social relationships and a restricted range of expression of emotions in interpersonal settings. The essential features of schizotypal personality is a pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for, close relationships as well as by cognitive or perceptual distortions and eccentricities of behaviour. Schizotypal personality disorder is more prevalent among the first-degree biological relatives of individuals with schizophrenia.

Schizophrenia, schizophreniform psychosis, schizoaffective disorder, and schizotypal personality disorder are sometimes referred to as schizophrenia spectrum disorder (SSD), due to the overlap in symptoms and the familial aggregation (Kendler, Neale & Walsh 1995).

1.1.3 Childhood development

Although the typical symptoms of schizophrenia usually appear in young adulthood, precursors of the disorder may be present during childhood. The children have been described as slightly different from their age peers with regard to motor performance, cognitive development, activity control and social interaction. If this is a "predisposition" or should be regarded as subtle symptoms of the disease has been disputed. Bleuler writes in his monograph:

"Whether there exists an individual disposition to the disease is questionable. Undoubtedly, many of the later schizophrenics were peculiar, withdrawn, and autistic already in the youth. But at this time, we cannot decide whether such behavior is the expression of a disposition to the disease or the surreptitious beginnings of the disease itself.

In any event, intelligence is not related to this predisposition. Elminger and Lugarno have observed many cases of strikingly superior intelligence among their patients, whereas we ourselves could at least exclude predominance of individuals with inferior intelligence."

Kraepelin wrote that premorbid personality could be of value in the differential diagnosis of dementia praecox and manic depressive disorder. The personality type which most often precedes dementia praecox is "…shy, whimsical, repellent [or] incalculable, stubborn, rough and violent…"and is characterized by "seclusiveness…[where] conversation with strangers, entering a new environment, unusual demands, and difficulties appear to a patient as unsurmountable obstacles" (Krapelin 1921 in Kendler, 1986)

In the prospective study of the British 1946 birth cohort, differences between children who developed schizophrenia as adults and the general population were found in a range of developmental domains. Speech problems, low educational test scores, solitary play preference, and self-reported anxiety in social situations during childhood were factors associated with schizophrenia in adulthood (Jones, Rodgers, Murray et al. 1994). Another extensive cohort-study, the National Child Development Study, found that individuals who later developed schizophrenia differed from schoolmates in several social and emotional domains (Done, Crow, Johnstone et al. 1994; Leask et al. 2002). Deviant behaviours at age 4 years and both social and language impairment by age 7 years were found in another prospective cohort study by (Bearden, Rosso, Hollister et al. 2000).

Home-videos of patients with schizophrenia as children have been analysed in comparison with siblings in a unique study by Elaine Walker (Walker, Grimes, Davis et al. 1993; Walker, Savoie & Davis 1994). According to this,

children who later developed schizophrenia showed more negative emotions and frequently had unusual motoric features than their healthy siblings. In 1972, a sample of young Danish children (age 11-13) was videotaped in a standardized condition as part of the Copenhagen High-Risk study (Schiffman, Walker, Ekstrom et al. 2004). Adult psychiatric status was later ascertained. The analysis of the videotapes showed that the individuals who developed schizophrenia, as a group, showed deficits in sociability.

Given that genetics are important risk factors for schizophrenia, several high-risk studies have longitudinally followed children who have one or two parents with schizophrenia. Problems in motor and neurological development, deficits in attention and verbal short-term memory, poor social competence, are factors that appear to predict schizophrenia in these studies (Erlenmeyer-Kimling & Cornblatt 1987; Weintraub 1987; Mednick, Parnas, & Schulsinger 1987; Erlenmeyer-Kimling, Rock, Roberts et al. 2000; Niemi, Suvisaari, Tuulio-Henriksson et al. 2003).

1.1.4 Childhood onset schizophrenia

Childhood onset schizophrenia (COS) is defined as schizophrenia with onset prior to the age of 13 years. COS is nowadays considered a very rare condition with a frequency less than 1 in 10 000 children (Gillberg 2000; Remschmidt & Theisen 2005; Kennedy, Kumar & Datta 2007). A Cochrane review on antipsychotic medication for COS affirms that the low prevalence of childhood schizophrenia makes it difficult to study (Kennedy et al. 2007). COS is a severe condition with poor long-term prognosis (Ropcke & Eggers 2005). Impairments in social development, speech and language is common before onset of COS (Rapoport, Chavez, Greenstein et al. 2009). Neurological soft signs (Biswas, Malhotra, Malhotra et al. 2007) as well as minor physical anomalies (Hata, Iida, Iwasaka et al. 2003) are significantly more frequent in COS than in adult onset schizophrenia. The US National Institute of Mental Health (NIMH) study of COS includes children of 6 – 18 years of age meeting DSM-III-R/DSM-IV criteria for schizophrenia with onset before their 13th birthday, recruited nationally. Premorbid IQ of less than 70 as well as significant medical or neurological conditions, were exclusion criteria. In this sample of 75 patients, 19 (25 %) had a lifetime diagnosis of PDD. Early symptoms of PDD in children with COS have also been reported in five other independent studies (Sporn, Addington, Gogtay et al. 2004). COS is suggested to be associated with a greater familial vulnerability. Parents of patients with COS have higher rate of schizophrenia spectrum disorders than do patients with adult-onset illness (Nicolson, Brookner, Lenane et al. 2003; Rapoport et al., 2009).

1.1.5 Attenuated psychosis syndrome/At Risk Mental State/Prodromal Risk syndrome

The prognosis for schizophrenia is severe, only about 15% of the whole group achieve sustained recovery (Harrison, Hopper, Craig et al. 2001; Robinson, Woerner, McMeniman et al. 2004). In order to improve the prognosis and to prevent full-blown illness, large efforts have been put into early intervention. Different sets of criteria have been proposed to identify individuals at risk for schizophrenia. At the University of Melbourne, Yung, McGorry and colleagues developed Ultra High Risk (UHR) criteria for help-seeking who presented to the clinic. These criteria could predict a very high transition rate to psychosis (40% within 12 months). Individuals meeting UHR criteria are said to have an "At Risk Mental State" (ARMS) (Yung, McGorry, McFarlane 1996; McGorry, Yung, Phillips et al. 2002; Yung, Phillips, Yuen et al. 2003). Researches at Yale University developed a similar set of criteria for "Prodromal risk syndrome" (McGlashan, Miller & Woods 2001). The largest study examining transition from prodromal risk syndrome to psychosis is the North American Prodrome Longitudinal Study, which has reported that up to 40% of individuals who met risk syndrome criteria converted to psychosis over 2.5 years (Cannon, Cadenhead, Cornblatt et al. 2008; Woods, Addington, Cadenhead et al. 2009).

In a study aimed to detect prodromal risk syndrome among 11-13 years old in the general population, the prevalence was 0.9–8.0% depending on whether or not the criterion of "a 30% decrease in functioning in the last year" was applied. Nonpsychotic psychiatric disorders were present in 63% of the adolescents with prodromal risk syndrome (those without decreased function included). Depressive disorder was the most common, and 16% had ADHD (Kelleher, Murtagh, Molloy et al. in press). The study did not assess specifically for ASD.

The research about prodromal risk factors has evolved to a proposed new diagnosis for the next version of the Diagnostic and Statistical Manual of Mental Disorders, the DSM 5. The diagnosis is, at present, called "Attenuated Psychosis Syndrome". The goal of the new diagnosis is to provide a diagnostic category that facilitates identification, treatment, and research. This proposal has led to a great deal of debate among leading researchers in the field (Corcoran, First & Cornblatt 2010; Drake & Lewis 2010; McGlashan et al 2010; McGorry 2010; Ruhrmann, Schultze-Lutter & Klosterkotter 2010; Yung, Nelson, Thompson et al. 2010; Woods, Carlson, Carpenter 2011). The proposed criteria are delusions, hallucinations or disorganized speech with intact reality testing, but of sufficient severity

and/or frequency that it is not discounted or ignored. Symptoms must be present in the past month and occur at an average frequency of at least once per week in past month. Furthermore, the symptoms must have begun in or have become significantly worsened during the past year and have to be sufficiently distressing and disabling for the patient or parent/guardian to lead them to seek help.

1.2 Autism spectrum disorder

Autism spectrum disorders (ASD) are considered to be neurodevelopmental disorders with a spectrum of signs and symptoms, the essential features being a triad of impairments of social interaction, communication and imagination (associated with behavioural restriction). ASD affect children of normal as well as subnormal intelligence, and, in the vast majority of cases, persist into adulthood (Howlin, Goode, Hutton et al. 2004; Billstedt, Gillberg & Gillberg 2007; Cederlund, Hagberg, Billstedt et al 2008).

1.2.1 Former classifications of autism

In 1943, Leo Kanner described eleven case studies of children with a condition that he found differed markedly from anything reported so far. He borrowed the term autism from Bleuler to define the condition, Early Infantile Autism. About the same time, in 1944, independently of Kanner, Hans Asperger described autistic psychopathy. Kanner's descriptions became more spread and well-known probably due to the fact that Hans Asperger's work was published only in German.

Lauretta Bender, and others, argued that early infantile autism was an early manifestation of schizophrenia (Bender 1971). She argued for the importance to recognize the biological components for deviant development in children and for the needs of the children.

"We have concerned ourselves with the biological vicissitudes to which the child is exposed in early life: in utero, at birth, and as a vulnerable developing infant. Every child whose development is deviant must be explored in the light of these early-life exposures. It is all too easy for some workers to overlook the significant and provable episodes that may occur in such child's period of life. They tend to label the deviant child "autistic" and assume that the cause and cure are psychological.

Needless to say, every child who is biologically damaged and/or psychologically deprived will, depending on his capacities, benefit from psychological understanding, tender loving care, more attention, and appropriate routine for his experiences to learn. Also, there are probably many children with lesser

amount of biological damage or psychological insult who may need no referral to a professional. No child appears to be completely protected from damaging experiences. Life is like that."

There were several different opinion about the aetiology of autism (Magnusson, Rydell & Dahlin 1975). Bettelheim, who had been detained in Nazi concentration camps, likened the difficulties of the autistic children with that of prisoners in such camps. According to him, autism was a state of mind developed in reaction to "extreme situations" created by maternal rejection and hostility (Bettelheim 1967). Rimland argued, on the basis of empirical research, that there was a neurological basis for autism and that there was no evidence to support a psychogenic theory (Rimland 1964)

In 1971, Kolvin published seven articles on "Studies in Childhood psychosis" in one issue of British Journal of Psychiatry. (Kolvin 1971; Kolvin, Garside & Kidd 1971; Kolvin, Humphrey & McNay 1971; Kolvin, Ounsted, Humphrey et al. 1971; Kolvin, Ounsted, Richardson et al. 1971; Kolvin, Ounsted & Roth 1971). He presented a study of 80 children admitted to hospitals in Oxford and Newcastle for intensive assessment of their psychosis. Their clinical pictures were analysed in detail. He classified the conditions according to age of onset. The Infantile Psychosis (IP) had onset prior to age 3 years (and included Kanner's early infantile autism), and Late Onset Psychosis (LOP) with onset during the main school period of 5 – 15 years. There were no children in the study with onset at 3-5 years of age. The late onset psychosis resembled adult schizophrenia in symptomatology. This work was of major importance for the conclusion that autism and schizophrenia are separate conditions. Kolvin showed that in the LOP group 87% (29 out of 33) had a history of premorbid oddity, 67% had an insidious onset, whereas 12 % had an acute onset (the rest insidious with acute exacerbations). A vast majority (88%) of the IP had speech delay, 28 % had never spoken words at any time. In the LOP 46% had had a speech delay, no one was mute. There was a marked difference in IQ. In the IP group 50% were untestable or had IQ below 50, another 27% had IQ in the interval 51-69. In the LOP group 76% had IQ above 70 (Kolvin, Humphrey & McNay 1971). Looking at capacity for making relationships both groups had marked difficulties but the IP group had more severe impairment. All children in the IP group were uninterested in people and mixed poorly with other children. Gaze avoidance was present in 85% of the IP cases and 79% avoided contact with people. In the LOP group 33% were uninterested in people, and 50% avoided contact with others. Only 6% showed gaze avoidance. It was also found that 25 out of 33 in the LOP group had suffered from severe and cruel

teasing by other children prior to the onset of clear-cut psychotic picture (Kolvin, Ounsted, Humphrey et al. 1971).

It is important to recognize that although Hans Asperger had described autism in individuals with normal och superior intelligence, his work was only read and known by few at this time. Van Krevelen (1971) writes the same year:

"Kanner's publications are well known internationally. I doubt sincerely whether this can be said about Asperger's work. This might create - and has in fact sometimes created - the erroneous impression that Asperger's autistic psychopathy refers to analogous cases described by Kanner. The two clinical pictures differ considerably."

Van Krevelen described that the manifestation age of Early Infantile Autism is early, sometimes as early as the first month of life. In contrast, the manifestation age of autistic psychopathy described by Asperger, is in the first years of elementary school, or earlier if the parents have not been able to adjust themselves to the individualistic behaviour of their child. Never is the diagnosis made in infancy. The school community requires adjustment to rules and norms. Moreover, schoolmates soon observe everything out of the ordinary. He described that the child with early infantile autism walks earlier than he speaks and the language does not attain the function of communication. The child lives in a world of his own. The child with Asperger's syndrome walks late but speaks early. Language aims at communication but remains "one-way traffic". The child lives in our world in his own way. Early infantile autism is, according to van Krevelen, a psychotic process whereas the latter is more of a personality trait.

Both before and after Hans Asperger's classic article, children with similar behaviour and appearances had been described in the literature. First by Eva Ssuchareva in 1926 (Wolff 1995), she called the condition "schizoid personality disorder of childhood". Sula Wolff also used the term schizoid personality disorder to describe children with a pattern of detachment from relationships and restricted expressions of emotions. She later found that many of these children with schizoid personality did meet criteria for Asperger's disorder (Wolff & McGuire 1995).

Lorna Wing in 1981, published a seminal article based on Hans Asperger's work and beyond that, on 34 cases, age 5-35 years, personally examined by the author. She declared that the term Asperger's syndrome is to be preferred since the term psychopathy may be misinterpreted as sociopathic behaviour.

She describes in detail and illustrates with cases, the same syndrome in children, adolescents and adults (Wing 1981). This article was important for the awareness among clinicians and researchers, that Asperger's syndrome (AS) exists and can be recognised.

In an epidemiological study of early childhood psychoses, Wing in collaboration with Judith Gould, identified children under age 15 who had any features which were frequently associated with autism. A triad of impairments were often found together; deficits in social communication, verbal and nonverbal communication along with lack imagination (symbolic play). They found few children who fitted Kanner and Eisenberg's strict criteria, another few who fitted Asperger's descriptions but many more who had varied mixtures of features from both. Wing was first to suggest that autism was not a discrete, categorical disorder but rather a continuum, a spectrum, of impairments and competencies. (Wing & Gould 1979; Wing 2005)

The first set of operationalized criteria for AS was formulated by Christopher Gillberg in 1988/1989, and elaborated in 1991 (Gillberg & Gillberg 1989). These criteria are based on Hans Asperger's original publication. Gillberg was also first to suggest that Asperger syndrome and autism exist on a spectrum with other disorders of empathy, and to introduce the concept of an empathy quotient, that, by and large, is comparable to intelligence quotient, with a Gaussian distribution of scores except in the lowermost portion where "pathological" cases (including some with autism and Asperger syndrome) confound the picture and skew the distribution somewhat (Gillberg 1992). Later, Gillberg (2010) suggested the need for a broad categorisation of early symptomatic syndromes related to abnormal neurodevelopment (ESSENCE, see below).

1.2.2 Current classifications of autism

In the DSM-IV (and DSM-IV-TR) the ASD are listed under the title Pervasive Developmental Disorders as: autistic disorder, Asperger's disorder and Pervasive Developmental Disorders Not Otherwise Specified (PDD-NOS). The diagnostic criteria include early childhood onset major social-communication impairment (characterised by a failure of the development of social instinct) and severely impaired imagination with restriction in the behavioural repertoire as shown by stereotyped movements or interests. Qualitative impairment in communication is a criterion for autistic disorder but not for Asperger's disorder. In Asperger's disorder there must not, according to DSM-IV-TR be any clinically significant delay in language,

cognitive development, self-help skills and curiosity about the environment. This criterion has been strongly criticized, not one of Hans Asperger's clinical cases would fulfil this criterion (Leekam, Libby, Wing et al. 2000)

The proposal at present for DSM 5 is that ASD will not be divided into subgroups. The rationale for this being: "Differentiation of autism spectrum disorder from typical development and other "nonspectrum" disorders is done reliably and with validity; while distinctions among disorders have been found to be inconsistent over time, variable across sites and often associated with severity, language level or intelligence rather than features of the disorder." (www.dsm5.org)

ASD was previously assumed to be a rare condition, but according to recent epidemiologic studies using DSM-IV or ICD-10 criteria, the prevalence of ASD is 0.5-1.1% of the child population (Baird, Simonoff, Pickles et al. 2006; Coleman & Gillberg 2011).

1.3 Other related conditions

1.3.1 Multiple Complex Developmental Disorder (MCDD)

If one follows the subdivision of ASD in the DSM-IV, the least well-defined group, the PDD-NOS, has the highest prevalence, higher than autistic disorder or Asperger's disorder. Multiple Complex Developmental Disorder (MCDD) has been proposed as a subgroup of PDD-NOS. It is not included in the DSM or the ICD diagnostic manuals. Classification rules for MCDD have been published and have been used in several studies. The criteria are (1) impaired regulation of affective state and anxieties; (2) impaired social behavior, (3) presence of thought disorder. Each criterion is defined by several descriptions, items (van der Gaag, Buitelaar, den Ban et al. 1995; Buitelaar & van der Gaag 1998). Follow-up of 55 children with MCDD revealed an elevated risk for schizophrenia spectrum disorders (van Engeland & Van der Gaag 1994). Adolescents with MCDD have been compared to adolescents with "At Risk Mental State" (ARMS) and healthy controls. The MCDD group and the ARMS group had both more schizotypal traits than healthy controls and did not differ from each other in that sense. Furthermore, 78% of the MCDD group met criteria for ARMS (Sprong et al., 2008)

1.3.2 Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE)

The acronym ESSENCE refers to the fact that the early presentations of disorders, such as attention-deficit/hyperactivity disorder, oppositional defiant disorder, tic disorder, developmental coordination disorder, and autism spectrum disorder are often similar across disorders (Gillberg 2010). Children may have impairing symptoms before age 3-5 years in the fields of (a) general development, (b) communication and language, (c) social inter-relatedness, (d) motor coordination, (e) attention, (f) activity, (g) behaviour, (h) mood, and/or (i) sleep. Although children are often referred for one type of the symptoms, major problems in at least one ESSENCE domain before age 5 years often signals major problems in the same or overlapping domains years later. Language delay and sleep problems may well be the first symptom of AST in one child, but on the other hand, be the first symptoms of ADHD in another child. ESSENCE implies that if a child has impairing symptoms in one field, it is not appropriate to adopt a "wait-and-see" approach. Something needs to be done (diagnosis and intervention) and most likely, not just for the first presented symptom.

1.3.3 Attention-Deficit/Hyperactivity Disorder (ADHD)

In the DSM-IV-TR there are nine criteria for inattention and nine separate criteria for hyperactivity/impulsivity. For the diagnosis of ADHD combined type, 6 criteria for in-attention and 6 criteria for hyperactivity/impulsivity are required. If 6 out of 9 criteria for inattention are met, but not 6 criteria for hyperactivity/impulsivity, the diagnosis of ADHD predominantly inattentive type may be applied. If 6 out of 9 criteria for hyperactivity/impulsivity are met, but not 6 criteria for inattention, the diagnosis ADHD predominantly hyperactive-impulsive type is applicable. The DSM-criteria for ADHD were developed for children. Many of them are age-specific, for example "often runs about or climbs excessively" or "often has difficulty playing or engaging in leisure activities quietly." These criteria are usually not applicable in adulthood. Wender, already in 1976, suggested operational criteria which better specify characteristics that are more directly relevant for ADHD in adults (Wender, Wolf, & Wasserstein 2001). The Wender Utah adult ADHD criteria include both a childhood history consistent with the DSM criteria and specific adult characteristics. The adult characteristics are composed of seven symptoms: 1. Attention deficits, 2. Motor hyperactivity, 3. Affective lability, 4. Hot temper, explosive short-lived outbursts, 5. Disorganization, inability to complete tasks, 6. Emotional over reactivity 7.

Impulsivity. The first two symptoms are both required along with at least two of the remaining five symptoms.

Retrospective studies on individuals with SP, as well as studies on high-risk populations, have shown that ADHD symptoms are more common in these groups than in the general population (Niemi, Suvisaari, Tuulio-Henriksson et al. 2003; Peralta, de Jalon, Campos et al. 2011). There have been several publications about AS and co-existing ADHD in children (Sinzig, Walter, & Doepfner 2009). However, studies on the same "comorbidity" in adults have been few and far between (Nydén, Niklasson, Stahlberg et al. 2010).

Nicotine dependency and substance abuse

Nicotine dependency is more common among patients with psychiatric disorders than in the general population (Aubin, Rollema, Svensson et al. 2012). Among the mentally ill, smoking prevalence is highest in patients with SP. Heavy smoking and high nicotine dependency are more frequent in smokers with SP as compared with the general population (de Leon & Diaz 2005). Patients with SP live substantially shorter lives than the general population and the primary cause of death is tobacco-related medical illness, such as cardiovascular disease, chronic obstructive pulmonary disease and lung cancer (Brown, Inskip, & Barraclough, 2000; Hennekens, Hennekens, Hollar et al. 2005; George & Ziedonis, 2009). Childhood ADHD is strongly associated with early initiation of cigarette smoking (Milberger, Biederman, Faraone et al. 1997; Charach, Yeung, Climan et al. 2011). Patients with autism spectrum disorders (including those with AS), as well as those with obsessive-compulsive disorder, have, on the contrary, been reported to have a low prevalence of smoking (Bejerot & Humble, 1999; Bejerot & Nylander, 2003).

It is well known that substance abuse (i.e. abuse of alcohol, cannabis, amphetamine and similar) is often associated with psychiatric illness. Prospective studies have shown that mental disorders are a risk factor for developing substance abuse (Swendsen, Conway, Degenhardt et al. 2010). Cannabis use is a risk factor for developing schizophrenia. Cannabis is also frequently used as self-medication to reduce symptoms, although the long-term effects are often intensified symptoms instead.

1.4 Social cognition

The term social cognition is defined in various ways, but generally it refers to the mental operation underlying social interactions. It involves various

abilities, such as emotion perception, social perception, theory of mind, and social knowledge. Social cognition is related to, though distinct from, basic neurocognition (Sergi, Rassovsky, Widmark et al. 2007).

1.4.1 Social cognition in schizophrenia

In 1992, Chris Frith proposed that several symptoms of schizophrenia could be explained by insufficiencies in theory of mind. Delusions of reference, misidentification and persecution are characterized by a misinterpretation of another person's behavior or intentions. These symptoms may well arise as a result of deficit in a system which enables us to infer what is in the minds of other people. Frith assumed that the initial development of mentalising abilities is normal and that these abilities become impaired as the illness develops (Frith 1992). There has been intense research on social cognition in schizophrenia since then. Patients with schizophrenia have, according to tests, in comparison to controls, impairments in emotion processing (Archer, Hay & Young 1994), social perception (Corrigan & Green 1993; Toomey, Schuldberg, Corrigan et al 2002), theory of mind (Roncone, Falloon, Mazza et al. 2002; Greig Bryson & Bell 2004), and social knowledge (Corrigan & Addis 1995; Penn, Ritchie, Francis et al. 2002). In a meta-analysis of theory of mind in in schizophrenia it was shown that the patients had significant impairment in theory of mind also during remission. Therefore, according to the authors, the impaired mentalising is not just a consequence of the acute phase but may be regarded as a trait marker of schizophrenia (Sprong, Schothorst, Vos et al. 2007). However, there has been serious criticisim that there is a lack of research on the psychometric properties of many of the different tests used for tapping into mentalising skills (Harrington, Siegert & McClure 2005; Sprong et al. 2007).

The ability to infer other persons' intentions are associated with and possibly a risk factor for general delusions and positive symptoms (Mehl, Rief, Lullman et al. 2010). Social cognition impairment has been shown to be a predictor of poor functional outcome in schizophrenia (Schmidt, Mueller & Roder 2011). Furthermore, impaired social and rule functioning appear to be a risk factor for converting to psychosis in a prospective study of individuals with clinical high risk for psychosis. Interestingly, onset of psychosis did not further disrupt social difficulties (Cornblatt, Carrion, Addington et al. in press).

1.4.2 Social cognition in ASD

Qualitative impairment in social interaction is a central criterion for diagnosing ASD, including AS. It is an impairment that greatly affects

everyday life for people with ASD and their families. Many of the tests in the field have been developed in order to explore what component of the social cognition ability that is impaired in ASD rather than to develop a test to be used in clinical practice. Tests have also been used in experiments with functional magnetic resonance imaging (fMRI) to examine which part of the brain is activated during a certain cognitive processes. Theory of mind (cognitive perspective taking/empathy), has, through such studies, been linked to the medial prefrontal cortex, the superior temporal sulcus and the adjacent temporal junction (Gillberg 1992; Happe, Ehlers, Fletcher et al 1996; Frith & Frith 2006). The ability to share the *feelings* of others, on the other hand, activates insular and anterior cingulate cortices, areas relevant for emotion processing. Difficulties in sharing feelings with others are related to difficulties representing one's own emotions. This is observed in some, but not in all individuals with ASD (Bird, Silani, Brindley et al. 2010).

Although several tests have been developed, there are no standardised tests for measuring the different components of social cognition. As has already been pointed out, there is a lack of research on the psychometric properties of many of these tests. In individuals with severe problems in the autism spectrum the social interaction impairment is easily observed and special tests to confirm this is not needed in clinical practice. For individuals with less apparent impairment on the other hand, it has been complicated to develop useful tests (Happé 1994; Dahlgren & Trillingsgaard 1996). Many interesting ideas have been tested and failed due to the fact that many high-functioning individuals with ASD have been able to get good scores on the tests despite huge difficulties with social cognition in real life. One reason for this is timing differences in tests and real life: in the test situation the person has time to reflect, whereas in real life the social interaction needs to be rapid. People with ASD are usually very slow in "social processing" (Coleman & Gillberg 2011).

1.4.3 Another hypothesis about social cognition in schizophrenia and ASD

Recently, a hypothesis that psychosis and autism should be regarded as *diametrical* disorders of the social brain, has been proposed by Badcock and Crespi (2008). They suggest that individuals with psychosis, including schizophrenia and bipolar disorder, have superior social cognition, "hyper-mentalistic" cognition, in contrast to the deficits in social cognition that are typical in autism. The hypermentalistic cognition leads to delusions of being spied on, paranoid and conspiratorial delusions etc. The aetiologies of the different conditions is, according to this hypothesis, genomic imprinting

leading to enhanced expression of paternally-active genes and reduced expression of maternally-active genes in the brain of individuals with autism on the one hand and the enhanced expression of maternally-active genes in the brains of persons with psychosis. They cite a wide range of genetic and neuroimaging data to support their hypothesis and have had some influence in the schizophrenia research field.

Conversely, other genetic studies have shown numerous direct and indirect *links* between ASD and schizophrenia (McCarthy, Makarov, Kirov et al. 2009; Craddock & Owen 2010; King & Lord 2011; Poot, van der Smagt, Brilstra et al 2011). Specific copy number variants associated with schizophrenia are also linked to a range of neurodevelopmental disorders including ASD, intellectual disability and ADHD (Owen, O'Donovan, Thapar et al. 2011). Neurexin-1, a vulnerability gene for both schizophrenia and ASD, has been proposed to influence brain structure and cognitive function in both disorders (Voineskos, Lett, Lerch et al., in press). Family history data supports a link between ASD and schizophrenia (Ghaziuddin 2005). Two case-control studies have shown that parental schizophrenia is a significant risk for autism (Larsson, Eaton, Madsen et al 2005; Daniels, Forssen, Hultman et al 2008). Also, neuroimaging studies have shown brain structural concordance between autism and schizophrenia (Cheong, Yu, Climans et al. 2010). In a magnetic resonance study by Toal at al. (2009), adults with ASD with or without a history of psychosis and healthy controls were compared. The group with ASD differed from controls in brain regions that are also implicated in schizophrenia. The authors put forward ASD as an alternative 'entry-point' to schizophrenia based on developmental brain abnormalities, suggesting that people with ASD may only require relatively subtle additional abnormalities to develop the positive symptoms of psychosis such as delusions and hallucinations.

2 AIMS

The main goal of the thesis is to explore how the childhood neurodevelopmental problems found in patients with schizophrenia relate to the current concept of ASD. The specific aims are to

- examine the rate of ASD in patients with a clinical diagnosis of schizophrenia;
- analyse whether or not ASD is more common in any particular subtype of schizophrenia or if any specific subtype of ASD is more strongly related to schizophrenia;
- explore, in detail, the similarities and differences in early childhood development and ASD symptomatology across adult individuals with clinically diagnosed schizophrenia spectrum disorders and in individuals with clinically diagnosed AS;
- explore the occurrence of "comorbid" ADHD in adult patients with either SP or AS, and in particular, whether or not nicotine use and substance abuse in SP or AS is related to the presence of ADHD;
- examine the applicability of different ADHD rating scales in individuals with SP or AS.

In order to examine aspects of social cognition (facial emotion/mind recognition) with a test now universally used in ASD, reference values and evaluation of the psychometric properties of this test were needed. The further specific aims of this thesis therefore were to

- provide Swedish non-patient reference values for the Reading the Mind in the Eyes Test; and
- examine test-retest reliability, and elucidate strengths and weaknesses of the Reading the Mind in the Eyes Test.

2.1 Ethics

The study was approved by the Medical Ethical Board at Uppsala. All participation was voluntary. All patients and parents participating in studies II, III and IV gave a written informed consent.

3 PARTICIPANTS AND METHODS

3.1 Participants

The number of participants in the different substudies is presented in Table 1. Details about the recruitment procedures for the different study groups, numbers of eligible patients and attrition are described in the text.

Table 1. Participants in the different substudies

Study	I (Eyes Test)	II (ASD in SP)	III (Early development)	IV (ADHD and substance abuse)
Object of study	Provide Swedish non-patient reference values, examine test-retest reliability	Prevalence of ASD in schizophrenia	Similarities and differences in early childhood development in schizophrenia and AS	Prevalence of ADHD in schizophrenia and AS. Prevalence of nicotine and substance abuse
Students	158			
Age years	23.9 (SD 3.3)			
Male:Female	75:83			
Schizophrenia group		32	32	41
Age years		27.8 (SD 4.6)	27.8 (SD 4.6)	28.9 (SD 4.5)
Male:Female		21:11	21:11	25:16
Study specific inclusion criterion		*Parent participated in interview*	*Parent participated in interview*	*SCID verified schizophrenic psychosis*
Asperger syndrome group			45	54
Age years			27.2 (SD 3.9)	27.0 (SD 3.9)
Male:Female			22:23	26:28
Study specific inclusion criterion			*Parent participated in interview*	
Population sample				7551

3.1.1 Students

Students at the University of Karlstad were invited to voluntarily participate in study I. The 158 included students (75 men and 83 women, age 19–32 years, mean age 23.9, SD 3.3) were studying on different programmes such as those for engineers, teachers, economists and nurses. Fifty-eight of them, 25 men and 33 women, completed the test a second time, three weeks later. Participants received a lottery ticket in recognition of their contribution.

3.1.2 Individuals with schizophrenia

In total, 46 young adult patients (29 male, 17 female) with a clinical diagnosis of schizophrenia, schizophreniform disorder or schizoaffective disorder participated.

Our original aim was to include 30 men and 30 women born between 1972 and 1986, with schizophrenic psychosis in the study. Individuals with diagnosed intellectual disability would not be included. In attempts to get as representative a sample as possible, we strived to reach and invite for study every patient (born in the years mentioned) with a clinical diagnosis of schizophrenia, schizophreniform disorder or schizoaffective disorder, in the county of Värmland, Sweden. The total population of individuals in Värmland born in the target years was about 44 000 (www.scb.se).

In Värmland all adult psychiatric services were in the public domain at the time of the study and organized at the county level into one clinic. The staff at the different psychiatric out-patient departments around the county was informed about the study and asked to screen their service for patients with schizophrenia, schizoaffective disorder or schizophreniform psychosis. They were asked to inform the patient about the study, to give a standard (oral and written) full description of the study (approved by the Ethics committee). Patients who did not have a current contact were sent a participation inquiry. Individuals with current severe psychotic symptoms requiring hospitalisation were approached when symptoms were considered less florid. Patients accepting to participate were included and contacted by one of two clinical researchers (MUH and TL) only after written informed consent had been received from each individual, with the exception of a few who wanted to meet the researchers in person before deciding on participation. Because of recruitment difficulties we decided to include three individuals with schizophrenia born in beginning of 1987. In due course, a total of 84 patients, 58 men and 26 women were deemed eligible for the study.

This number eligible we found is in equivalence with the number found in Värmland in a nation-wide Swedish study using register data performed at the same time, by Hultman and colleagues as part of the International Schizophrenia Consortium study (ISC 2008). In that study 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, and secondary diagnoses. Patients with discharge diagnoses 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, subnormal intelligence was not an exclusion criterion. Numbers are not widely discrepant from those that we found, providing some 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. According to both studies the prevalence of schizophrenic psychosis in Värmland for people born in 1972 to 1986 is approximately 0.2%.

Thirty men from Värmland (52% of the whole eligible group) accepted to participate, but two of them with-draw 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 was not confirmed by a psychiatrist. Finally, 28 men and 14 women with schizophrenic psychosis from Värmland participated in the study. In order to increase the number of participants, we approached an outpatient clinic for patients with psychosis in the city of Gothenburg, from which we unfortunately only managed to recruit one man and three women.

Hence, in the end, 29 men and 17 women with clinical diagnoses of schizophrenia, schizoaffective disorder or schizophreniform psychosis (SP) were included. The participants were asked especially for permission for us to contact their parents for an interview. Six participants did not give such permission. The other parents were contacted by mail with a separate participation inquiry. Parents to four returned the inquiry informing that they did not want to participate, parent to four other (including parents who partially lived abroad) did not answer despite reminders. Parents of 21 men and 11 women accepted to participate and were interviewed. These 21 men and 11 women, whose parents were interviewed, make the schizophrenia spectrum group in the studies II and III, see figure 2.

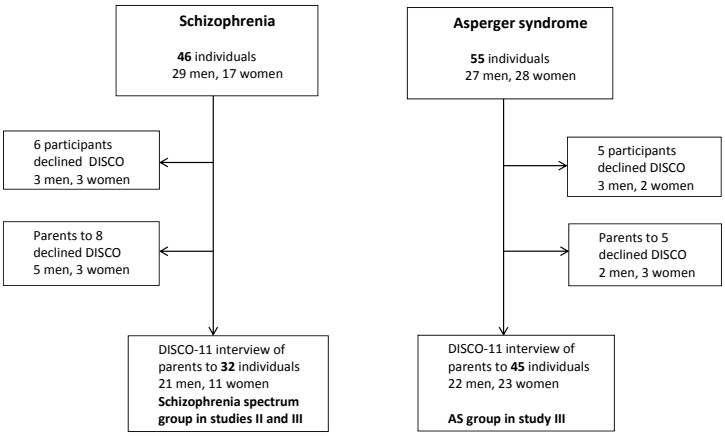

Figure 2. Flow-chart showing participation in the DISCO-11 study

All included were interviewed with the SCID-I in order to confirm or refute the clinical diagnoses. Two patients were shown to have bipolar I disorder instead, one patient had "only" substance-induced psychotic disorder and another two did not have psychotic disorder. The SCID-I diagnoses for the remaining 41 individuals, 25 men and 16 women, were: Schizophrenia paranoid type (12 men and 7 women), schizophrenia undifferentiated type (5 men and 1 woman), schizoaffective disorder (2 men and 6 women), schizophreniform disorder (3 men), and psychotic disorder (3 men and 2 women). These 41 individuals comprise the schizophrenic psychosis (SP) group in study IV.

3.1.3 Individuals with AS

As in the SP group, the original aim was to include 30 men and 30 women with AS in the study group. For this purpose, individuals born 1972-1986 with AS were recruited from two Värmland county-wide services for individuals with ASD, the Department of Adult Habilitation (DAH) in Karlstad, Värmland County and the Neuropsychiatric Clinic for Children and Adolescents (NCCA) in Karlstad. The DAH is an out-patient clinic for individuals aged 19 years plus with a diagnosis of ASD. Its focus is on neurodevelopmental disorders and not on psychiatric treatment. The majority of adults who have been given a clinical diagnosis of AS living in the county

are known at DAH. NCCA is an outpatient clinic for children and adolescents under age 19 years for evaluation of ASD or other neurodevelopmental problems. Most children and adolescents diagnosed with AS in the county are evaluated at NCCA. Thus, when intending to systematically reach clinically diagnosed young adult individuals, regardless of age at AS diagnosis, the two clinics are the most adequate to approach in this particular geographic area.

At DAH and NCCA, all patients with a registered clinical diagnosis of AS, born between 1972 and 1986, and still living in Värmland were considered eligible for the study. Recruitment and assessment of participants was done in order of age, starting with the oldest individuals. Assessments were performed during 2006-2010. A total of 155 eligible individuals were sent a participation inquiry including a complete description of the study, a response sheet and a stamped envelope. 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.

An estimation of the prevalence of AS in Värmland for people born in 1972 to 1986 was 0.35% according to the number of eligible individuals found.

Forty-eight of the 155 eligible individuals (31%) did not respond at all, 46 (30%) actively declined participation and 61 (39%) agreed to participate, they all gave a written informed consent. Six individuals left the study before assessment was completed. Finally 55 individuals (27 men and 28 women) with a clinical diagnosis of AS participated in the study.

All 55 participants were asked particularly for permission for us to contact their parents for an interview. When approved the parents were contacted by mail with a separate participation inquiry. Four participants did not want us to make such a contact and for one participant the life circumstances changed and an interview turned out to be inappropriate. Parents of five did not respond despite reminders or actively declined participation. The 45 (22 men and 23 women) for whom we obtained parental information comprise the AS-group in study III (see figure 1).

In study IV one participant was excluded since essential data for the study was missing, hence the AS-group in study IV consists of 54 individuals, 26 men and 28 women.

3.1.4 Population based sample

In study IV the prevalence of nicotine dependency in the two clinical groups is compared to data from a population based sample from a study called "Life and Health 2008". The area investigated covered 55 municipalities in five counties, (Södermanland, Värmland, Västmanland, Uppsala and Örebro county) in central Sweden with approximately one million inhabitants. The sampling was random after stratification for gender, age group, county and municipality. A questionnaire was sent to a total of 68 522 individuals. Data collection was completed after two postal reminders. The response rate was 52.9%. The applicable age-group (18-34 years) consist of 7551 individuals.

3.2 Methods

3.2.1 Reading the Mind in the Eyes Test

The Reading the Mind in the Eyes Test is a widely used facial affect recognition test. The original version of the test was developed by Simon Baron-Cohen and first published in 1997 (Baron-Cohen, Jolliffe, Mortimore et al. 1997). The participant is shown 25 photographs of the eye region illustrating complex mental states (e. g. "embarrassed", "suspicious": emotions requiring inferences about others beliefs and intentions in contrast to basic emotions) and is asked to choose which of two words best describes what the person in the photograph is feeling or thinking. Responses are scored 1 or 0 for correctness. The possibility of "correct" answer by chance is 50% on each picture which lead to a too narrow range of individual differences and "ceiling effects". In 2001, an elaboration of the "Reading the Mind in the Eyes Test" was published (Baron-Cohen, Wheelwright, Hill et al. 2001). In order to improve the test the number of photographs was increased to 36 and for each photograph there were four (rather than two) words to choose between. A glossary of all terms was added to be presented to the participant. In 2001 Baron-Cohen presented a children's version of the Eyes Test, which consists of 28 photographs. The main differences between the revised adult version and the child version are the words being used, not the actual photographs. In the child version, the words are easier and no glossary is used (Baron-Cohen, Wheelwright, Spong et al. 2001).

A Swedish translation of the child version of Eyes Test (28 items) was used. The child version, in which the words are elementary and a separate glossary is unnecessary the risk of influence of verbal knowledge is reduced. To begin with, a pilot study was performed in which 100 students at the University of Karlstad completed the test. The distribution of chosen

answers was compared to those from the original paper on the child version by Baron-Cohen (Baron-Cohen, Wheelwright, Spong et al. 2001). On six of the 28 items the majority of participants did not opt for the expected word. In order to improve the translation, subtle changes of the translations of "worried" and "not believing" were made. The Swedish adjusted version (see Appendix) was used in study I. This version was later used in a comparison study between the schizophrenic psychosis group, the AS group and a group of 50 non-clinical controls (Lungegård, Hallerbäck, Hjärthag et al. submitted)

3.2.2 SCID-I

All participants included had a definite or (in a few cases) preliminary clinical diagnosis of schizophrenic psychosis. In order to confirm these diagnoses, the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First & Gibbon 2004) was used in face-to face interview with the participants.

DSM-IV Axis-II diagnosis was assessed using the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) (First & Gibbon 2004). In order to make our issues possible to investigate, exclusion criteria for PDD were disregarded

SCID-I and SCID-II were assessed by Dr Tove Lugnegård.

3.2.3 DISCO-11

Parents were interviewed with the Diagnostic Interview for Social and COmmunication Disorders (DISCO-11) (Wing, Leekam, Libby et al. 2002). The DISCO is a semi-structured interview and covers a wide range of developmental domains. An algorithm is included for different diagnostic categories :ICD-10 criteria for Autism, Asperger syndrome, Atypical autism with atypical onset age and or/ atypical symptoms (World Health Organization, 2004), Kanner and Eisenberg criteria for Autism (Eisenberg & Kanner 1956), Gillberg criteria for Asperger syndrome (Ehlers & Gillberg 1993), and Wing and Gould criteria for Autistic spectrum disorder (Wing & Gould 1979). The DISCO schedule is investigator based; the interviewer is to elicit enough information from the informant to make a judgement as to the most appropriate rating for each item. The interviewer shall encourage the informant to describe examples of behaviour or to relate illustrative anecdotes. In order to facilitate recollection bringing photographs and dairies are encouraged. Since recall of the timing of events is much less reliable than the memory of their occurrence the ages when a specific behaviour

occurred is not coded, apart from a few items concerning developmental skills. The interviewer is to code behaviour that the informant remembers easily and clearly. If the informant has to search their memory and remains uncertain the item is coded as absent or not known. The interview is structured to collect information about the current situation ("current") as well as information about development and previous ("ever") behaviour. In the present study, one primary aim was to explore the behaviour during childhood development. Hence, in scoring the DISCO-11, the score "ever" was consistently used only for earlier behaviour, meaning that if behaviour was currently present but was not present during childhood it would be scored only as "current".

Another adaptation of the DISCO-11 was to leave out the questions about schizophrenia. Schizophrenia is an exclusion criterion for autism in the algorithm which would preclude assessment of whether or not the two conditions might co-exist.

The clinical researcher (MUH) who carried out all the interviews, was trained in the administration of the DISCO by the originators of the interview and by the persons responsible for the Swedish version.

3.2.4 Patient records

All participants were asked if they had been in contact with child and adolescent psychiatry (CAP). Four men and seven women in the schizophrenia group recalled such contact and they all gave permission to use their psychiatric files in the study. The records were analysed according to age at contact, diagnoses, recorded developmental deviation, and type of care. Data relating to these 11 individuals are presented as short clinical vignettes in study II. In the AS-group 39 individuals recalled such contact and gave permission to use the files. Information from the files was used to confirm age at ASD diagnosis in study III, but will not be presented further in this context.

3.2.5 Autism Spectrum Quotient (AQ)

The AQ is a self-administered questionnaire developed for the explicit purpose of measuring autistic traits in adults of normal intelligence (Baron-Cohen, Wheelwright, Skinner et al. 2001). The AQ is widely used in clinical settings as well as in research to screen for ASD. Participants rate to what extent they agree or disagree with the statements about personal preferences and habits on a 4-point Likert scale (from Definitely agree to Definitely disagree with Slightly agree and Slightly disagree in between). All the agree

scores (Definitely or Slightly) are rated as 1 point and the total possible maximum score is 50. A high AQ score has been proposed to indicate a likely diagnosis within the autism spectrum.

3.2.6 Clinical ADHD diagnosis

ADHD has been reported to be quite often associated with ASD in children. Both ADHD and ASD are part of the ESSENCE group of early onset neurodevelopmental disorders and are often difficult to separate from each other in early childhood. All participants in the present study were asked about prior diagnostic assessments, and specifically if they had been examined for or clinically diagnosed with ADHD.

3.2.7 Wender Reimherr Adult Attention Deficit Diagnostic Rating Scale (WRAADDS)

The Wender Reimherr Adult Attention Deficit Diagnostic rating scale (Rosler, Retz Thome et al. 2006) is based on the Utah criteria for adult ADHD. It was originally designed as an interview. The Swedish version has been modified to serve as a self-rating scale. There are 35 descriptions, and the individual is asked to rate how appropriate each description is on a five-point scale: 0-not, 1-a little bit, 2-moderately, 3-quite a bit, to 4-very much. The scale yields a total score (range 0-140) and 7 subscale scores for: (1) Attention deficits, (2) Hyperactivity, (3) Affective lability, (4) Hot temper, (5) Disorganization, inability to complete tasks, (6) Emotional overreactivity and (7) Impulsivity.

3.2.8 Swanson, Nolan And Pelham questionnaire (SNAP)

The Swanson, Nolan And Pelham questionnaire (SNAP) (Swanson, Kraemer, Hinshaw et al. 2001) for ADHD (and oppositional-defiant disorder/ODD) symptoms is based on the DSM-IV criteria. The questionnaire was given in two versions, one referring to childhood symptoms and the other to present time. We made some minor alternations and replaced the words “playing”, “classroom” and “homework” (see Appendix). Parents were given the questionnaire with a stamped envelope in connection with a face-to-face DISCO interview and were asked to complete it at home and return it in the mail.

3.2.9 Nicotine use

The health, habits of living and living conditions in the general population was examined in a postal survey questionnaire at the time of the present study (Life and health 2008). This was the third time socioeconomic

conditions, lifestyle factors (including smoking and snuffing habits) and self-rated health was examined in this population in this manner (Molarius, Berglund, Eriksson et al. 2007; Arne, Jansson, Jansson et al. 2009). The age-group 18-34 years was used as a comparison group in the present study. The questionnaire included the following questions about tobacco use: ”Do you smoke cigarettes?” with the options: “No, I have never smoked regularly”; “No, I have quit smoking”; “Yes, I sometimes smoke” and “Yes, I smoke daily”. Questions about snuff were framed in the same way.

Participants in the AS and SP groups completed the Fagerström Tolerance questionnaire (Fagerstrom & Schneider 1989; Pomerleau, Majchrzak, & Pomerleau 1989), which includes general questions about cigarette and snuff use: “Do you smoke?” and “Do you use snuff?” with the options: “Yes”;” No”; “I have done so previously but not at present”.

3.2.10 Substance abuse

All participants were asked about current and previous substance use and abuse in the SCID-I interview. Abuse of alcohol, cannabis, amphetamine or other drugs was analysed in relation to diagnoses (SP, AS and ADHD) and in relation to nicotine dependency.

4 RESULTS

4.1 The Reading the Mind in the Eyes Test

Table 2 presents the Eyes test findings in the 158 students. Results are shown as the percentage of individuals who chose each word on each item.

Table 2. Distribution of responses in percentages (n = 158);"correct" response according to original study in bold

Item	Answer A	Answer B	Answer C	Answer D
1	23.4	5.1	**35.4**	36.1
2	9.5	2.5	3.2	**84.8**
3	**62.0**	11.4	2.5	24.1
4	4.5	**94.9**	0.6	0.0
5	3.2	**88.0**	2.5	6.3
6	1.3	1.9	**46.2**	50.6
7	7.0	22.2	**62.0**	8.9
8	**84.1**	3.2	5.7	7.0
9	0.6	0.0	3.2	**96.2**
10	17.7	2.5	**76.6**	3.2
11	15.2	**79.1**	1.9	3.8
12	1.3	2.5	0.0	**96.2**
13	**81.6**	2.5	5.1	10.8
14	5.7	**85.3**	0.6	8.2
15	**59.5**	7.0	10.1	23.4
16	**93.0**	1.3	1.3	4.4
17	3.8	45.6	8.2	**42.4**
18	**71.5**	1.3	4.4	22.8
19	4.4	17.7	6.3	**71.5**
20	1.9	6.4	**89.2**	2.5
21	**72.7**	3.2	20.3	3.8
22	7.0	7.0	1.3	**84.7**
23	7.0	**84.8**	4.4	3.8
24	**81.0**	7.0	10.7	1.3
25	4.4	30.4	5.7	**59.5**
26	18.4	21.5	**52.5**	7.6
27	1.3	2.5	**45.6**	50.6
28	3.2	1.3	**76.5**	19.0

On four items the target word was selected by fewer than 50% of the subjects, items. For one item (item 1), the reason was probably that the photograph is dark. In the pilot study in which we had lightened up the picture, 68% chose the target word in contrast to 35% who chose the target word in the present study where we used the original. For three other items (items 6, 17 and 27) the target words were selected by 42%-46% of the subjects. The score of "correct" answers out of 28 items was calculated. The range was 15-27 and the mean score was 20.5 (SD 2.4). Since the validity of items 1, 6, 17 and 27 was questionable, results with and without these items were analysed separately. The mean score for all participants on the 24 item "version" was 18.9 (SD 2.1), range 13-24.

4.1.1 Test-retest reliability

Fifty-eight students performed the test twice. The mean score of "correct" responses was 20.7 (SD 2.5) and 20.9 (SD 2.8). When the four questionable items were excluded the mean scores were 19.2 (SD 2.2) and 18.9 (SD 2.6), respectively. There was no significant difference between the scores using two related sample Wilcoxon Signed Ranks test ($p=.35$). There was, as expected, a significant positive correlation between the scores the first and second time, Pearson correlation $r = 0.60$, $p<.01$.

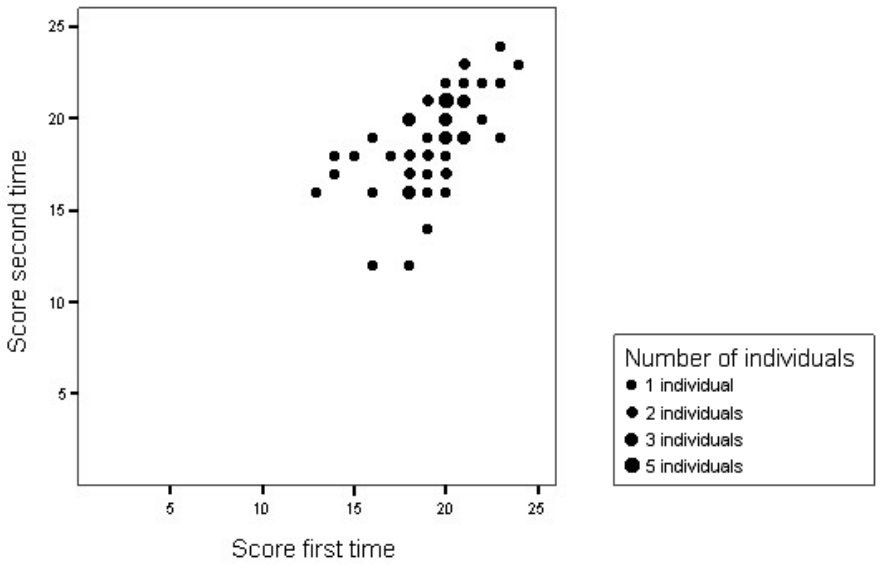

Figure 3. Correlation between Reading the Mind in the Eyes total scores (maximum 24) the first and second time, n=58

"Correlation" measures the strength of a relation between two variables, not the agreement between them. To examine the test-retest reliability we used the Bland Altman method to measure the limits of agreement (Bland & Altman 1986). This is a statistical method designed to examine the agreement between two test methods or, as in our case, the repeatability of a method. Using this statistical method it is possible to both visualize and calculate the agreement between two test times. For each student the difference between the two test scores is plotted against the mean score for the same student. The limits of agreement are the limits within which 95% of the differences are found, that is within two times the standard deviation.

The mean difference for all students was 0.33 with standard deviation 2.16. The upper limit of agreement was 4.65 and the lower limit of agreement was -4.00. Since the mean difference can be regarded as 0, the 95% limits of agreement can be described as ± 4.3. These limits are shown in the Bland Altman plot in figure 4.

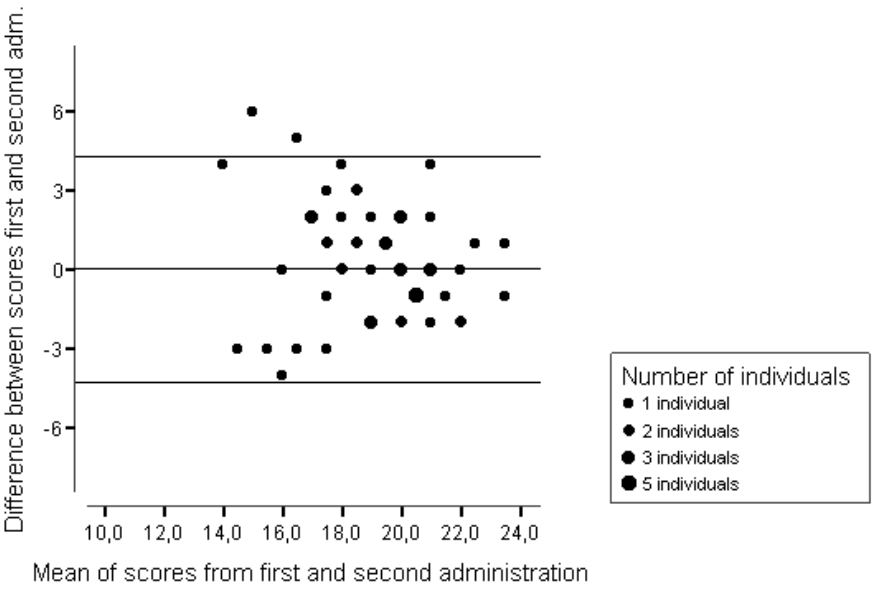

Figure 4. Reading the Mind in the Eyes: agreement between two test administration times, total score 24, n = 58 shown in a Bland – Altman plot

4.2 ASD and SP, studies II and III

4.2.1 SCID I and SCID II

The clinical diagnoses were re-evaluated with the SCID. Of the 46 participants with SP, 12 men and 7 women met criteria for schizophrenia paranoid subtype, including one woman and one man who had had episodes of substance induced psychosis in addition to schizophrenia. One woman and five men met criteria for schizophrenia undifferentiated subtype. Two men and six women met criteria for schizoaffective disorder. Three men met criteria for schizophreniform disorder. Five individuals (three men, two women) met criteria for psychotic disorder not otherwise specified, and in two of these the psychosis was deemed to be substance induced. One man had substance induced psychosis "only". Two men did not meet criteria for a psychosis in the schizophrenia spectrum according to the SCID, but met

criteria for Bipolar disorder type I instead. For two participants (one man, one woman) psychoses could not be confirmed by SCID.

For clarity and completeness, some results published in a thesis by Tove Lugnegård (2012) will be presented here. They are not, strictly speaking, results of the present thesis, but will, hopefully, allow the reader to have a fuller picture of the complexity of the clinical findings.

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 (SAD), 12 (22%) had generalized anxiety disorder (GAD), seven (13%) had panic disorder, eight (15%) had agoraphobia and four participants (7%) had obsessive-compulsive disorder (OCD). Two individuals met criteria for psychosis (one brief psychotic episode, and one psychotic syndrome 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) (Lugnegård, Hallerbäck & Gillberg 2011).

The prevalence of personality disorder (PD) according to DSM-IV-TR in the AS-group was examined with the SCID-II. Twenty-eight of the 54 participants (52 %) did not meet criteria for any PD. Twenty-one participants (7 women and 14 men) met criteria for one PD and 5 participants (3 men and 2 women) met criteria for at least two PD. Fourteen participants (5 women and 9 men) met criteria for schizoid personality disorder. Seven participants (3 women and 4 men) met criteria for avoidant personality disorder. Ten participants (3 women and 7 men) met criteria for obsessive-compulsive personality disorder. One participant (a woman) met criteria for schizotypal personality disorder. No participant met criteria for paranoid, antisocial, histrionic, borderline, narcissistic or dependent personality disorder (Lugnegård, Hallerbäck & Gillberg in press).

4.2.2 DISCO-ASD-algorithm diagnoses

The DISCO-11 interviews with parents of the 32 individuals with schizophrenia were analyzed according to the diagnostic algorithm of DISCO-11. Thirteen individuals met criteria for one or more ASD diagnoses. Focusing only on those for whom a schizophrenic psychosis (schizophrenia paranoid or undifferentiated subtype, schizoaffective disorder or schizophreniform disorder) was confirmed by SCID and for whom a DISCO-interview was obtained, 12 out of 23 (52%) met criteria for an ASD diagnosis according to the DISCO algorithm. The rate of any ASD was particularly high (60%) in the group with a SCID-diagnosis of paranoid schizophrenia.

The distribution of the different ASD diagnoses was explored. There was a marked overlap between the diagnoses. Nine participants met criteria for more than one ASD diagnosis. One individual had classic autism (F 84.0, ICD 10). Two other individuals also met symptom criteria for classic autism, but parents were not sure about symptoms before age 3 years, hence the diagnosis "Autism with atypical age of onset" (F 84.10, ICD 10) was applied. Six individuals met criteria for "Autism with atypical age of onset and atypical symptomatology" (F 84. 12, ICD 10), since, although there had been symptoms of autism during childhood, no clear symptoms before age 3 years were reported, and the autism criteria for communication were not quite met.

The Gillberg criteria for Asperger syndrome are the only criteria for this disorder that are based on Hans Asperger's case studies (Gillberg & Gillberg 1989; Gillberg 1991). Five individuals (all male) met these criteria and thus conformed to the phenotype originally described by Hans Asperger.

Table 3. Distribution of SCID- DISCO algorithm diagnoses in 32 DISCO examined individuals

	DISCO diagnoses						
SCID Psychosis subtype n = parent interview (total)	No ASD	ASD any type	AS ICD 10	Autism ICD 10	Autism with atypical age of onset	Autism with atypical age of onset and symp.	AS Gillberg criteria
Schizophrenia, paranoid subtype n = 10 (19)	4	6	M1 M2 M3 F1 F2 F3		M1 F3	M3 F1	M2
Schizophrenia undifferentiated subtype n = 6 (6)	3	3				M4 F4	M5
Schizoaffective disorder n = 5 (8)	3	2	F5	M6		F5	M6
Schizophreniform disorder NOS n = 2 (3)	1	1	M7			M7	M7
Psychotic disorder NOS n = 5 (5)	4	1	M8				M8
Bipolar disorder type I n = 2 (2)	2						
Substance induces psychosis only n = 0 (1)							
No psychosis n = 2 (2)	2						
Total	19	13	9	1	2	6	5

Short vignettes from the CAP reports together with results from the SCID and DISCO are presented in table 4 and 5. CAP reports were available from

7 women and 4 men, including three participants for whom parents did not participate in an interview.

Table 4. Clinical vignettes and results from SCID I and DISCO for 7 women with clinical schizophrenic psychosis diagnosis

	CAP report	Age at first psychosis (years)	SCID	DISCO
F1	Referred by school psychologist to the CAP at age 16 because of depression. Found personal relationships difficult, few friends, no close friends since age 11. Did not want to look people in the eyes, found it difficult to understand their behaviour. Preferred intellectual dialogues to social small talk. The depression was treated successfully with medication and supportive therapy. Contact ended after seven month.	23	Schizo-phrenia paranoid subtype	Autism with atypical age of onset and symptoma-tology.
F2	Contact with CAP at age 14 and 16. Psychiatric problems described were: Obsessions and compulsions, anxiety, self-injurious behaviour, sleep problems, school refusal and conflicts in the family. Described as being hyperactive during early childhood.	21	Schizo-phrenia paranoid subtype	Asperger syndrome ICD-10
F4	Referred for neurodevelopmental examination at age 12. Hyperactive with verbal and motor tics. Teacher described some difficulties in relation to classmates, did not know have to relate to them, controlling, made naïve comments. Diagnosed with Tourette syndrome and ADHD.	20	Schizo-phrenia undiffer-entiated subtype	Autism with atypical age of onset and symptoma-tology
F5	Mother contacted CAP on behalf of her 17 year-old daughter. The daughter had, after moving for studies to a nearby town, established relationships with delinquent teenagers. Few friends during childhood and was therefore pleased finally finding friends but were drawn to alcohol and drug use and was badly beaten in a dispute. Parents and the social services decided she should move back home. She was offered therapy but refused. The situation resolved and contact ended after two months.	22	Schizo-affective disorder	Autism with atypical age of onset and symptoma-tology

F6	Contact with CAP acute at age 15. Depressed, signs of psychosis. In-patient treatment for three years for schizophrenia. Described as always odd, difficulty making friends, school problems.	15	Schizo-affective disorder	Parents did not participate in an interview.
F7	Contact with CAP at age 17 because of self-injurious behaviour, anxiety and phobia. Difficulties in relation to classmates; had been bullied. School problems.	18	Schizo-affective disorder	Parents did not participate in an interview
F8	Referred to CAP at age 17. Compulsions and obsessed with her appearance, few friends, very demanding. Attended clinic only once. Refused further contact. Parents came three times.	25	Schizo-phrenia paranoid subtype	Parents did not participate in an interview

Table 5. Clinical vignettes and results from SCID I and DISCO for 47 men with clinical schizophrenic psychosis diagnosis

	CAP report	Age at first psychosis (years)	SCID	DISCO
M2	Contact with CAP at age 9 because of depression. Always avoided other children, anxious in new situation and with change. Preferred to stay at home, temper tantrums.	22	Schizo-phrenia paranoid subtype	Asperger syndrome ICD-10.
M5	Mother contacted CAP because her 16-year-old son was depressed. Was ambitious in school until the last year when he started to fail. Brooding about his appearance, avoided crowds. Alcohol and drug misuse.	20	Schizo-phrenia undiffer-entiated subtype	Asperger syndrome (Gillberg criteria).
M6	Referred acutely to CAP because of confusion at age 15. In-patient treatment several times due to psychosis. Delayed language development, later a correct somewhat pedantic speech. Major difficulties in relation to peers during childhood. Intelligent and had great knowledge in certain fields.	15	Schizo-affective disorder	Autism and Asperger syndrome (Gillberg criteria).
M9	Referred for a neuropdevelopmental examination at age 16. Other family members have Asperger syndrome and the patient was concerned about having the same diagnosis. The patient had some personality traits in the broader phenotype but did not meet criteria for diagnosis.	21	Bipolar I	No ASD

4.2.3 The similarities and differences of early childhood development in SP and AS

To further explore the similarities and differences in early childhood development across adult individuals with clinically diagnosed schizophrenia spectrum disorders and Asperger syndrome, the results from the schizophrenia spectrum group was compared to the results from the AS-group on the DISCO.

We divided the schizophrenia group into those with an ASD diagnosis according to the DISCO algorithm (SCH-ASD) and those for whom parents reported normal or less marked problems during childhood (SCH-TD). If this subdivision had not been done, the characteristics of the deviations suggesting an ASD diagnosis according to DISCO interview might have been overshadowed by the more typical early development in the SCH-TD-group. However, looking closely at the data we found that many individuals in this subgroup did have ASD-associated problems, even though full criteria for ASD were not met.

Core features of ASD such as symptoms of qualitative impairment of social interaction and communication as well as symptoms of restricted behaviour, interests, activities and imagination, present in half or more cases in any of the groups (SCH-TD, SCH-ASD or AS) are listed in Table 6. Developmental or behavioural abnormalities in other areas, present in half or more cases in any of the groups are listed in Table 7. Frequencies in the tables are sorted with descending values in the SCH-ASD columns.

Table 6. Core DICSO-11 features of ASD. Listed are those problems encorsed by more than half of all individuals in any of the subgroups (SCH-TD, SCH-ASD or AS)

DISCO symptoms	SCH-TD n = 19		SCH-ASD n=13		AS n=45	
	Per cent	marked/ minor problem	Per cent	marked/ minor problem	Per cent	marked/ minor problem
Qualitative impairment in social Interaction						
Quality of friendship	16 %	0/3	85 %	6/5	96 %	28/15
Quality of interaction	21 %	0/4	85 %	4/7	87 %	21/18
Sharing interests and enjoyment	11 %	0/2	77 %	4/6	58 %	13/13
Awareness of others' feelings	16 %	1/2	69 %	6/3	62 %	19/9
Bullying and teasing by age peers	42 %	2/6	62 %	7/1	73 %	28/5
Friendship with age peers	5 %	0/1	62 %	2/6	64 %	11/18
Interaction with age peers	5 %	0/1	38 %	2/3	67 %	15/15
One sided social approaches	16 %	0/3	38 %	4/1	62 %	20/8
Disturbed behaviour to visitors	5 %	0/1	31 %	0/4	51 %	3/20
Avoidance of age peers	5 %	1/0	23 %	2/1	58 %	18/8
Embarrassing remarks in public	0	0/0	8 %	1/0	51 %	19/4
Qualitative impairment in communication						
Facial expressions	11 %	2/0	62 %	7/1	58 %	25/1
Use of body language	5 %	1/0	54 %	7/0	67 %	27/3
Literal understanding	16 %	0/3	46 %	5/1	73 %	26/7
Long winded, pedantic speech	5 %	0/1	38 %	5/0	53 %	18/6
Restricted repetitive behaviour, interests and activities						
Collecting facts on specific Subjects	42 %	5/3	85 %	10/1	89 %	33/7
Talks intensely on a few themes	21 %	1/3	77 %	9/1	91 %	39/2
Repetitive activities related to special skills	11 %	1/1	62 %	8/0	71 %	26/6
Fascination with TV/DVD	21 %	4/0	46 %	5/1	76 %	29/5
Collecting objects	16 %	1/2	38 %	5/0	69 %	25/6
Same routines	11 %	1/1	38 %	5/0	62 %	24/4
Clinging to objects	16 %	1/2	38 %	5/0	60 %	27/0
Food fads	5 %	0/1	15 %	1/1	58 %	23/3
Maintenance of sameness of Environment	5 %	1/0	15 %	1/1	58 %	18/8
Restricted imagination						
Sharing imaginative activities*	5 %	0/1	62 %	3/5	64 %	14/15
Copying imaginative activities*	0 %	0/0	46 %	0/6	58 %	11/15
Repetitive pretend play**	0 %	0/0	23 %	1/2	53 %	14/10

* no imaginative play included under marked problems

**no imaginative play excluded

Table 7. Non-core ASD DISCO-11. Half or more in any of the subgroups (SCH-TD, SCH-ASD or AS) reported problems

DISCO symptoms	SCH-TD n = 19		SCH-ASD n=13		AS n=45	
	Per cent	marked/ minor problem	Per cent	marked/ minor problem	Per cent	marked/ minor problem
Motor co-ordination						
Poor co-ordination in PE	21 %	3/1	77 %	7/4	69 %	21/10
Clumsiness	16 %	1/2	54 %	6/1	51 %	20/3
Self-care – dressing						
Awareness of suitability of clothing	5 %	1/0	62 %	5/3	53 %	17/6
Slowness when dressing	11 %	2/0	23 %	2/1	69 %	27/4
Emotions						
Unhappiness, misery	5 %	1/0	38 %	5/0	53 %	12/12
Changeable mood	21 %	2/2	38 %	4/1	51 %	14/9
Special fears	11 %	2/0	31 %	3/1	53 %	15/9
Lack of emotional expressions	11 %	1/1	31 %	3/1	58 %	15/11
Other behaviours						
Anger towards parents	21 %	2/2	69 %	7/2	42 %	13/6
Willingness to help	5 %	1/0	54 %	4/3	64 %	18/11
Scatters things around	16 %	1/2	54 %	6/1	47 %	14/7
Lack of common sense	16 %	1/2	46 %	5/1	69 %	24/7
Temper tantrums	11 %	1/1	23 %	2/1	51 %	18/5

There were no marked differences between the SCH-ASD-group and the AS group according to the results on the DISCO. Two-thirds or more of both the AS and the SCH-ASD had reported early problems with "*Awareness of others feelings*" and "*Having a close friend*". Although some were described to have friends, the *"Quality of friendship"* was a problem for a large majority of those in the AS and SCH-ASD groups, such as just sharing the same interest or the person being totally passive. *"Quality of interaction with age peers"* was a problem (for example *passive, dominant, aggressive, one-sided as opposed to friendly and reciprocal)* for a large majority of both the AS and the SCH-ASD groups. The following descriptions of repetitive behaviour were frequently reported from both the AS and the SCH-ASD: "*Talks intensely on one or a few themes", "Collecting facts on specific subjects", "Fascination with TV/DVD"* and *"Repetitive activities related to special skills".*

The SCH-TD subgroup was defined as the group not meeting full DISCO-algorithm criteria for any ASD diagnosis. Nevertheless, some of them did have reported problems during childhood. Three men had ADHD clinically diagnosed by psychiatrists. Five individuals were described as having few friends, being reserved in contact with other children. Three others were described as dominant and too straightforward and honest in social situations. Generally, there was scarce information about characteristics of early symbolic play.

CAP contact

A large majority, 32 of the 45 (71%), in the AS-group interviewed had had contact with CAP during childhood or adolescence. The percentage was almost identical for the whole group of 55 individuals. Seven individuals (54%) in the SCH-ASD subgroup and one (5%) in the SCH-TD subgroup had had CAP contact ($p<.01$). Four of the 14 (29%) in the AS group who could not be assessed with the DISCO, were reported to have been in contact with CAP.

Age at AS diagnosis

The age when the diagnostic assessment for AS was done was examined in relation to the year of birth in order to examine change over time regarding age at diagnosis. All participants in the AS group had a clinical diagnosis of Asperger syndrome when included. However, some of them had been given another ASD diagnosis first, such as autism or autistic-like condition. The age at diagnosis of any ASD was used here, not the year when the specific diagnosis was revised to AS. There was a clear change over time with the diagnoses being given at earlier ages for the younger participants. For those 20 individuals who were born prior to 1980, only 3 individuals (15%) had been identified as children (under 19 years) to have difficulties within the autism spectrum. In contrast, 23 out of 35 (66%) who were born 1980 or later, had been given a diagnosis of ASD before age 19 years ($p<.05$).

4.3 ADHD in SP and AS

A total of 20 of the 95 patients in study IV had a clinical ADHD diagnosis made by psychiatrists. All the clinical ADHD diagnoses had been assigned either by a psychiatrist or by a psychiatric team (psychiatrist, psychologist and other professionals) at a centre for neurodevelopmental diagnostic assessments. Two men and two women in the SP group (4/41, 10%) had an ADHD diagnosis, and all of these had been given their ADHD diagnosis in adult age. Eight men and eight women in the AS group (16/54, 30%) had an

ADHD diagnosis. Three of these had been given a clinical diagnosis of ADHD when they were children, two of whom had had their ADHD diagnoses assigned prior to the AS diagnosis. Another 13 had been clinically diagnosed with ADHD when they were 20 years or older, after the diagnosis of AS had been made.

4.3.1 Rating scales and clinical ADHD diagnosis

The different rating scales for ADHD were examined in relation to clinical ADHD diagnoses.

WRAADDS

WRAADDS scores were available for 93 individuals (missing data from one man in the SP group and one man in the AS group), including all of the 20 individuals with clinical ADHD diagnoses. The WRAADDS total score differed significantly between the groups with and without clinical ADHD diagnoses, see table 8.There were significant differences on five of the seven symptom scales (attention deficits; hyperactivity; disorganization, inability to complete tasks; emotional over-reactivity, and impulsivity). There was no difference on any of the WRAADDS scales when comparing the SP group with the AS group.

Table 8. Results on the WRAADDS for those with and without clinical ADHD

	Clinical ADHD diagnosis n=20		No ADHD diagnosis n=73		Mann Whitney U-test
	mean	SD	mean	SD	
Total score	78.1	19.6	54.8	25.0	p<.001
Attention deficit	9.0	3.2	6.0	3.8	p=.002
Hyperactivity	13.1	4.5	7.2	4.5	p<.001
Disorganization	17.8	4.9	11.8	6.6	p<.001
Emotional overreactivity	8.4	3.2	6.7	3.4	p=.043
Impulsivity	12.3	5.5	8.0	5.3	p=.003
Affective lability	8.7	3.7	7.3	4.3	ns
Hot temper	8.9	4.4	7.7	4.0	ns

To further explore the effectiveness of the WRAADDS total score as a measure of ADHD symptoms/diagnosis, the sensitivity versus 1-specificity for WRAADDS total score and clinical ADHD diagnosis was plotted on a ROC curve (AUC= 0.77, p<.001) (Figure 5).

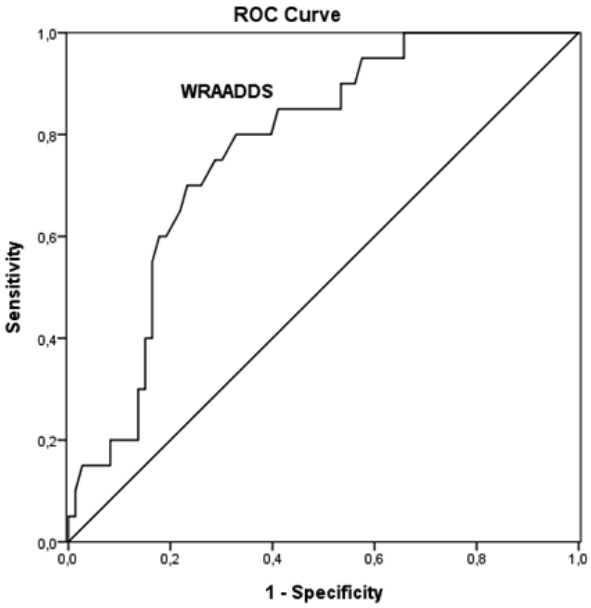

Figure 5. ROC curve for clinical ADHD diagnosis and WRAADDS total score (AUC=0.77, p< .001)

SNAP

SNAP scores were available for 63/95 (66%) of the individuals, including 15/20 (75%) with a clinical ADHD diagnosis. However, for two individuals in the AS group, parents only returned the SNAP adult version. Neither of these had clinical ADHD diagnosis.

The SNAP childhood total scores clearly separated the groups with and without clinical ADHD diagnoses (median 24.0 vs 10.0, mean 23.7 vs 12.8, SD 14.2 vs 12.1, p=.008 Mann-Whitney U). In contrast, the SNAP adult total scores did not differ significantly between those with and those without a clinical ADHD diagnosis (p=.08, Mann-Whitney U). Correspondingly, the AUC on the ROC curve was significant for the SNAP childhood (0.73, p=0.009) but fell just short of statistical significance for the SNAP adult (0.67, p=0.053) in relation to clinical ADHD diagnosis (Figure 6).

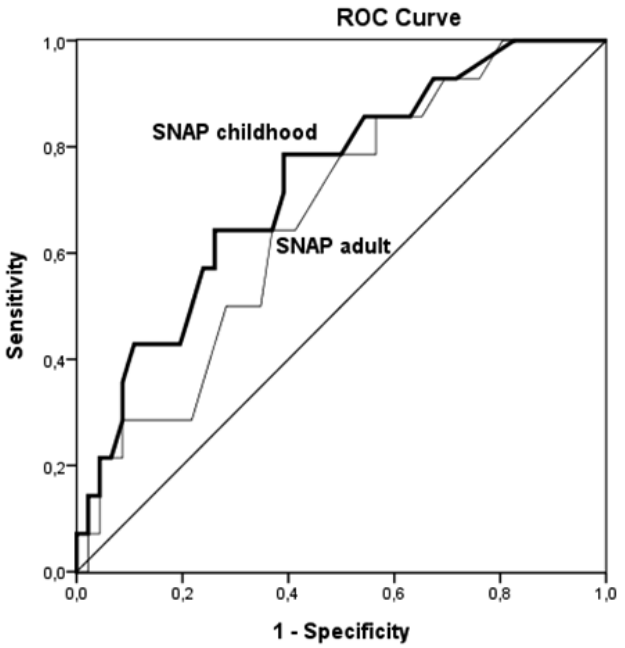

Figure 6. SNAP childhood (AUC=.73, p=.009), and SNAP adult (AUC=.67, n s)

Nicotine use

Current nicotine use was significantly more frequent in the collapsed patient group than in the general population (Table 9). Nicotine use was more common among those with a clinical ADHD diagnosis in both the AS and the SP group (Table 10).

Table 9. Nicotine use in the Swedish population and in the study group

	Population study 18–34 year-olds n= 7551	Study group AS and SP n=95	Fisher's exact test two-tailed sign.
Nicotine use, current	20.5%	44.2%	p<.0001
Cigarette use	9.9%	35.8%	p<.0001
Snuff use	11.4%	23.4%	p=.0017

Table 10. Nicotine and substance abuse in relation to clinical diagnoses (schizophrenic psychosis (SP) with or without ADHD and Asperger syndrome (AS) with or without ADHD)

	Clinical diagnoses			
	SP + ADHD	SP - ADHD	AS +ADHD	AS -ADHD
	4	37	16	28
Nicotine use, current	4 (100%)	22 (59%)	10 (62%)	7 (18%)
Substance abuse, ever	4 (100%)	9 (24%)	5 (31%)	1 (3%)
– alcohol	1 (25%)	5 (13%)	3 (19%)	1 (3%)
– cannabis		3 (8%)	2 (12%)	
– amphetamine	3 (75%)	4 (11%)	4 (25%)	
– other drugs			2 (12%)	

Substance abuse

There were 19 individuals who reported substance abuse (i.e. abuse of alcohol, cannabis, amphetamine or other drugs), but only one participant had a current substance abuse. Substance abuse was closely linked to nicotine dependency. With one exception (a man with Asperger syndrome and previous alcohol abuse) all participants with substance abuse had a current or previous nicotine dependency.

4.4 Gender effects

There was a small but significant sex difference on the Reading the Mind in the Eyes Test. Females scored higher than males, 19.2 SD 2.3 versus 18.5 SD 1.9. Since the scores were not perfectly normally distributed according to Kolmogorov-Smirnov test ($p<.001$), the nonparametric Mann-Whitney U-test was used. The asymptotic 2-tailed significance was $p= .01$.

The intention in the original study protocol had been to include 30 men and 30 women with schizophrenia in studies II, III and IV. Since schizophrenia is rare among young adult women, the typical age of onset being later than in men, we had great difficulties recruiting women. Finally 17 women with clinical diagnosis of SP participated in the study but parental information was only possible to obtain from 11 of them. Five of these 11 (45%) had some kind of ASD according to the DISCO-algorithm, yet none of them met Gillberg criteria for AS. - Twenty-nine men with SP participated, and parents of 21 of them (72% of the men in the study) were interviewed. Eight (38%) had some kind of ASD according to the interviews; five of these (5/8, 63%) met Gillberg criteria for AS.

There were 10 men and 10 women with clinical ADHD diagnosis, two men and two women in the SP group, and 8 men and 8 women in the AS group. Looking at the different questionnaires and how WRAADDS total score differed by gender, there were significant differences between those with and without clinical ADHD diagnoses for both men and women (men $p=.001$, women $p=.026$, Mann-Whitney U). However, the ROC curve analysis of WRAADDS was significant for men (AUC 0.90 $p=.001$), but not women, AUC (0.73, $p=.09$ ns).

The gender differences were more pronounced for SNAP childhood. The total scores differed significantly between individuals with or without clinical ADHD, for men (p=.004) but not for women, (p=.38). The ROC curve analysis was significant for men but not for women (men AUC 0.83, p=.006 and women AUC 0.63, p=.34).

Substance abuse was more common among men (15/51, 30%) than women (4/44, 9%, p<.05).

5 DISCUSSION

This study has shown that, although schizophrenia has been around as a diagnostic entity for 100 years, the definitions of the diagnosis and the boundaries vis-à-vis other diagnoses are still evolving. When parents of young adults with a clinical (and research) diagnosis of schizophrenic psychosis are interviewed about the childhood development of their son or daughter, clear developmental and behavioural difficulties that resemble (or that, in fact, *are*) ASD, are present in about half of the cases. – The study also showed that ADHD, another early symptomatic syndrome often eliciting neurodevelopmental assessment before adolescence, was present in a proportion of cases, even though "comorbid" ADHD was considerably more common in a group of adults with AS. Nicotine use was strongly associated with ADHD in the AS group, but occurred at high rates in the schizophrenia group regardless of whether or not ADHD was also present. – Finally, the study also demonstrated that the Reading the Mind in the Eyes teat, despite being widely used in research and clinical practice for tapping into problems associated with ASD, needs to be psychometrically examined in much more detail. The test-retest reliability was tested here for the first time ever, and the results raised questions about the reliability of the test.

There are several limitations that need to be discussed before any clear conclusions can be drawn regarding the applicability of the findings to clinical practice and their implications for further research. The strengths and limitations of each substudy will first be discussed, before more general aspects will be presented towards the end.

5.1 Validity and reliability of the Reading the Mind in the Eyes Test

The Reading the Mind in the Eyes Test is a widely used, freely and easily available test of facial affect recognition, which is easy to administer and easy to score. Most studies present their results of the Eyes Test simply as a score of "correctly" chosen items whereas the distribution of the three "non-correct" responses is not shown. This facilitates the statistical procedure and comparison between groups. When introducing such a restriction, one assumes that the test is valid and reliable. However, the validity of the test is difficult to examine as there is no gold standard against which to validate it. Hypothetically, facial affect recognition abilities are normally distributed in a healthy population. It is desirable that the test be sufficiently difficult so as

to allow discrimination between different levels of ability. Not every item should be "obvious" to everyone; some items need to be difficult and correctly identified by only the most "skilled" in facial affect recognition. Other items should be easier and correctly recognized by the majority. In contrast, it is not desirable that an item be of low quality (dark photograph, misleading target word etc.), which will lead to random answers.

In the study included in this thesis, the distribution of responses indicated that it is not always clear that one response is more "correct" than another. Four items showed particular ambiguity according to the disparity of chosen responses. It is unclear if this is due to the target word, the foil words, the quality of the photographs or if the items are truly difficult. Probably, this question of validity of items is not unique to our study, but is a problem in all different versions of the test.

This is the first study ever published on test-retest reliability of Reading the Mind in the Eyes Test. The data showed such reliability to be only fair (and not good or excellent). However, when the test is used, either in research or clinical practice, one has to take into account that an obtained test score must be regarded as an approximation. A test score variation in the range of ±4 (out of 24 possible) is to be expected for the same individual. In the literature, a specific cut-off level for "suspected autism" is often suggested. Our test-retest data suggest that, given the very substantial variation over a brief period of time in terms of how "normal" young people respond (in some cases in the "autism range" at Time 1 but well below cut-off at Time 2 or vice versa), the test cannot be used as a categorical "diagnostic aid".

In spite of the present study being one of the largest ever published on adults completing the Reading the Mind in the Eyes Test, numbers were still too small to provide a baseline for the general population of young adults. Only university students were included which is another limitation. Neither our group, nor any other, has clearly shown whether or not the test score obtained depends strongly on the individual's general intelligence. Further research needs to take both verbal and performance IQ into account.

In spite of these problems with the test, we did use, as planned, this psychometrically tested Swedish version of the Reading the Mind in the Eyes Test in the schizophrenia group, the Asperger group and in non-clinical comparison cases. Patients with schizophrenia showed poorer results compared to non-clinical controls, however no other group differences were seen (Lugnegård, submitted). This, in my view, adds to the need for caution

when assuming that "poor" results on the Eyes Test are usually indicative of ASD.

5.2 Schizophrenia and ASD

The major finding of this substudy was that about half of the cases with a clinical and research diagnosis of a schizophrenic psychosis had ASD according to results obtained at parental DISCO-interview. This is a strikingly high proportion, and one clearly at odds with the widespread clinical notion that there is little or no overlap between autism and schizophrenia. The findings underscore the need to revisit the DSM "either-or" stance in relation to ASD and schizophrenia.

The studies by Israel Kolvin (1971) forty years ago are still often quoted as one of the major bases for upholding the strict dichotomy between autism and schizophrenia. These studies were very important in the history of the recognition of autism as a separate neurodevelopmental disorder, at a time when schizophrenia and psychosis were poorly defined and associated with a wide range of theories. However, the concept of autism has changed in a major way since then. The cases with autism ("IP" or "infantile psychosis") that Kolvin studied were a group of children with severe disabilities. A vast majority of these had intellectial disability/mental retardation, and many did not speak at all. It is interesting to speculate about the children with "LOP" or "late onset psychosis" in Kolvin´s studies. How would child and adolescent psychiatrists of today classify this condition? Considering the low frequency of COS, it is unlikely that they would be classified as having schizophrenia.

Bryan King and Catherine Lord, both members of the DSM5 Neurodevelopmental disorders work group, recently published a review titled "Is schizophrenia on the autism spectrum?" (2010). They emphasise that the broader phenotype of the disorders clearly intersect. There are Theory of Mind deficits in both disorders and there is genetic overlap between autism and schizophrenia. Their speculations are in line with our findings. Rather than two distinct entities, the two diagnostic spectra could be illustrated as in Figure 7.

Several case reports have been published of patients with a diagnosis of schizophrenia re-evaluated as having ASD. The results of these studies suggest that these disorders overlap also from the symptomatological point of view (Roy & Balaratnasingam 2010; van Niekerk, Groen, Visser et al.

2010; Woodbury-Smith, Boyd & Szatmari 2010). The patients in our study were recruited on the basis of the clinical diagnosis and the diagnoses were in most cases confirmed by a SCID interview. Hence, our results indicate that a considerable proportion of those with a clear (clinical and research) diagnosis of schizophrenia have apparent signs of ASD when an in-depth parent interview is performed.

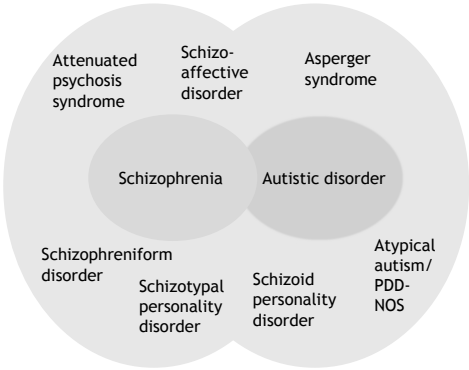

Figure 7. Diagnostic overlap between schizophrenia spectrum and autism spectrum

According to the DSM-IV-TR (American Psychiatric Association, 2000), the diagnoses Asperger's disorder, atypical autism and pervasive developmental disorder not otherwise specified are by definition not given if criteria for schizophrenia are met. However, schizophrenia may co-exist with Asperger's disorder if the onset of Asperger's disorder clearly preceded the onset of schizophrenia. This is straightforward if the Asperger's disorder diagnosis has been assessed during childhood, but causes a dilemma for clinicians who meet young adults with clear schizophrenia and with a history of difficulties corresponding with Asperger's disorder (Nylander, Lugnegård & Hallerbäck 2008). Our findings about age at diagnosis show that diagnostic assessments of children have changed over time. For individuals with ASD and IQ within the normal range born prior to 1980 it is unlikely that their difficulties would have been identified as ASD (or "Asperger´s disorder") during childhood although the individual may well have suffered.

According to the SCID-II 14 individuals (26%) in the AS group met criteria for schizoid personality disorder (Lugnegård, Hallerbäck & Gillberg in press). In the AS group one man had psychotic syndrome UNS, and one woman had had a brief psychotic episode, according to the SCID-I. Another 7 individuals with AS (13%) had recurrent auditory hallucinations, but none of these met full criteria for a psychotic disorder. 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 (Lugnegard, Hallerbäck & Gillberg 2011).

Even though, as outlined, about two in five of all the young adults with AS in the present study had either a "broad schizophrenia spectrum disorder" (schizoid personality disorder) or had had hallucinations, not one individual met criteria for schizophrenia (Lugnegard, Hallerbäck & Gillberg 2011). This is in stark contrast with the high rate of ASD found in the SCH group. No obvious explanation for this discrepancy comes to mind. There was as relatively high proportion of non-responders among the individuals with AS eligible and invited for participation in the study. Other studies have shown a wide variation in the co-occurrence rate between autism and schizophrenia (Skokauskas & Gallagher 2010). On the basis of the results obtained here it is impossible to decide either way, but it might be reasonable to speculate that, at least in some cases, the early diagnosis of AS in a proportion of cases, followed, at least hypothetically, by an "autism-friendly" environment in these cases (Billstedt, Gillberg & Gillberg 2011), could have prevented the "psychotic breakdown" that might otherwise have occurred if the condition had remained undiagnosed and misunderstood for another several years.

Another explanation for the discrepancy could be that individuals with atypical autism, and particularly MCDD, have not been clinically recognised to the same degree as those with a more typical clinical picture. Using the method of the present study, it was, unfortunately, not possible to differentiate MCDD from atypical autism. Retrospective parental interview is not a reliable method to examine childhood presence of thought disorder (one of the criteria for MCDD). The MCDD diagnosis is not included in the DISCO diagnostic algorithm. Individuals with MCDD would probably be "DISCO-classified" as having atypical autism (autism with atypical age of onset or autism with atypical age of onset and atypical symptomatology) by the DISCO.

The diagnostic criteria for schizoid personality disorder resemble those for Asperger's syndrome. The diagnostic criteria for schizotypal personality disorder, on the other hand, resemble MCDD.

The description, by Kraepelin, of the premorbid personality as someone who finds conversation with strangers, entering a new environment and unusual demands, to be tremendously difficult, resembles the description of an individual with ASD. While the diagnosis of a "schizophrenia-prone" premorbid personality or ARMS would signal the possibility that something terrible might come about over time, an early ASD diagnosis may actually be both helpful and comforting. For many, it is an explanation why they have always felt different from other people. The diagnosis helps them to realise that they are not alone (Wing 2005).

5.2.1 ADHD in schizophrenia and ASD

The rate of clinically diagnosed ADHD in SP was relatively low (two men and two women), even though probably considerably higher than in "non SP" populations. This is, perhaps, a somewhat surprising finding, considering the very high rates of antecedent neurodevelopmental problems (including high rates of ADHD) reported in studies of schizophrenia and other psychosis with onset in the teenage period (Gillberg, Wahlström, Forsman et al 1986). Both of the women in the SP group with ADHD also had a DISCO-diagnosis of ASD. None of the men with ADHD in the SP group met ASD-criteria.

Clearly, ADHD is a very common clinical "comorbidity" in adults with AS. Thirty per cent of the AS group (and ten per cent of the SP group) in our study had been given a clinical diagnosis of ADHD even before they were examined in the present context. As compared with general population figures of a few per cent of adults meeting ADHD diagnostic criteria, this would suggest about a ten-fold increased risk in AS. Only three individuals (all in the AS group) in the study (3% of the whole sample) had been given a diagnosis of ADHD during childhood; the vast majority of the clinical ADHD diagnoses (85%) had been assigned/diagnosed after age 18 years. There are at least two explanations for this finding. One is that the health services for assessing ADHD in children in the county of Värmland was limited before the mid-1990s. Accessibility for both children and adults with ADHD symptoms (and other neurodevelopmental problems) has increased markedly during the latest 10-15 years, starting from a very low level in the mid-1990s. Consequently, only a fraction of individuals with ADHD born in 1972-1987 (birth year range of our study group) would have been clinically

identified as having a diagnosis of ADHD in childhood. The other explanation for the very low rate of childhood diagnosis of ADHD in AS is that it was common clinical practice throughout the 1980s and the 1990s, as suggested/required by the most commonly used diagnostic manuals in the field (the DSM and ICD), not to diagnose ADHD at all in individuals with AS. In the very recent past it has become more common to identify both diagnoses when they co-occur, and to treat both problem types accordingly.

5.2.2 ADHD rating scales

For a long time, ADHD was considered to be a condition that only affected children. The DSM-IV diagnostic criteria are, accordingly, based on studies of children. The scales most frequently used for adults as well as children are based on these DSM-IV criteria. Although words such as "playing", "classroom" and "homework" have been removed, many of the symptom descriptions appear to be inappropriate for adults. In our study, the parent ratings of *current* DSM-IV ADHD criteria using the SNAP in adulthood appeared to be of little value, at least when screening for ADHD in patients with AS or SP. Parents' *retrospective* rating of symptoms during childhood was much more useful in this context.

In contrast, the patients' self-rating of ADHD symptoms as described on the WRAADDS was clearly connected to clinical ADHD diagnosis. This is noteworthy, bearing in mind that the participants in this study, having other psychiatric problems, might be presumed to have decreased ability to carry out self-rating.

5.2.3 Nicotine dependency, substance abuse and their relation to SP, AS and ADHD

Nicotine use was markedly overrepresented among individuals with SP with and without ADHD as compared to the general population in our study.

In the AS group the rate of nicotine use was also higher than in the general population, but only in the subgroup with "comorbid" ADHD. Despite smoking being a major risk factor for cardiovascular disease, lung cancer and other disorders causing premature mortality it is often overlooked in the psychiatric care and psychiatric treatment programmes (Berrettini 2004).

The findings suggest that all individuals with SP or AS (and particularly those with comorbid ADHD) should be informed about the dangers and possible helpful interventions of all kinds of substance use, particularly perhaps, those related to nicotine dependency.

5.2.4 Gender

There was a marked gender difference in the clinical presentation of ASD in the schizophrenia group. While 5 of the 8 men in the schizophrenia group, who met criteria for ASD according to the DISCO, had a clinical presentation during childhood in accordance with Hans Asperger's original description (and fulfilled the Gillberg criteria for AS), not even one of the 5 women, with ASD according to the DISCO, matched this description. This is of great importance since it indicates that the clinical presentation of ASD in women (with normal intellectual ability) is different from the clinical presentation of ASD in men. Hans Asperger only described boys in his original work so it is not unexpected that the description is more suitable for men. However, this means that clinicians need to be very cautious and thorough when looking for ASD in women. The clinical presentation is likely to be different from what we have learned to recognise as Asperger syndrome.

All the ADHD rating scales applied in our study appeared to be more valid for ADHD in men than in women. In men, the WRAADDS total score had good diagnostic performance vis-à-vis a clinical ADHD diagnosis, but the results were not significant for women. Nevertheless there was a significant difference in WRAADDS total score between women with a clinical diagnosis of ADHD and those without. The parent childhood SNAP total score rating corresponded relatively well with a clinical ADHD diagnosis in men, but not in women.

5.2.5 Limitations

The study groups were relatively small. Our original aim was to include 30 men and 30 women, with schizophrenic psychosis and 30 men and 30 women with AS. In the end, only 46 individuals with schizophrenic psychosis participated, and two of these actually did not have psychosis according to SCID interview. Also, it was more complicated than initially envisaged to get permission from both patient and parent to do the DISCO interview. This was particularly problematic in the group with paranoid schizophrenia given that among the 10 individuals who had DISCO-11 results, the rate of diagnosed ASD was much the highest in the whole study. This makes it important to interpret the finding in this respect with some caution.

Using retrospective parental interview for tapping into developmental and behavioural problems in the offspring is a method with advantages and disadvantages. Parents often know their children well and may better than

anyone describe their strengths and weaknesses, but recall bias needs to be considered.

With hindsight, it is clear that it was an oversight not to include any specific diagnostic instruments for ADHD. I had to rely on clinician´s "historical" diagnosis of this disorder. However, it was my clinical impression that these diagnoses had been made with care and a general degree of conservativeness, and that, if anything, "the real rate of ADHD" in both the SP and ASD groups was higher than reported here.

6 CONCLUSIONS

This study represents an attempt to introduce the modern concept of ASD into the research field of schizophrenia. The findings indicated that there is a clear overlap between the conditions. The co-existence of ASD and schizophrenia is clearly much more common than previously believed. This means that increased awareness of psychotic symptoms in AS and other ASD is needed. Conversely, taking a careful neurodevelopmental history and making a thorough "ESSENCE-style" diagnostic assessment will be important whenever a diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder is considered.

The Reading the Mind in the Eyes Test is widely used but essential psychometric properties of the test is lacking. This study is the first, and at present, the only, published article about the test-retest reliability. The variation in scores for one individual repeating the test is not insignificant. This illustrates that one single result on the test must be interpreted with great caution and can never be used as an indicator for or against any particular diagnosis.

ADHD is not uncommon among patients with schizophrenia or AS. The WRAADDS, a self-rating scale for ADHD, can be very useful in the diagnostic assessment, although it cannot be seen as a diagnostic tool if used in isolation.

7 IMPLICATIONS FOR CLINICAL PRACTICE AND RESEARCH

During the 20th century, psychiatry was influenced by intense discussions and disputes between biological and psychodynamic concepts. Both the fields of autism and schizophrenia have been very much affected by this. Instead of research to improve our understanding of the complex interaction between biology and psychology, many researchers (and clinicians) ended up as representatives of one of these two diametrically opposed viewpoints.

Today the situation is different. The biological aspects of both autism and schizophrenia are well recognised even though there is still no complete understanding of the biological background. Likewise, there is agreement that traumatic experiences and/or deprivation during childhood may lead to severe psychiatric complications and in some case, directly affect the brain. Interactions, communication and different circumstances within the family, have clear impact on the growing child, but in contrast to what was believed in the 1950s-70s, these factors do not cause either ASD or schizophrenia.

For children with ASD the support and understanding that they get from their family, school and peers are essential for their development. Still, some of the features of ASD are associated with an increased risk of encountering quite the opposite. Children who do not easily interact with peers, who have an extremely strong conviction of what they want and do not want to do, who get temper tantrums when teachers or other people have demands on them, are at risk of meeting hostility, resentment and misunderstandings. This will not improve their ability to interact and function together with others. I believe that in the past, many people with ASD were placed in mental hospitals because of their difficult and different behaviours. They were probably given different diagnoses, including dementia praecox and schizophrenia. Many case descriptions by both Bleuler and Kraepelin support this notion.

With more knowledge in society, among parents, siblings, teachers, peers, and neighbours as well as social services and psychiatry, future generations of people with ASD will hopefully be better understood. With adequate support, many children with ASD can learn to manage life quite well. However, one should be aware that, even with the best support in early life, many will need lifelong support. Others will need support from time to time,

when life is too challenging. To create social services and healthcare based on these insights is an essential task for society.

This study showed that ASD and schizophrenia co-exists more often than presumed. The biological and/or psychological reasons for this remain to be explained. At present, the knowledge about schizophrenia among experts in autism is often scarce. Likewise, there is limited knowledge about the modern concept of ASD among many experts in schizophrenia. More collaborative work between professionals (clinicians as well as researchers) in the two fields will be necessary. The whole ESSENCE "catalogue" of symptoms and developmental problems needs to be covered in research about the diagnosis and background factors both in the field of schizophrenia research and in systematic studies of ASD.

Programmes of early intervention in psychoses need to include thorough neurodevelopmental "ESSENCE-style" assessments in the diagnostic process. It would probably be very distressing for adolescents with ASD, not previously diagnosed, to be classified as having "attenuated psychosis syndrome", and getting treatment focused solely on psychosis intervention. Conversely, it would probably be distressing for individuals with ASD and a risk of developing psychosis if they were not getting proper interventions aiming at inhibiting progression, because of unawareness among professionals of the risk of psychosis in ASD.

In order to provide better treatment for those many individuals who do have both schizophrenia and ASD new psycho-educative methods need to be developed. Much more research concerning the prevalence and meaning of the common co-existence of the two "disorders" is needed.

ACKNOWLEDGEMENTS

There are many friends and professionals, who in different ways have supported me throughout this process and to whom I am very grateful. Some of them will be acknowledged here.

First I wish to express my deepest gratitude to my supervisor **Christopher Gillberg,** for inspiring and brilliant guidance. It has been a true privilege to have had the opportunity to work with you. When Tove and I first approached you, with our questions about the relationship between schizophrenia and autism spectrum disorders, we were both novices in the field of research. You were positive to our ideas and helped us to systematize and set up our study, you encouraged us throughout periods of disappointment and frustration. Your outstanding clinical and scientific knowledge, along with your reassuring support for us have been invaluable.

Tove Lugnegård, my co-author, colleague and above all, dear friend, I have sincerely appreciated working with you. It has been ten years with discussions and hard work, but moreover, many unforgettable moments and laughter.

Fredrik Hjärthag, co-author and friend, for interesting discussions and valuable collaboration.

Kjerstin Almqvist, professor at Karlstad University and head of the Research Unit at the Psychiatry Division at the County Council of Värmland, for important support at the start of the project and encouraging support throughout the years.

Magnus Segerström and **Iréne Westlund** for doing the neuropsychological assessment with contributions from **Per-Nicklas Olofsson, Inga-Lill Sverkström** and **Anna Göransson.**

Maria Persson, for transcriptions and entering data promptly.

Many fellow researchers at the Gillberg Neuropsychiatry Centre have contributed by means of advice and discussions, **Gudrun Nygren, Lena Nylander, Elisabet Wentz** and **Eva Billstedt**, to mention but a few.

Fredrik Lundin, statistician at the Research Unit at County Council of Värmland, for giving advice on suitable methods and for explaining statistics in a very comprehensible way.

The staff at the Medical Library, Central Hospital, Karlstad for help with litterature search and assistance with reference management.

The staff at the Department of Adult Habilitation, at the Psychiatric Outpatient Clinic in Värmland as well as the staff at the NåUt team in Gothenburg, for helping recruit study participants.

I am truly grateful to all study participants and their parent who gave us their time and effort. Without you this would not have been possible. Apart from the results presented in this study, you have given me invaluable insights in the life circumstances of young adults with SP and AS, and of their families.

Friends and co-workers at the Child and Adolescent Psychiatry Clinic in Värmland, for encouraging me in different ways.

My brother and sister, **Jonas** and **Karin Unenge** with families, for your support and optimism.

My sister-in-law **Margareta Hellgren** with family, for your enthusiasm and interest in my project.

My beloved children, **Sofia** and **Rickard** for your positive support and concern. I am grateful and proud to be your mother.

And finally and foremost, **Per-Olof,** my love and closest friend, thank you for being there.

Financial support for this research was provided by grants for doctoral studies from the Centre for Clinical Research and the Psychiatry Division at the County Council of Värmland, the Wilhelm and Martina Lundgrens Vetenskapsfond, the Gillberg Neuropsychiatry Centre, and from grants to Christopher Gillberg from the Swedish Science Council.

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APPENDIX

7.1 Reading the Mind in the eyes

7.1.1 Example

Övningsexempel

svartsjuk rädd

avspänd hatar

7.1.2 Protocol

Kod nr_____

Övn	svartsjuk	rädd	avspänd	hatar
1	hatar	förvånad	vänlig	arg
2	ovänlig	arg	förvånad	ledsen
3	vänlig	ledsen	förvånad	orolig
4	avspänd	bekymrad	förvånad	upphetsad
5	ursäktande	få någon att göra något	skämtsam	avspänd
6	hatar	ovänlig	bekymrad	uttråkad
7	ursäktande	uttråkad	intresserad	skämtsam
8	minns	lycklig	vänlig	arg
9	förargad	hatar	förvånad	tänker på något
10	vänlig	blyg	skeptisk	ledsen
11	översittaraktig	hoppfull	arg	äcklad
12	förvirrad	skämtsam	ledsen	allvarlig
13	tänker på något	upprörd	upphetsad	lycklig
14	lycklig	tänker på något	upphetsad	vänlig
15	tveksam	vänlig	lekfull	avspänd
16	beslutsam	skämtsam	förvånad	uttråkad
17	arg	vänlig	ovänlig	fundersam
18	tänker på något ledsamt	arg	översittaraktig	vänlig
19	arg	dagdrömmande	ledsen	intresserad
20	vänlig	förvånad	missnöjd	upphetsad
21	intresserad	skämtsam	avspänd	lycklig
22	lekfull	vänlig	förvånad	tänker på något
23	förvånad	säker på något	skämtsam	lycklig
24	allvarlig	skamsen	förvirrad	förvånad
25	blyg	skyldig	dagdrömmande	bekymrad
26	skämtsam	avspänd	nervös	ledsen
27	skamsen	upphetsad	misstänksam	belåten
28	äcklad	hatar	nöjd	uttråkad

Hallerbäck/Lugnegård feb 2005

7.2.1 SNAP childhood in Swedish

The SNAP-IV Teacher and Parent Rating Scale
James M. Swanson, Ph.D., University of California, Irvine, CA 92715

Kodnummer:_____

Beskriv hur det var när er son/dotter gick i grundskolan

Ringa in den siffra som bäst beskriver barnets beteende:

	Inte alls	Bara lite	En hel del	Väldigt mycket
1. Var ofta ouppmärksam på detaljer eller gjorde slarvfel i skolarbetet eller andra aktiviteter……....	0	1	2	3
2. Hade ofta svårt att hålla kvar uppmärksamheten på uppgifter eller lekar……	0	1	2	3
3. Verkade ofta inte lyssna på direkt tilltal……	0	1	2	3
4. Följde ofta inte givna instruktioner och misslyckades med att genomföra skolarbete eller arbetsuppgifter…….....	0	1	2	3
5. Hade ofta svårt att organisera uppgifter och aktiviteter…….	0	1	2	3
6. Undvek ofta, ogillade eller var ovillig att utföra uppgifter som kräver mental uthållighet (t ex skolarbete eller läxor)..	0	1	2	3
7. Tappade ofta bort saker som är nödvändiga för olika aktiviteter (t ex leksaker, läxmaterial, pennor eller böcker).	0	1	2	3
8. Var ofta lättdistraherad av yttre stimuli……..	0	1	2	3
9. Var ofta glömsk i det dagliga livet……..…	0	1	2	3
11. Hade ofta svårt att vara stilla med händer och fötter eller kunde inte sitta still……	0	1	2	3
12. Lämnade ofta sin plats i klassrummet eller i andra situationer där man förväntades sitta kvar……..0	0	1	2	3
13. Sprang ofta omkring eller klättrade mer än vad som är lämpligt för situationen……0	0	1	2	3
14. Hade ofta svårt att leka eller utöva fritidsaktiviteter lugnt och stilla……..	0	1	2	3
15. Verkade ofta vara på språng eller på högvarv……0	0	1	2	3
16. Pratade ofta överdrivet mycket……	0	1	2	3
17. Kastade ofta ur sig svaret innan frågan är färdigställd……0	0	1	2	3
18. Hade ofta svårt att vänta på sin tur……	0	1	2	3
19. Avbröt eller störde ofta andra (tex kastade sig in i andras samtal eller lekar)…….....	0	1	2	3

Var god vänd!!

21. Tappade ofta besinningen……. 0 1 2 3

22. Argumenterade ofta mot vuxna……..….. 0 1 2 3

23. Trotsade ofta aktivt eller vägrade underordna sig vuxnas krav eller regler…….. 0 1 2 3

24. Förargade ofta andra med avsikt…….…… 0 1 2 3

25. Skyllde ofta på andra för egna misstag eller dåligt uppförande.0 1 2 3

26. Var ofta lättretad och stingslig……..… 0 1 2 3

27. Var ofta arg och förbittrad…….…… 0 1 2 3

28. Var ofta hämndlysten eller elak……..…0 1 2 3

29. Grälade ofta……...… 0 1 2 3

30. Var ofta negativ, trotsig, olydig, eller fientlig mot vuxna…… 0 1 2 3

10. Hade ofta svårt att hålla sig alert och följa uppmaningar och anvisningar…… 0 1 2 3

20. Hade ofta svårt att vara still, vara tyst, eller hålla tillbaka impulser i klassrummet eller hemma…… 0 1 2 3

7.2.2. SNAP adulthood in Swedish

The SNAP-IV Teacher and Parent Rating Scale
James M. Swanson, Ph.D., University of California, Irvine, CA 92715

Kodnummer:_____

Ringa in den siffra som bäst beskriver er sons/dotters beteende idag:

	Inte alls	Bara lite	En hel del	Väldigt mycket
1. Är ofta ouppmärksam på detaljer eller gör slarvfel	0	1	2	3
2. Har ofta svårt att hålla kvar uppmärksamheten på uppgifter…….....……	0	1	2	3
3. Verkar ofta inte lyssna på direkt tilltal……..	0	1	2	3
4. Följer ofta inte givna instruktioner och misslyckas med att genomföra arbetsuppgifter…….…….....	0	1	2	3
5. Har ofta svårt att organisera uppgifter och aktiviteter……	0	1	2	3
6. Undviker ofta, ogillar eller är ovillig att utföra uppgifter som kräver mental uthållighet…….....	0	1	2	3
7. Tappar ofta bort saker som är nödvändiga för olika aktiviteter ……	0	1	2	3
8. Är ofta lättdistraherad av yttre stimuli……	0	1	2	3
9. Är ofta glömsk i det dagliga livet……	0	1	2	3
11. Har ofta svårt att vara stilla med händer och fötter eller kan inte sitta still……..	0	1	2	3
12. Lämnar ofta sin plats i situationer där man förväntas sitta kvar……..0	0	1	2	3
13. Springer ofta omkring eller rör sig mer än vad som är lämpligt för situationen……	0	1	2	3
14. Har ofta svårt att utöva fritidsaktiviteter lugnt och stilla……	0	1	2	3
15. Verkar ofta vara på språng eller på högvarv……	0	1	2	3
16. Pratar ofta överdrivet mycket……	0	1	2	3
17. Kastar ofta ur sig svaret innan frågan är färdigställd……	0	1	2	3
18. Har ofta svårt att vänta på sin tur……	0	1	2	3
19. Avbryter eller stör ofta andra (tex kastar sig in i andras samtal eller aktiviter)……..	0	1	2	3

Var god vänd!!

21. Tappar ofta besinningen..…… 0 1 2 3

22. Argumenterar överdrivet länge, ger sig inte…..…… 0 1 2 3

23. Trotsar ofta aktivt eller vägrar underordna sig krav eller regler…… 0 1 2 3

24. Förargar ofta andra med avsikt…… 0 1 2 3

25. Skyller ofta på andra för egna misstag eller dåligt uppförande..0 1 2 3

26. Är ofta lättretad och stingslig…… 0 1 2 3

27. Är ofta arg och förbittrad…… 0 1 2 3

28. Är ofta hämndlysten eller elak……0 1 2 3

29. Grälar ofta……0 1 2 3

30. Är ofta negativ, trotsig, olydig, eller fientlig mot vuxna…… 0 1 2 3

10. Har ofta svårt att hålla sig alert och följa uppmaningar och anvisningar…… 0 1 2 3

20. Har ofta svårt att vara still, vara tyst, eller hålla tillbaka impulser i arbetet eller hemma……..… 0 1 2 3

7.2.3 SNAP childhood in English

SNAP-IV Parent and Teacher Rating Scale

Code number:_____

Describe how your son/daughter was during Compulsory school
For each of item, circle the number which best describes the behaviour of the child

	Not at all	Just a little	Quite a bit	Very much
1. Often failed to give close attention to details or made careless mistakes in schoolwork or tasks	0	1	2	3
2. Often had difficulty sustaining attention in tasks or play activities	0	1	2	3
3. Often did not seem to listen when spoken to directly	0	1	2	3
4. Often did not follow through on instructions and failed to finish schoolwork, chores, or duties	0	1	2	3
5. Often had difficulty organizing tasks and activities	0	1	2	3
6. Often avoided, disliked, or was reluctant to engage in tasks that require sustained mental effort	0	1	2	3
7. Often lost things necessary for tasks or activities (e.g., toys, assignments, pencils, books)	0	1	2	3
8. Often distracted by extraneous stimuli	0	1	2	3
9. Often was forgetful in daily activities	0	1	2	3
10 Often had difficulty maintaining alertness, orienting to requests, or executing directions	0	1	2	3
12. Often left seat in classroom or in other situations in which remaining seated was expected	0	1	2	3

13. Often ran about or climbed excessively in situations in which it was inappropriate	0	1	2	3
14. Often had difficulty playing or engaging in leisure activities quietly	0	1	2	3
15. Often was "on the go" or often acted as if "driven by a motor"	0	1	2	3
16. Often talked excessively	0	1	2	3
17. Often blurted out answers before questions had been completed	0	1	2	3
18. Often had difficulty waiting turn	0	1	2	3
19. Often interrupted or intruded on others (e.g., butted into conversations/games)	0	1	2	3
21. Often lost temper	0	1	2	3
22. Often argued with adults	0	1	2	3
23. Often actively defied or refused adult requests or rules	0	1	2	3
24. Often deliberately did things that annoyed other people	0	1	2	3
25. Often blamed others for his or her mistakes or misbehaviour	0	1	2	3
26. Often was touchy or easily annoyed by others	0	1	2	3
27. Often was angry and resentful	0	1	2	3
28. Often was spiteful or vindictive	0	1	2	3
29. Often was quarrelsome	0	1	2	3
30. Often was negative, defiant, disobedient, or hostile toward authority figures	0	1	2	3
11. Often fidgeted with hands or feet or squirmed in seat	0	1	2	3
20. Often had difficulty sitting still, being quiet, or inhibiting impulses in the classroom or at home	0	1	2	3

7.2.4 SNAP adulthood in English

SNAP-IV Parent and Teacher Rating Scale

Code number _____

For each of item, circle the number which best describes the behaviour of your son/daughter today:

	Not at all	Just a little	Quite a bit	Very much
1. Often fails to give close attention to details or makes careless mistakes	0	1	2	3
2. Often has difficulty sustaining attention in tasks	0	1	2	3
3. Often does not seem to listen when spoken to directly	0	1	2	3
4. Often does not follow through on instructions and fails to finish chores, or duties	0	1	2	3
5. Often has difficulty organizing tasks and activities	0	1	2	3
6. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort	0	1	2	3
7. Often loses things necessary for tasks or activities	0	1	2	3
8. Often is distracted by extraneous stimuli	0	1	2	3
9. Often is forgetful in daily activities	0	1	2	3
11. Often fidgets with hands or feet or squirms in seat	0	1	2	3
12. Often leaves seat in classroom or in other situations in which remaining seated is expected	0	1	2	3
13. Often runs about or moves around in situations in which it is inappropriate	0	1	2	3

14. Often has difficulty engaging in leisure activities quietly	0	1	2	3
15. Often is "on the go" or often acts as if "driven by a motor"	0	1	2	3
16. Often talks excessively	0	1	2	3
17. Often blurts out answers before questions have been completed	0	1	2	3
18. Often has difficulty awaiting turn	0	1	2	3
19. Often interrupts or intrudes on others (e.g., butts into conversations/activities)	0	1	2	3
21. Often loses temper	0	1	2	3
22. Often argues excessively, do not resign	0	1	2	3
23. Often actively defies or refuses demands or rules	0	1	2	3
24. Often deliberately does things that annoy other people	0	1	2	3
25. Often blames others for his or her mistakes or misbehaviour	0	1	2	3
26. Often touchy or easily annoyed by others	0	1	2	3
27. Often is angry and resentful	0	1	2	3
28. Often is spiteful or vindictive	0	1	2	3
29. Often is quarrelsome	0	1	2	3
30. Often is negative, defiant, disobedient, or hostile toward authority figures	0	1	2	3
10 Often has difficulty maintaining alertness, orienting to requests, or executing directions	0	1	2	3
20. Often has difficulty sitting still, being quiet, or inhibiting impulses at work or at home	0	1	2	3

7.3 WRAADDS Self – rating version

The statements below relate to how you generally have been as adult. Mark how appropriate the different descriptions are for you. The numbers correspond to: 0 - Not at all; 1 - To some degree; 2 - Quite a bit; 3; - Very much; 4 - Absolutely

1	**Attention Difficulties**					
	I have difficulties keeping my attention on things, I am easily distracted	0	1	2	3	4
	Others complain that I do not listen, that I don't pay attention to them when they're talking?	0	1	2	3	4
	I have difficulties keeping my mind on reading	0	1	2	3	4
	I am forgetful; I frequently lose things like keys, purse, or wallet	0	1	2	3	4
2	**Hyperactivity/Restlessness**					
	I am fidgety (picking and pilling)	0	1	2	3	4
	I have difficulties sitting still, often restless and always on the go	0	1	2	3	4
	I talk too much, at least according to others	0	1	2	3	4
	I have difficulties relaxing	0	1	2	3	4
	I have difficulties to sit and watch a whole movie or TV show, and/or remaining seated at the table after a meal	0	1	2	3	4
3	**Affective Lability**					
	I often have periods of being sad, blue, or discouraged	0	1	2	3	4
	I have periods of being excessively active, getting too excited, going too fast	0	1	2	3	4
	My mood change frequently, going up and down	0	1	2	3	4
	I often have periods of being discouraged, self-critical or down on myself	0	1	2	3	4
4	**Temper**					
	I frequently feel touchy or irritable	0	1	2	3	4
	I have a "short fuse" and lose my temper easily	0	1	2	3	4
	When I get angry it is over quickly	0	1	2	3	4
	When I get angry I react verbally	0	1	2	3	4
	When I get angry I act it out on things	0	1	2	3	4
	When I get angry I act it out on animals or people	0	1	2	3	4

5	**Disorganization**					
	I have difficulties working in an organized manner when I have to do many things in a row	0	1	2	3	4
	I have trouble staying with tasks/projects to completion	0	1	2	3	4
	I have difficulties planning ahead	0	1	2	3	4
	I have difficulties being on-time	0	1	2	3	4
	I have difficulties keeping a budget	0	1	2	3	4
	I frequently forget where I have put important things	0	1	2	3	4
	I have problems getting started with demanding or effort-requiring projects, I rather put them off	0	1	2	3	4
6	**Emotional Over-Reactivity**					
	With pressures or stresses, I often become anxious, disorganized or confused	0	1	2	3	4
	I frequently feel wound up by too many impressions	0	1	2	3	4
	I overreact to pressure, blow things out of proportion	0	1	2	3	4
7	**Impulsivity**					
	I am reckless	0	1	2	3	4
	I make sudden decisions without thinking, particularly when I am angry	0	1	2	3	4
	I tend to interrupt others talking	0	1	2	3	4
	I get into trouble because I say things without thinking	0	1	2	3	4
	I am impatient	0	1	2	3	4
	I tend to “act first and think (and regret) afterwards”	0	1	2	3	4