The comorbidity of schizophrenia and pervasive developmental disorders in adolescence

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ABSTRACT

The onset of schizophrenia before the age of 18 is commonly categorized as early onset schizophrenia. It accounts for less than 4% of all cases of schizophrenia, the prevalence of which is about 1% worldwide. Premorbid abnormalities seem to be very typical, and prognosis is often poor. Besides the negative and positive symptoms, severe neurocognitive deficits also occur.

Schizophrenia and pervasive developmental disorders share a common history. From 1970 onwards these disorders have been regarded as separate conditions. These disorders have different ages of onset as well as developmental courses. Nevertheless, the clinical symptoms as well as the results of genetic and neuroimaging studies overlap.

The participants in this thesis were adolescent schizophrenia patients (n = 18; 7 males, 11 females). The mean age of the participants at recruitment was 15.6 years (studies I-III) and at the time of psychological assessment 16.2 years (study IV). Study IV also included 15 adolescents with PDD without psychotic disorder (n = 15; 7 males, 8 females). Their mean age at recruitment was 16.1 years. All participants had a primary IQ over 70.

Study I of this thesis assessed the possible comorbidity of early onset schizophrenia and pervasive developmental disorders. We found that a total of 44% of adolescents with schizophrenia had some pervasive developmental disorder already in childhood. However, most of the adolescents had a correct comorbid diagnosis until the onset of psychotic symptoms and the diagnosis of schizophrenia.

Study II evaluated the number and nature of catatonic features among adolescents with schizophrenia. A further comparison was made of the nature and numbers of those features between adolescents suffering from schizophrenia alone and those schizophrenia patients with comorbid pervasive developmental disorder. All adolescents with schizophrenia presented many lifetime catatonic features. Adolescents with schizophrenia and comorbid pervasive developmental disorder had an earlier onset of catatonic features, more catatonic features and a greater variety of catatonic features compared to schizophrenia patients without comorbidity.
Study III aimed to assess the developmental skills of adolescents with schizophrenia. All of the adolescents with schizophrenia exhibited some developmental delays. Adolescents with schizophrenia and comorbid pervasive developmental disorders exhibited more delays in developmental skills than did those schizophrenia adolescents without comorbidity.

Study IV investigated neurocognition and social cognition between adolescents suffering from schizophrenia alone, those schizophrenia patients with comorbid pervasive developmental disorder and adolescents with pervasive developmental disorder only. The profiles of the neurocognitive abilities and disabilities between these three groups differed. The adolescents with schizophrenia and comorbid pervasive developmental disorder did not have more severe problems than the other two groups. The comorbid group displayed a combination of the visual strengths those are typical for PDDs and the deficits in processing speed associated with schizophrenia.

These study findings showed that among adolescents with early onset schizophrenia is a subgroup of adolescents with comorbid pervasive developmental disorder. The symptoms of these adolescents seem to be more severe, and this subgroup should be taken into account in psychiatric services and rehabilitation.
TIIVISTELMÄ

Skitsofrenian esiintyvyys on maailmanlaajuisesti noin 1 %. Ennen 18 ikävuotta puhkeavaa skitsofreniaa kutsutaan varhain alkavaksi skitsofreniaksi. Sen esiintyvyydeksi on arvioitu alle 4 % kaikista skitsofreniatapauksista. Varhain puhkeavalle skitsofrenialle tyypillisiä piirteitä ovat kehitykselliset poikkeavuutut ennen psykoosioireiden puhkeamista sekä huono ennuste. Negatiivisten ja positiivisten oireiden lisäksi sairauteen liittyy merkittävä neurokognitiivisia poikkeavuuksia.


Tämän väitöskirjan tutkimuskohteen muodostivat skitsofreniaan sairastuneet nuoret (n = 18; 7 poikaa, 11 tyttöä), joiden keski-ikä oli 15.6 vuotta (Osajulkaisuissa I-III) ja psykologisen tutkimuksen aikaan 16.2 vuotta (Osajulkaisu IV). Osajulkaisussa IV oli mukana myös 15 nuorta, joilla oli diagnosointi laaja-alainen kehityshäiriö, mutta ei psykoosairautta (n = 15; 7 poikaa, 8 tyttöä). Heidän keski-ikänsä oli 16.1 vuotta. Kaikkien tutkittavien primaari älykkyysosamäärä oli yli 70.

Väitöskirjan ensimmäisessä osatyössä selvitettiin, mikä on varhain alkavan skitsofrenian ja laaja-alaisten kehityshäiriöiden yhteissairastavuus. Tutkimuksessamme 44%:lla nuorista skitsofreniapotilaista esiintyi samanaikainen laaja-alaisten kehityshäiriö. Kuitenkin suurimmalle osalle nuorista kyseinen diagnoosi asetettiin vasta skitsofrenian puhkeamisen yhteydessä.

Toinen osatyö selvitti skitsofreniaa sairastavien nuorten katatonisten oireiden määrää ja laatua. Lisäksi vertailtiin katatonisten oireiden määrää ja laatua niillä nuorilla, jotka sairastivat ainoastaan skitsofreniaa ja niillä, jotka sairastivat sekä skitsofreniaa että samanaikaista laaja-alaista kehityshäiriötä. Skitsofreniaan sairastuneilla nuorilla esiintyi runsaasti katatonisia oireita. Nuorilla, joilla oli sekä skitsofrenia että laaja-alaisten kehityshäiriö, katatonisia piirteitä esiintyi nuoremmanlailla iällä, oireita oli enemmän ja ne olivat laaja-alaisempia verrattuna nuoriin, joilla sairastivat pelkästään skitsofreniaa.
Kolmas osatyö keskittyi tutkimaan skitsofreniaan sairastuneiden nuorten kehityksellisiä taitoja. Kaikilla skitsofreniaan sairastuneilla nuorilla oli havaittavissa viiveitä kehityksellisissä taidoissa. Ne nuoret, jotka sairastivat sekä skitsofreniaa että samanaikaisia laaja-alaista kehityshäiriöitä omasivat enemmän viiveitä kehityksellisissä taidoissaan kuin ne nuoret, jotka sairastivat ainoastaan skitsofreniaa.


Nämä tulokset osoittivat, että varhain alkava skitsofreniaan sairastuneiden nuorten joukossa on alaryhmä, jolla on samanaikainen laaja-alainen kehityshäiriö. Tämän alaryhmän oirekuva näyttäytyy vaikeampana ja tämä ryhmä tulisi huomioida psychiatrisissa hoito- ja kuntoutuspalveluissa.
ACKNOWLEDGEMENTS

The preparation of my thesis took many years. These were busy years for me that were filled with work, not least because of this project. I completed most of the thesis alongside the daily duties of my career in addition to everything else that was going on in my life. John Lennon was absolutely right when he noted that “Life is what happens while you are busy making other plans”.

I want to express my sincerest gratitude to my thesis supervisors, who were my support and functioned as my project group. They encouraged me to keep going and believed in me: even when I might have thought about giving up. With the deepest gratitude I thank my supervisor, Docent Pekka Tani. I admire your courage to take on the supervision of my thesis and your tireless perseverance over the years. I am eternally grateful for all the times you have so generously given to me from your already full schedule and also for your determination in guiding and advancing my work. I greatly admire your spectrum of knowledge and your understanding of my field of study. My heartfelt appreciation also goes to my second supervisor, Professor Nina Lindberg, for her guidance during these last years. I admire your dedication to the field of science and for your input into this project. I am forever indebted for your proficiency and your drive, energy and extremely efficient way of working. Without the highly professional supervision from both Pekka and Nina, I would not have completed my thesis. I would also like to thank Professor Laura Hokkanen for her guidance in the last years of this project. I am greatful for your supportive, professional and constructive comments. Without them, finalizing this thesis would have been much harder. To all my supervisors, I extend my sincerest gratitude for all the time you have given me for this project.

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Last but not least, I would like to dedicate this work to the memory of my dearly beloved father, who always supported me in my ventures and who had the foresight and faith to see that this challenge would end successfully. And to my two sons, Noel and Ruben, who are my world.
LIST OF ORIGINAL PUBLICATIONS

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


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ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADHD</td>
<td>Attention-Deficit/Hyperactivity Disorder</td>
</tr>
<tr>
<td>ADI-R</td>
<td>Autism Diagnostic Interview- Revised</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
</tr>
<tr>
<td>AOS</td>
<td>Adult onset schizophrenia</td>
</tr>
<tr>
<td>AS</td>
<td>Asperger’s disorder</td>
</tr>
<tr>
<td>ASD</td>
<td>Autism Spectrum Disorder (before DSM-5)</td>
</tr>
<tr>
<td>CBT</td>
<td>Cognitive Behavior Therapy</td>
</tr>
<tr>
<td>COS</td>
<td>Childhood Onset Schizophrenia</td>
</tr>
<tr>
<td>DISCO-11</td>
<td>Diagnostic Interview for Social and Communication Disorders, 11th version</td>
</tr>
<tr>
<td>DSM-III</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 3th edition</td>
</tr>
<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 4th edition</td>
</tr>
<tr>
<td>DSM-IV-TR</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 4th edition text revised</td>
</tr>
<tr>
<td>DSM-5</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 5th edition</td>
</tr>
<tr>
<td>EOS</td>
<td>Early onset schizophrenia</td>
</tr>
<tr>
<td>HFA</td>
<td>High-Functioning autism</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Classification of Diseases, 10th edition</td>
</tr>
<tr>
<td>IQ</td>
<td>Intelligence Quotient</td>
</tr>
<tr>
<td>K-SADS-PL</td>
<td>The Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children – Present and Life-Time</td>
</tr>
<tr>
<td>MANCOVA</td>
<td>Multivariate analysis of covariance</td>
</tr>
<tr>
<td>MCDD</td>
<td>Multiple Complex Developmental Disorder</td>
</tr>
<tr>
<td>MeCP2</td>
<td>methyl-CpG-binding protein 2</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>NOS</td>
<td>Not Otherwise Specified</td>
</tr>
<tr>
<td>PDD</td>
<td>Pervasive Developmental Disorder</td>
</tr>
<tr>
<td>PDD-NOS</td>
<td>Pervasive Developmental Disorder- Not Otherwise Specified</td>
</tr>
<tr>
<td>SCH</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>SPDC</td>
<td>Schizoid Personality Disorder of Childhood</td>
</tr>
<tr>
<td>ToM</td>
<td>Theory of Mind</td>
</tr>
<tr>
<td>PIQ</td>
<td>Performance IQ</td>
</tr>
<tr>
<td>VIQ</td>
<td>Verbal IQ</td>
</tr>
<tr>
<td>WAIS-III</td>
<td>Wechsler Adult Intelligence Scale, third edition</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WISC-III</td>
<td>Wechsler Intelligence Scale for Children, third edition</td>
</tr>
<tr>
<td>3di</td>
<td>The Developmental, Dimensional and Diagnostic Interview</td>
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1 INTRODUCTION

Schizophrenia and pervasive developmental disorders share a long common history. Schizophrenia and autism have been regarded as separate conditions since the 1970s. Despite the fact that these two conditions are separate entities, the question about the distinction between these disorders has arisen again in recent years. Participants in the research studies that this thesis summarizes were adolescent patients with schizophrenia and/or pervasive developmental disorder. We chose to study this particular age group because there is a paucity of published study results in adolescents, in contrast to the published studies that exist on children and adults with the same conditions. Indeed we are not aware of any previous published studies on adolescents with schizophrenia and comorbid pervasive developmental disorder.

1.1 Schizophrenia

Schizophrenia (SCH) is a severe, pervasive mental disorder with a prevalence of about 1% worldwide (McDonell & McClellan, 2007). This overall disorder is divided into subcategories in the International Classification of Diseases 10th edition (ICD-10), namely; paranoid, hebephrenic, catatonic and undifferentiated type of SCH, undifferentiated SCH, post-schizophrenic depression and residual SCH. The disorder is more common (male: female ratio = 1.4) among males (McGrath, 2006). SCH is a heterogeneous disorder with multiple etiologies. Currently no single cause for the disorder has been identified (McClellan & Stock, 2013).

The onset of the disorder is usually in early adulthood and symptoms are divided into positive and negative domains. Prominent hallucinations, delusions, disorganized speech or behavior or catatonia are categorized as positive symptoms and negative symptoms include marked apathy, paucity of speech, and blunting or incongruity of emotional responses. After the onset of the disorder social and occupational dysfunction also occurs (WHO, 1992). Antipsychotic medication is essential treatment for positive symptoms. Medication or psychological interventions has limited effects on negative symptoms however (Fusar-Poli et al., 2014). Negative symptoms are associated with cognitive disability, especially deficits in verbal memory (Puig et al., 2008; Villalta-Gil
et al., 2006). Negative symptoms and cognitive deficits, are associated with disability in functioning. Patients with SCH have not shown significant improvement in cognitive deficits with antipsychotic treatment (Bowie et al., 2012).

The disorder has different phases. Prior to the onset of psychotic symptoms most individuals will experience a prodrome period during which functions will begin to deteriorate. The acute phase is dominated by positive psychotic symptoms. Then active psychosis begins to remit, which characterizes the recovery phase that follows on. This is in turn followed by the residual phase during which negative symptoms are present but positive symptoms are minimal. Usually these phases follow each other in cycles, and they show an increasing deterioration trend in each cycle.

Symptom criteria for SCH in ICD-10 and Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) classifications (Table 1) are similar to each other, except for the requirement for duration of symptoms. The requirement is at least one month in the ICD-10 classification whereas it is six months in the DSM-IV classification. There are only a few changes in the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) criteria from the previous version: a rise of symptom threshold from one specified symptom to two is one major difference. The diagnostic criteria no longer identify subtypes. There is also a change in the present requirement for positive symptoms: a patient must now have at least one of three “positive” symptoms (hallucinations, delusions, disorganized speech; American Psychiatric Association, 2013). The diagnostic criteria are the same for the children, adolescents and adults.

Onset of SCH before 13 years of age is quite rare (McClellan & Stock, 2013). One early form of SCH has an insidious onset in most cases and it can be referred as childhood-onset schizophrenia (COS). The prevalence of COS is 1 in 10 000 children (Remschmidt & Theisen, 2005).

Onset of SCH before the age of 18 is commonly categorized as early onset schizophrenia (EOS). It is characterized by either an acute or gradual onset. There is a remarkable increase in SCH frequency between 13 and 18 years of age (Remschmidt & Theisen, 2005) with the prevalence of SCH-related disorders in adolescence of about 1–2% (Kessler et al., 1994; Patel et al., 2007). EOS accounts for less than 4% of all cases of SCH (Vyas et al., 2011).
Premorbid abnormalities such as delays in development, behavioral problems, motor problems and language problems seems to be very typical for EOS, especially for COS patients (Alaghband-Rad et al., 1995; Schaeffer & Ross, 2002). Over half of the patients with COS had premorbid language, motor, and social impairments according to a cohort study (Nicolson et al., 2000). However, delays in language and motor developments were found only in 10% of individuals who later developed AOS in the 1946 British Birth Cohort (Jones et al., 1994). Prognosis of EOS is often poor (Clemmensen et al., 2012; Hallerbäck et al., 2012; Rapoport et al., 2009), but the same types of neurobiological correlates and phenotypic deficits are seen in EOS as in adult-onset schizophrenia (AOS) (Vyas et al., 2011). However, some genetic variations, for example a 22q11 deletion, may occur more frequently in EOS and COS patients than in AOS patients (Vyas et al., 2011).

<table>
<thead>
<tr>
<th>ICD-10 F 28 Schizophrenia</th>
<th>DSM-IV 295 Schizophrenia</th>
<th>DSM-5 295 Schizophrenia</th>
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<tbody>
<tr>
<td>Symptoms must be present for most of the time during an episode of psychotic illness lasting for at least 1 month (or at some time during most of the days)</td>
<td>A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated): 1. delusions 2. hallucinations 3. disorganized speech (e.g., frequent derailment or incoherence) 4. grossly disorganized or catatonic behavior 5. negative symptoms, i.e., affective flattening, alogia, or avolition</td>
<td>A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated): 1. delusions 2. hallucinations 3. disorganized speech (e.g., frequent derailment or incoherence) 4. grossly disorganized or catatonic behavior 5. negative symptoms, i.e., diminished emotional expression or avolition</td>
</tr>
</tbody>
</table>
| At least one of the following:  
  a. thought echo, thought insertion or withdrawal, or thought broadcasting  
  b. delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception  
  c. Hallucinatory voices giving a running commentary on the patient’s behavior, or discussing the patient among themselves, or other types of hallucinatory voices coming from some part of the body  
  d. Persistent delusions of other kinds that are culturally inappropriate and completely impossible (e.g., being able to control the weather, or being in communication with aliens from another world) | B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas such as work, interpersonal relations, or self-care is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning). | B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas such as work, interpersonal relations, or self-care is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning). |
| Or at least two of the following:  
  a. persistent hallucinations in any modality, when occurring every day for at least 1 month, when accompanied by delusions (which may be fleeting or half-formed) without clear affective content, or when accompanied by persistent over-valued ideas  
  b. neologisms, brocades, or word salad in the train of thought, resulting incoherence or irrelevant speech  
  c. disorganized behavior, such as extremes, posturing, or waxy flexibility, negativism, mannerisms, and stereotypes  
  d. "negative" symptoms, such as reduced speech, paucity of content, blunting or inexpressiveness of emotional responses (it must be clear that these are not due to depression or to medicolegal medication) | C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences). | C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences). |

D. Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either: (1) no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.  

E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.  

F. If there is a history of Autism Spectrum Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least 1 month (or less if successfully treated).  

G. If there is a history of Autism Spectrum Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least 1 month (or less if successfully treated).
1.2 Pervasive developmental disorders

The symptomatology for pervasive developmental disorders (PDD) was described by Leo Kanner (1943). That author stated that PDD begins during the child’s first years and typical characters are social withdrawal, obsessiveness, stereotypy and echolalia. Symptoms are quite stable during that time. A year later Hans Asperger (1944) introduced quite similar symptomatology of which the most obvious characteristic is impairment of reciprocal social interaction. Other characteristics described by Asperger were: repetitive activities, problems in non-verbal communication and motor coordination.

Asperger’s disorder (AS), childhood autism and atypical autism were classified as PDDs in ICD-10 (WHO, 1992) and in DSM-IV (American Psychiatric Association, 1994). The other eight subgroups of PDDs in the ICD-10 classification (F84.0) are Rett’s syndrome, childhood disintegrative disorder, overactive disorder associated with mental retardation and stereotyped movement, other pervasive developmental disorders and pervasive developmental disorder unspecified (residual category). Recently there have been major changes in diagnostic categories since the introduction of DSM-5 (Table 2; American Psychiatric Association, 2013). A new umbrella term, Autism spectrum disorder, has replaced all the previous mentioned subgroups. Rett’s syndrome is caused by mutations in the X-linked gene encoding methyl-CpG-binding protein 2 (MeCP2). This syndrome differs from other subgroups of PDD because Autism spectrum disorder is defined by specific symptoms in behaviors, not etiologies. Those patients who met Rett’s syndrome criteria in DSM-IV can be described in DSM-5 under “Autism spectrum disorder”, but the specifier term “with known genetic or medical condition” should be used. The term PDD has been used throughout this text as being equivalent with the terms autistic spectrum disorder and autism spectrum disorder (ASD) used by Lorna Wing, long before DSM-5 was published. Wing’s term covers the range of presentation from classic autism described by Kanner to Asperger’s disorder. The triad of impairments is characteristic of Wing’s description of ASD, and in DSM-5 the triad has been changed to a dyad, by combing two symptoms.

Prevalence of PDDs is 0.6–1% of the children in general population (Baird et al., 2006; Fernell & Gillberg, 2010; Nygren et al., 2012). All the PDDs were reported to be more common among males than among females (male: female 123.2:30.8) in a study
There has been an increase in prevalence of PDD rates during the past decades because of changes in diagnostic criteria, concepts, definitions and changes in the policies for special education and the increasing availability of services (Fombonne, 2009).

The etiology of these complex neurodevelopmental disorders remains unclear although many candidate genes have been reported (Piggot et al., 2009). There is increasing evidence for PDDs genetic heterogeneity (Kim & Leventhal, 2015).

The diagnosis of PDD is made on the basis of behavioral symptoms and same diagnostic criteria apply to children and adults. The onset of PDDs occurs in infancy and diagnosis is usually made during early childhood. Nevertheless, it is common that diagnosis is also made later (Begeer et al., 2013). The ICD-10 and DSM-IV classified PDDs share a core triad of abnormalities: 1) qualitative impairments in reciprocal social interactions, 2) qualitative impairments in verbal and non-verbal communication, and 3) restricted social imagination with repetitive and stereotyped patterns of interests and behavior (WHO, 1992).

The diagnosis of childhood autism (Table 3) requires the manifestation of abnormal or impaired development before the age of three years at least in one of the following areas: social communication, the development of selective social attachments, reciprocal social interaction or functional or symbolic play. In the case of atypical autism atypicality can occur in age of onset, in symptomatology or in both the age of onset and symptomatology (WHO, 1992).

There is not any clinically significant general delay in spoken or receptive language or cognitive development in AS. There are qualitative abnormalities in reciprocal social interactions in AS that are similar to autism and an unusually intense circumscribed interest or restricted, repetitive, and stereotyped patterns of behavior, interests and activities can also occur.

AS is often regarded as same condition as high functioning autism (HFA). Language development in childhood in HFA is delayed whereas in AS, the child’s language development is normal. However, the study results about differences between these two conditions are very heterogeneous. Some studies show that individuals with AS have significantly higher full-scale intelligence quotient (IQ), verbal IQ (VIQ), and performance IQ (PIQ) with significantly higher VIQ than PIQ than individuals with
HFA, whereas VIQ in HFA is similar to PIQ (Chiang et al., 2014). Differences in grey and white matter volumes have also been reported (McAlonan et al., 2008; McAlonan et al., 2009). However, other studies indicate that there are no differences between AS and HFA children for non-verbal, motor or psychosocial adaptation (Noterdaeme et al., 2010; Ozonoff et al., 2000) and that these conditions have the same fundamental symptomatology (Ozonoff et al., 2000). There are no differences in theory of mind (ToM) performance in adults with AS and HFA (Spek et al., 2010). Thus, it is quite difficult to foresee the clear developmental trajectory of a single individual in the transition from childhood into adulthood based on childhood symptomatology. There are no qualitatively separable subcategories under Autism spectrum disorders in DSM-5 the classification.

1.2.1 Comorbidity

Within the ICD-10 classification “childhood autism exclusion criteria” states that the clinical picture is not attributable to SCH (F20) of unusually early onset. Likewise, simple SCH has been excluded for AS criteria (F20.6). Despite the fact that ICD-10 states that SCH is an exclusion criterion for PDD, many studies agree that these disorders can coexist (Hallerbäck et al., 2012; Rapoport et al., 2009). Patients with PDD may get the additional diagnosis of SCH, if they have prominent positive symptoms (hallucinations and delusions) for at least one month and if the onset of PDD clearly precedes the onset of SCH.

The comorbidity criterion in DSM-5 has been re-evaluated and there is no longer the restriction about comorbidity of these two disorders. Deficits in social interaction and impairments of communication detailed in DSM-5 have been combined into deficits in social communication and social interaction. Symptom severity is evaluated on three levels and sensory problems are added to the criteria. There is also the new diagnosis of Social (Pragmatic) Communication Disorder under heading 315.39 of DSM-5, which differs from Autism spectrum disorder in a lack of restricted/repetitive patterns of behavior, interest, and activities during the early development.
1.2.2 Treatment

PDD is a lifelong disorder in which even individuals with high cognitive abilities have significant disadvantages regarding social relationships, employment, physical and mental health and quality of life (Howlin & Moss, 2012). Core symptoms of PDDs respond poorly to medication (Ghaziuddin, 2005). Early interventions when the child is under two years of age, are reported to be effective because there is evidence of neuroplasticity and critical periods of development in infancy. These interventions are usually parent-mediated procedures (Bradshaw et al., 2014) that are intended to develop optimal outcome for infants and toddlers with PDD and their families. Often core features such as deficits in communication, language or social skills are put under scrutiny by the child’s caregiver and behavioral interventions strategies or positive behavior support are used (Boyd et al., 2010). Deficits in social skills render individuals with PDD vulnerable to depression and anxiety. There is evidence that Cognitive behavior therapy (CBT) has potential in treating those patients with PDD who have symptoms of depression and stress (McGillivray & Evert, 2014).

It is usual that coexisting/comorbid medical conditions, psychiatric disorders and behavioral and motor dyscontrol symptoms are associated with autism and AS. Coexisting conditions such as depression, tics, Tourette’s, ADHD, catatonic motor behavior, obsessions and compulsions and psychotic disorders can be treated with medications (Ghaziuddin, 2005; Gillberg & Billstedt, 2000).

<table>
<thead>
<tr>
<th>ICD-10 F84.5 Asperger’s syndrome</th>
<th>DSM-IV 299.80 Asperger’s Disorder</th>
<th>DSM-5 299.08 Autism Spectrum Disorder</th>
</tr>
</thead>
</table>
| A. A lack of any clinically significant general delay in spoken or receptive language or cognitive development. Diagnoses require that single words should have developed by two years of age or earlier and that communicative phrases be used by three years of age or earlier. Self-help skills, adaptive behaviour and curiosity about the environment during the first three years should be at a level consistent with normal intellectual development. However, motor milestones may be somewhat delayed and motor clumsiness is usual (although not a necessary diagnostic feature). Isolated special skills, often related to abnormal preoccupations, are common, but are not required for diagnosis. | A. Qualitative impairment in social interaction, as manifested by at least two of the following:  
1. Marked impairment in the use of multiple nonverbal behaviors, such as eye-to-eye gaze, facial expression, body posture, and gestures to regulate social interaction.  
2. Failure to develop peer relationships appropriate to developmental level.  
3. A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest to other people).  
4. Lack of social or emotional reciprocity. | A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:  
1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation, to reduced sharing of interests, emotions, or affect; to failure to sustain or return to social interactions.  
2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated and stereotyped verbal and nonverbal communication to aberrantities in eye contact and body language or deficits in using and understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.  
3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers. Specify current severity: Severity is based on social communication impairments and restricted repetitive patterns of behavior.  
B. Restricted, repetitive, and stereotyped patterns of behavior, interests, and activities, as manifested by at least two of the following, currently or by history:  
1. Stereotyped or repetitive motor movements, use of objects, or speech.  
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior.  
3. Hugely restricted, fixated interests that are abnormal in intensity or focus.  
4. Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment.  
C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).  
D. Symptom causes clinically significant impairment in social, occupational, or other important areas of functioning.  
E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur, to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level. |
| B. Qualitative abnormalities in reciprocal social interaction  
1. Failure adequately to use eye-to-eye gaze, facial expression, body posture and gesture to regular social interaction.  
2. Failure to develop (in a manner appropriate to mental age, and despite ample opportunities) peer relationships that involve a mutual sharing of interests, activities and emotions.  
3. A lack of socio-emotional reciprocity as shown by an impaired or deviant response to other people’s emotions, or a lack of modulation of behavior according to social context, or a weak integration of social, emotional and communicative behaviors. | C. The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning.  
D. There is no clinically significant general delay in language (e.g., single words used by age 2 years, communicative phrases used by age 3 years).  
E. There is no clinically significant delay in cognitive development or in the development of age-appropriate self-help skills, adaptive behavior (other than in social interaction), or curiosity about the environment in childhood.  
F. Criteria are not met for another specific pervasive developmental disorder or schizophrenia. |
Table 3. Diagnostic criteria for childhood autism, atypical autism, autistic disorder and pervasive developmental disorder not otherwise specified in ICD-10 (WHO, 1992) and DSM-IV (American Psychiatric Association, 1994).

<table>
<thead>
<tr>
<th>ICD-10 F84.0 Childhood autism</th>
<th>ICD-10 F84.1 Atypical autism</th>
<th>DSM-IV 299.80 Autistic Disorder</th>
<th>DSM-IV 299.80 Pervasive Developmental Disorder Not Otherwise Specified (Including Atypical Autism)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Presence of abnormal or impaired development before the age of three years, in at least one of the following areas: (1) receptive or expressive language used in social communication; (2) development of selective social attachements or reciprocal social interaction; (3) functional or symbolic play.</td>
<td>B. Qualitative abnormalities in reciprocal social interaction, manifest in at least one of the following areas: (1) failure adequately to use eye-to-eye gaze, facial expressions, body posture and gesture to regulate social interaction; (2) failure to develop peer relationships that involve a mutual sharing of interests, activities and emotions; (3) A lack of socio-emotional reciprocity as shown by an impaired or deviant response to other people’s emotions or lack of modulation of behavior according to social context, or a weak integration of social, emotional and communicative behaviors.</td>
<td>A. A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3).</td>
<td>This category should be used when there is a severe and pervasive impairment in the development of reciprocal social interaction or verbal and nonverbal communication skills, or when stereotyped behavior, interests, and activities are present, but criteria are not met for a specific Pervasive Developmental Disorder, Schizophrenia, Schizotypal Personality Disorder, or Avoidant Personality Disorder.</td>
</tr>
<tr>
<td>C. Qualitative abnormalities in communication, manifest in at least two of the following areas: (1) a delay in, or total lack of, development of spoken language that is not accompanied by an attempt to compensate through the use of gesture or mime as alternative modes of communication; (2) incoherent or inaudible speech with there is reciprocal and from responsiveness to the communications of the other person; (3) abnormal and repetitive use of language or idiosyncratic use of words or phrases; (4) abnormalities in pitch, stress, rate, rhythm and intonation of speech.</td>
<td>D. Restricted, repetitive, and stereotyped patterns of behavior, interests, and activities, manifest in at least two of the following areas: (1) an encompassing preoccupation with one or more stereotyped and restrictive patterns of interest that are not normal in content or focus, or one or more interests that are abnormal in their intensity and consummated nature although not abnormal in their content or focus; (2) apparent compulsive adherence to specific, non-functional, routines or rituals; (3) stereotyped and repetitive motor mannerisms that involve either hand or finger flapping or twisting, or complex whole body movements; (4) preoccupations with part-objects or non-functional elements of play materials (5) distress over changes in small, non-functional, details of the environment.</td>
<td>E. The clinical picture is not attributable to the other varieties of pervasive developmental disorder, schizophrenia (F20) or unusually early onset. (This has been shortened)</td>
<td>For example, this category includes “atypical autism” presentations that do not meet the criteria for Autistic Disorder because of late onset at age of onset, atypical symptomatology, or subthreshold symptomatology, or all of these.</td>
</tr>
</tbody>
</table>

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1.3 Common history of SCH and PDDs

De Sanctis published case reports between 1906 and 1909 about young children who had relatively normal development at first and then underwent marked changes that occurred, abruptly or gradually. He named this disorder “dementia praecosisssima”. These children had catatonic symptoms, negativism, emotional blunting and outbursts of anger (Lay, 1938). Emil Kraepelin observed similar cases and named the condition as “dementia praecox”. The patients had early onset of the illness and prognosis was poor with a progressively deteriorating course (Berrios et al., 2003). Eugen Bleuler introduced term schizophrenia in 1911 and started to call the former condition “dementia praecox” by that term (Bleuler, 1950). He also used the term autism in reference to isolation of the self from social interaction as one of the core symptoms of SCH. He described autistic thinking thus: “The autistic thinking is the source of the delusions, of the crude offenses against logic and propriety, and all the other pathological symptoms” (Bleuler, 1950).

In 1943 Leo Kanner described a condition that differed in certain respects from previously reported cases, and named this condition early infantile autism. He presented the history of eight boys and three girls, all under 11 years of age. Kanner reported that two of his case patients had earlier been considered as schizophrenic. Kanner made a clear distinction between the schizophrenic withdrawal from formerly existing participation and the “extreme autistic aloeness these children seem to have from the beginning of their lives” (Kanner, 1943).

A year later in 1944, Hans Asperger also described a new disorder “autistic psychopathy” (Asperger, 1944), deriving its name from the concept of autism in SCH. According to Asperger, children showed characteristic features from the second year of life, which remain constant throughout the life span. The fundamental feature of the disorder is a limitation in the social relationships of the patients. Children described by Asperger had better cognitive abilities than those described by Kanner. Those studies were originally written in German and were translated into English by Lorna Wing in 1981 (Wing, 1981). She made this disorder more widely known almost 40 years since it had first been described. According to Wolff (1996), Eva Ssuchareva described children with similar behavior and symptoms and signs as those described by Asperger and named the condition “schizoid personality disorder of childhood” (SPDC) as early as
1926. Wolff and Barlow (1979) also used the term “schizoid personality in childhood” and they were the first researchers to compare SPDC children AS children and noted the clinical resemblance with Asperger’s autistic psychopath children. Those same authors, however, noted clear distinctions between the two conditions because children with SPDC lacked the repetitiveness that is a characteristic sign in autistic children had and the SPDC children were poorly motivated for tasks of cognition and memory. Later, Wolff & McGuire (1995) found that many of these children did indeed meet the criteria for AS.

Kurt Schneider proposed certain symptoms that have special diagnostic importance for SCH in 1958 (Schneider, 1958). Schneider referred to these symptoms as “first rank symptoms”. These symptoms are “thought echo”, “third-person hallucinatory voices”, “running commentary hallucinatory voices”, “somatic passivity”, “thought withdrawal”, “thought insertion”, “thought broadcasting”, “made affect”, “made impulse”, “made volition” and “delusional perception”. Schneider stated that these symptoms are not always present, but when they are and there is no evidence of organic brain disease, then the diagnosis of SCH is verified. Later the classification value of these symptoms was criticized because many other disorders share these same symptoms (O’Grady, 1990; Wing & Nixon, 1975). If these symptoms had been specific to SCH, then they would still be a valuable aid for diagnosis. Schneiders’ first rank symptoms are not typical for patients described by either Kanner or by Asperger.

SCH and autism have been regarded as separate conditions from the 1970s onwards. Kolvin and colleagues (1971a) postulated that SCH in children had to be differentiated from autistic disorders. Rutter also concluded in 1972 that a disorder similar to that of adult SCH may begin in childhood (Rutter, 1972). Autism was described as a subgroup of SCH, infantile psychosis in ICD-8 published in 1967 and ICD-9 published in 1978. Term PDD was first used in DSM-III (APA, 1980). Since the publication of DSM-III, children with SCH have been diagnosed according to the same criteria as adults. PDD was entered into the ICD-classification in 1993 in (ICD-10) for the first time. Autism spectrum disorder is now used as a new umbrella term in DSM-5 (American Psychiatric Association, 2013) under neurodevelopmental disorders and SCH continues to remain under schizophrenia spectrum.
Despite of the fact that these two conditions are separate entities, they share many overlapping symptoms. Both disorders share some neurocognitive deficits and negative symptoms and there is a continuum and spectrum in both disorders. However, positive symptoms are typical of patients with SCH but not of patients with PDD. There has again been the question about the distinction between these disorders during the recent past (Lugnegård et al., 2011; Rapoport et al., 2009).

1.4 Overlap in genetic and neuroimaging studies and clinical symptoms

1.4.1 Genetic studies

There is evidence that both SCH and PDD disorders are highly genetically determined, though the genetic background to PDD is heterogeneous (Kim & Leventhal, 2015) as is that of SCH (Rapoport et al., 2012). Candidate genes are not diagnosis-specific, however (Rapoport et al., 2005).

Genetic studies show some overlap between PDD and SCH (Rapoport et al., 2009). For example, 22q11.2 deletion syndrome, microdeletion and microduplication in the 16p11.2 region, disruption in gene DISC-1 (Raja & Azzoni, 2010) and missense mutations in Neurexin 1 (Voineskos et al., 2011) have been reported in both disorders.

1.4.2 Neuroimaging studies

Symptoms of PDD are often noticed earlier than those of COS, thus there are more studies of early brain development in PDD children compared with their COS counterparts. A common finding in PDD is that during the first years of life there is brain overgrowth and exaggerated gray and white matter volumes (Baribeau & Anagnostou, 2013). However, there is also evidence that upon structural magnetic resonance imaging (MRI) male infants with a high risk of developing SCH have larger brain volumes during the first months of their lives than normal male infant controls (Gilmore et al., 2010).

Both COS and PDD seem to manifest some decrease in white matter integrity in the corpus callosum and cingulum compared to controls (Baribeau & Anagnostou, 2013). Both conditions share also abnormalities in subcortical networks, which are opposite
types. For instance, deficits in local connectivity but with increased long-range connectivity have been proposed for SCH (Baribeau & Anagnostou, 2013) whereas in PDD long distance under-connectivity and local over-connectivity of the frontal cortex have been reported (Geschwind & Levitt, 2007; Vissers et al., 2012).

1.4.3 Clinical symptoms

Patients with PDD often show symptoms such as anhedonia, restricted facial expressions, poor use of gestures, alogia, poor social relatedness or presence of stereotypic behavior, all resembling negative symptoms in SCH (Ghaziuddin, 2005). Symptoms resembling positive symptoms of SCH are also seen in high-functioning PDD, such as elaborate fantasies or disorganized thinking (Ghaziuddin et al., 1995). There is no clear consensus on how the schizophrenic symptoms might qualitatively differ from those described for PDD (Hallerbäck et al., 2012; Raja & Azzoni, 2009; Raja & Azzoni, 2010).

1.5 Previously reported comorbidity

1.5.1 PDD in patients with SCH

It is reported that in COS, 30–50% of patients have comorbid PDD preceding the psychotic symptoms (Rapoport et al., 2009). According to results of a Diagnostic Interview for Social and Communication Disorders (DISCO-11) given to parents nearly half of the adults who had schizophrenic psychosis in young adulthood also had comorbid PDD (Hallerbäck et al., 2012). In the study by Sporn et al. (2004) 25% (19/75) of COS patients had a lifetime diagnosis of PDD. One of the COS patients met the criteria for autism, two for AS and 16 for PDD. It has also been pointed out that COS can be misdiagnosed because of its rarity. A study of 71 children and adolescents referred with history of childhood-onset psychosis, reported that only 19 referrals were diagnosed with SCH and six with PDD (McKenna et al., 1994). The author is not aware of studies concerning the prevalence of PDD in EOS-populations.
1.5.2 SCH in patients with PDD

Hans Asperger (1944) reported that among his 200 AS patients only one developed SCH. A recent Finnish combined community-and clinic-based sample of 50 adolescents with AS/HFA, found that none of the adolescents had SCH or related disorders (Mattila et al., 2010). Psychotic disorders are uncommon in young adults with AS (Lugnegård et al., 2011). This also seems to be true for the entire group of PDD patients, as was reported in the recent review there where only occasional cases of SCH in children and adults with PDD (Skokauskas & Gallagher, 2010). It is reported that in adults with PDD, 0–3% of patients have comorbid SCH (Abdallah et al., 2011; Hutton et al., 2008; Stahlberg et al., 2004).

Young adults with AS are at high risk of depression and anxiety disorders (Lugnegård et al., 2011). Ghaziuddin et al. (1995) studied eight children with PDD who were referred to them with psychotic symptoms. Those authors reported that SCH was suspected in only one child but was not confirmed and four other children had major depression diagnoses. Children with higher-functioning PDD can be especially mistaken as having a diagnosis of SCH instead of depression. In a recent cohort study (Sullivan et al., 2013) children with ASD and high-autistic trait scores were more likely to have psychotic experiences that associated strongly with depressive symptoms. It seems that it is much more common that patients with primary SCH will have comorbid PDD than will patients who have primary PDD and SCH as the comorbidity.

It is also suggested that there is subtype in PDD called Multiple Complex Developmental Disorder (MCDD), which is characterized by early childhood-onset affected dysregulation, high levels of anxiety, social impairment and thought disorder (Sprong et al., 2008). These children do not suffer from autism or SCH, but they do share certain symptoms with both disorders.

1.6 Catatonia

Catatonia was first coined by Karl Kahlbaum in 1874 (Kahlbaum, 1973). He described 25 patients with symptoms that included a wide range of motor abnormalities, “cataleptiform waxy flexibility” and echolalia or echopraxia. His patients often had affective disorders, cycles or stages of depression or mania. Emil Kraepelin cited
catatonia in 1893 as a main feature in “dementia praecox”, which was later became called SCH. Catatonia has been associated with SCH since then. The term has undergone changes in definitions and implications since it was first used by Kraepelin.

In earlier classifications both the duration and the number of symptoms required for diagnosis have varied. There have been at least six different rating scales for catatonia, which were: Modified Rogers Scales, Rogers Catatonia Scale, Bush-Francis Catatonia Rating scale, Northoff Catatonia Rating Scale, Braunig Catatonia Rating Scale and Kanner scale. Each of those scales was validated in different patient populations and with different items included (Sienaert et al., 2011).

Symptoms and signs that are often listed for catatonia clearly describe the motor and mood dysregulation aspects of this syndrome and these are: motor signs such as stupor, mutism, negativism, grimacing. Other symptoms and signs include impulsive acts, stereotypies and echopraxia/echolalia and withdrawal (Barnes et al., 1986; Bräunig et al., 1998; Rosebush et al., 1990; Taylor & Abrams, 1977). Catatonic symptoms are said to be unspecific (Taylor & Abrams, 1977) and quite common in acutely ill psychiatric patients (Banerjee & Sharma, 1995). The etiology of this disorder remains unknown. Effective treatments are electroconvulsive therapy (ECT) and medication (neuroleptic and benzodiazepine; Fink, 2013).

Catatonia as defined in DSM-IV remained associated with SCH (see Table 4), but it also appears in a separate class as “catatonic disorder due to a general medical condition” (American Psychiatric Association, 1994). Catatonia defined in ICD-10 is included in SCH and organic catatonic disorder (WHO, 1992). Recent research has shown that catatonia was found in up to 10% of people with an acute psychiatric disorder. Only quarter of them had psychotic disorder and nearly half of them had a mood disorder (Rosebush & Mazurek, 2010).

There has been a major change in the classification of catatonia in DSM-5 (Table 4), because catatonia has been separated from SCH and described as a disorder of its own. Catatonia can be associated with other mental disorders, or it can emerge within another medical condition, or it can remain unspecific (American Psychiatric Association, 2013).

Studies on adult patients with SCH-related and mood disorders have reported the incidence of catatonia that varied between 10–38% (Banerjee & Sharma, 1995; Bräunig
et al., 1998; Taylor & Abrams, 1977). Catatonia also occurs among children and adolescents (Cohen et al., 1999), but there are few studies on this age group. Estimated prevalence in young people is lower than in adults, and ranges between 0.6% and 17% (Cornic et al., 2007). General catatonia symptomatology and underlying disorders are similar in children, adolescents and adults. Incontinence was not reported in adult studies, but is frequently reported in children and adolescents with catatonia (Cornic et al., 2007).

In the study conducted by Green and colleagues (1992), 31.6% (12/38) of 38 hospitalized children with schizophrenic disorder showed catatonic features. Another study assessed all the hospitalized adolescent patients during the period of 1991 to 1997 for catatonic signs and found only 0.6% (n = 9) of them fulfilled the criteria of catatonia (Cohen et al., 1999). Six of these adolescent patients had a history of SCH and another two patients had PDD. Elsewhere it was reported that 17.7% (11/62) of the children and adolescents who suffered from affective and non-affective psychotic disorders showed at least two signs of catatonia (Thakur et al., 2003). A recent study by Ghaziuddin and colleagues (2012) reported that 17.8% (18/101) of the adolescents who were diagnosed with disorders with known risk for catatonia, such as PDD, psychosis-Not otherwise specified (NOS) intermittent explosive disorder, mental retardation or neuroleptic malignant syndrome manifested three or more symptoms of catatonia.

Besides the clinical diagnosis of catatonia, a wide range of chronic, less severe, and sometimes very subtle symptoms of posture, movement, speech, and behavior are considered to be catatonic in nature (Fink, 2013; Wing & Shah, 2006). The term “catatonia spectrum” is used to cover the whole range of these manifestations (Fink, 2013).

1.6.1 Catatonia and PDD

Catatonic features have also been related to PDDs (Dhossche et al., 2010; Mazzone et al., 2014). Behavioral features such as motor stereotypies, mannerism, rituals, mutism, echolalia and negativism are described in both catatonia and ASD. Wing and Shah (2000) found that those individuals with ASD who have impaired language and passivity in social interaction are more likely to have catatonic features. Autism spectrum disorder as defined in DSM-5 can be specified with catatonia, which provides some support for the association between these two disorders.
Two systematic studies investigated the prevalence of catatonia in ASD. A prospective population-based follow-up study of 120 individuals with autism reported that approximately 12% of the autistic persons met the criteria for catatonia during or after their adolescence (Billstedt et al., 2005). Similar results were shown by Wing and Shah (2000). None of their patients met the criteria for full syndrome of catatonia before 15 years of age. A total of 30 individuals (6%) of the 506 children and adults with ASD met the criteria for catatonia. All those individuals who met criteria for catatonia were over 15 years of age, thus they represented 17% (30/175) of all referrals for the >15 years age group (Wing & Shah, 2000). Lower rates of catatonia were seen in the follow-up study where 135 individuals with PDD were evaluated by through their responses to questionnaires, which indicated that 16% (21/135) participants had a psychiatric disorder, but only five patients had a comorbid obsessive-compulsive disorder and/or catatonia (Hutton et al., 2008).

Catatonic symptoms in PDD are often preceded by stressful life events (Hare & Malone, 2004; Wing & Shah, 2000). Catatonic symptoms, typical for autism, are slowness, difficulty in initiating movements, increased passivity, amotivation and a worsening of ritualistic and repetitive behaviors (Wing & Shah, 2000). Wing and Shah (2006) also studied catatonia-like features in 200 children and adults with ASD, which is a broad equivalent of PDDs. They found that most of the study participants had displayed some catatonic features during their lifetime. These features occurred in more than 150 of the participants and were: a lack of facial expression, delayed echolalia, odd intonation, poor eye contact, and lack of cooperation.

It was proposed that catatonia in the context of autism would be better described by the term “autistic catatonia” (Hare & Malone, 2004). Some forms of autistic catatonia might reflect a person’s extreme adaptations to environmental factors such as an escape from contingent demands. Underlying processes of autistic catatonia could be conceptualized from the same psychological processes that underlie other aspects of autistic behavior. For example, the lack of a central coherence model in this instance could lead to the inability to integrate discrete “bits” of both sensory data and motor action and it could lead to very slow responses and impairments in voluntary behavior.

<table>
<thead>
<tr>
<th>ICD-10 F20.2</th>
<th>Catatonic schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. The general criteria for Schizophrenia (F20.0 - F20.3 above) must eventually be met, though this may not be possible initially if the patient is uncommunicative.</td>
<td></td>
</tr>
<tr>
<td>B. For a period of at least two weeks one or more of the following catatonic behaviours must be prominent:</td>
<td></td>
</tr>
<tr>
<td>(1) Stupor or mutism;</td>
<td></td>
</tr>
<tr>
<td>(2) Excitement</td>
<td></td>
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<tr>
<td>(3) Posturing</td>
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<td>(4) Negativism</td>
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<td>(5) Rigidity</td>
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<td>(6) Waxy flexibility</td>
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<tr>
<td>(7) Command automatism</td>
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<tr>
<td>C. Other possible precipitants of catatonic behaviour, including brain disease and metabolic disturbances, have been excluded.</td>
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<tr>
<th>ICD-10 F06.1</th>
<th>Organic catatonic disorder</th>
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<tbody>
<tr>
<td>The general criteria for F06 must be met. Objective evidence and/or history of cerebral disease, damage or dysfunction, or of systemic physical disorder known to cause cerebral dysfunction, including hormonal disturbances and non-psychoactive drug effects.</td>
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<tr>
<td>One of the following must be present:</td>
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<tr>
<td>(1) Stupor i.e. profound diminution or absence of voluntary movements and speech, and of normal responsiveness to light, noise and touch, but in the presence of maintenance of normal muscle tone, static posture and breathing</td>
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<tr>
<td>(2) Negativism</td>
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<tr>
<td>C. Catatonic excitement</td>
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<td>D. Rapid and unpredictable alternation of stupor and excitement.</td>
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<tr>
<th>DSM-IV 295.20</th>
<th>Catatonic Type</th>
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<tbody>
<tr>
<td>A type of Schizophrenia in which the clinical picture is dominated by at least two of the following:</td>
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<tr>
<td>(1) Motoric immobility as evidenced by catalepsy (including waxy flexibility) or stupor</td>
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<td>(2) Excessive motor activity that is apparently purposeless and not influenced by external stimuli</td>
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<td>(3) Extreme negativism (can apparently motivate resistance to all instructions or maintenance of a rigid posture against attempts to be moved) or mutism</td>
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<tr>
<td>(4) Peculiarities of voluntary movement as evidenced by posturing (voluntary assumption of inappropriate or bizarre postures), stereotyped movements, prominent mannerisms, or prominent grimacing</td>
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<td>(5) Echolalia or echopraxia</td>
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<tr>
<th>DSM-IV 293.89</th>
<th>Catatonic Disorder Due to a General Medical Condition</th>
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<tbody>
<tr>
<td>A. The presence of catatonia as manifested by motoric immobility, excessive motor activity (that is apparently purposeless and not influenced by external stimuli), extreme negativism or mutism, peculiarities of voluntary movement, or echolalia or echopraxia.</td>
<td></td>
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<tr>
<td>B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.</td>
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<tr>
<td>C. The disturbance is not better accounted for by another mental disorder (e.g., a manic episode).</td>
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<tr>
<td>D. The disturbance does not occur exclusively during the course of a delirium.</td>
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<tr>
<th>DSM-5 293.89</th>
<th>Catatonia</th>
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<tbody>
<tr>
<td>The clinical picture is dominated by three (or more) of the following symptoms:</td>
<td></td>
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<tr>
<td>1. Stupor</td>
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<tr>
<td>2. Catalepsy</td>
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<tr>
<td>3. Waxy flexibility</td>
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<tr>
<td>4. Mutism</td>
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<td>5. Negativism</td>
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<td>6. Posturing</td>
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<td>7. Mannerism</td>
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<td>8. Stereotypy</td>
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<td>9. Agitation</td>
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<td>10. Grimacing</td>
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<td>11. Echolalia</td>
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<tr>
<td>12. Echopraxia</td>
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Catatonia in DSM-5 can be associated with another mental disorder (catatonia specifier), be due to another medical condition, or be unspecified.
1.7 Delays in developmental skills

1.7.1 Delays in development in SCH

A wide range of developmental delays for different domains, especially in motor, language, and behavior has been reported in children destined to develop SCH in later life. Walker and Lewine (1990) analysed childhood home movies of five AOS patients, and reported that they exhibited less responsiveness, eye contact and positive affect in addition to more problems in fine and gross motor co-ordination compared to their healthy siblings.

Developmental delays reported by several birth-cohort studies are reported among those children who subsequently developed SCH as adults. Speech problems and delays in milestones of motor development, especially in walking, were reported more often in children who later develop SCH than other children (Jones et al., 1994). A preference for solitary play at the ages of four to six was also associated with later SCH. It was reported that at the age of seven those children who later developed SCH had more social maladjustment than their controls. Among boys overreactivity, hostility and inconsequential behavior at age seven was common. Among girls it was noted that by the age of 11 they had become noticeably withdrawn compared to their age matched peers (Done et al., 1994). Another birth-cohort study reported there were delays in learning to stand, walk and become potty-trained among those children who later developed SCH compared to their healthy peers (Isohanni et al., 2000). Cannon and colleagues (2002) reported that adult patients suffering from SCH had learned to walk at a later age and managed worse in standard motor skills at the ages three, five and nine than did healthy controls. Receptive language development impairments were also related to SCH. Internalizing problems and peer rejection occurred more often among children aged five to 11 who later developed SCH than among healthy individuals. Moreover, 2% (13/789) of 11 year-old children reported psychotic symptoms. Those who had strong early psychotic symptoms had more problems in neuromotor development, receptive language, intelligence and emotional development than those who had no early psychotic symptoms or weak early psychotic symptoms (Cannon et al., 2002). There were deficits in overall academic achievements reported among those
who later develop SCH compared to controls, but the differences were quite small and statistically non-significant (Dickson et al., 2012).

Those children who develop COS or EOS are suggested to have more severe problems in language and motor development and more insidious onset of symptoms than in AOS (Alaghband-Rad et al., 1995; Vourdas et al., 2003). A cohort of 33 children who developed SCH between 5-15 years of age were investigated and it was found that 49% (16/33) had major milestone delays and 87% (29/33) premorbid abnormalities (Kolvin et al., 1971b). That study found that six out of 32 (19%) parents of children with SCH also had SCH and thus the prevalence of SCH was relatively high among the parents of children with SCH (Kolvin et al., 1971c).

1.7.2 Delays in development in PDD

A majority of parents whose child later manifested PDD reported their concern about the lack of progress in their child’s development when the infant reaches the age 19 to 24 months. The mean age at which parental concern was expressed was lower at a mean of 15 months for parents of mentally retarded children compared to 22 months for parents of a non-retarded PDD child (De Giacomo & Fombonne, 1998). According to Howlin and Asgharian (1999) parents of children with a diagnosis of autism were aware of developmental problems by 18 months of age and parents of a child with AS were aware of developmental problems at around 30 months of age. Some parents reported concern about their autistic child’s development as early as during the child’s first year of life (Gillberg et al., 1990).

Deficits in reciprocal social interaction and routines are essential features for diagnosis of PDDs according to ICD-10 (WHO, 1992) and DSM-IV (American Psychiatric Association, 1994). In childhood autism abnormal or impaired development is evident before the age of three years thus self-help skills, adaptive behavior and curiosity about the environment during the first three years should be at a level consistent with normal intellectual development in AS children. It is also mentioned that motor-skills milestones may be somewhat delayed and motor clumsiness is usual (although not required for diagnosis). Sensory deficits were added to diagnostic criteria for Autism spectrum disorders in DSM-5 (American Psychiatric Association, 2013).

Most studies compare groups of children with developmental delay, because a deficit is considered to be a core for PDD when it distinguishes children with PDD from
those children with other atypical developmental delay. Social deficits, especially early joint attention deficits are relatively unique for PDD (Ventola, 2007; Wetherby et al., 2007). Compared to other developmental delays, social problems, such as response to hearing one’s name, expression of affect and reduced use of gaze, using fewer communicative gestures are more prevalent in PDD children by the age 18 months (Mitchell et al., 2011).

Problems in language development are often the first focus of parental concern (De Giacomo & Fombonne, 1998). Children diagnosed with PDD may learn their first word late (Matson et al., 2010b). Emergences of receptive communication deficits are common by the age of 24 months (Landa & Garrett-Mayer, 2006; Paul et al., 2014).

Both gross and fine motor skills have been found to be more impaired in young children with PDD than in those children with atypical development or who have developmental delay due to other etiologies (Landa & Garrett-Mayer, 2006; Matson et al., 2010a; Provost et al., 2007). An analysis of home video recordings children with ASD aged between four to six months showed that delays in rolling over, sitting, crawling and walking skills (Teitelbaum et al., 1998).

Children with PDD differ from those children with other developmental delay before the age of two as they have more impaired daily living skills, in addition to self-help skills such as bathing, feeding and dressing (Paul et al., 2014). Significant discrepancy between overall cognitive ability and adaptive functioning favoring IQ over real-life skills is typical in PDD (Bölte & Poustka, 2002).

Children with AS may experience specific challenges to learning academic skills such as reading and spelling (Gross, 1994). Having PDD predicts that an individual is prone to problems in reading comprehension (Brown et al., 2013). Non-retarded PDD children show discrepancies between actual academic achievement levels and the levels predicted by their intellectual ability. It is also been suggested that improved social abilities may contribute to academic achievement (Estes et al., 2011).

We are not aware of any published studies in which a direct comparison of developmental delays in patients with SCH and PDD has been conducted.
1.8 Neurocognition

Neurocognition is a general term that covers many processes involved in human information processing, such as attention, memory, language skills and executive functions (Lezak, 1995). Deficits in neurocognition are common amongst different disorders.

1.8.1 Neurocognition in SCH

Cognitive deficits become evident many years before the onset of SCH. A prospective birth cohort study reported neuropsychological functioning at the age of 13 years in subjects at risk for developing SCH-related disorder by the age 26 (Cannon et al., 2006). Adolescents who later developed schizophreniform disorder had more impairment in attention and executive functions than adolescents with mood, and anxiety disorders when each group was compared to its respective healthy controls (Cannon et al., 2006). Another study reported that deficits in verbal memory, gross motor skills, and attention at the ages of seven to 12 years distinguished those who develop SCH-related psychoses in adulthood from those who did not among subjects at risk of SCH (Erlenmeyer-Kimling et al., 2000). Deficits in processing speed have been reported in young individuals who later developed SCH, compared to healthy controls and unaffected siblings (Niendam et al., 2003; Sørensen et al., 2006).

Deficits in memory are wide-ranging and consistently present in patients with SCH (Aleman & Hijman, 1999). Deficits in working memory (Silver et al., 2003) and declarative memory (Heinrichs & Zakzanis, 1998), slower processing speed (Dickinson et al., 2007) and impairments in executive functioning (Liu et al., 2011) are typical neurocognitive findings in adult SCH patients. A recent, longitudinal study by Dickerson and colleagues (2014) reported that there was no decline in cognitive functions during the 10-year follow-up period for middle-aged persons with SCH. In contrast a 10-year follow-up study by Stirling and colleagues (2003) concluded that visuo-spatial function may deteriorate over time but executive functions deficits do not deteriorate further.

There are deficits in attention (Frangou et al., 2007; McClellan et al., 2004), verbal memory (Frangou et al., 2007; Øie et al., 1999), visual memory (Øie et al., 1999) and executive functions (Kravariti et al., 2003) for EOS those are similar to those described
for AOS. Overall profiles in neurocognitive functions are said to be similar in EOS and AOS (Rhinewine et al., 2005). Longitudinal studies of EOS reveal deficits in most of the cognitive functions appear quite stable over the years (Frangou et al., 2007; Juuhl-Langseth et al., 2014). Immediate verbal memory and attention may show deterioration during the years, but speed of information processing may show an improvement suggesting aspects of normal brain-maturation in these patients (Frangou et al., 2007).

The opposite findings have also been reported. A longitudinal study over a period of 13 years compared patients with EOS, against ADHD and a control group (Øie et al., 2010). That study found deteriorations, in verbal memory, learning, attention and processing speeds the profile of which was unique to the SCH group. One explanation for this result was that the decline was specific for EOS due to the interaction between ongoing brain maturation during adolescence and disease-related mechanisms. It may also be secondary to neuroleptic treatment and/or to limited social stimulation.

1.8.2 Neurocognition in PDD

The neurocognitive deficits most often described for PDDs include deficits in weak central coherence and executive functions. Weak central coherence refers to processing bias that occurs as result of the subject focusing on details, specific features and local information instead of processing the global meaning (Frith, 1989). A person with a PDD often fails to see the “big-picture”: instead they focus only on details. Weak central coherence is also proposed to affect the ability to give global, contextually-appropriate answers to open-ended sentences (Happé, 1994) and to recognize facial emotions (Happé & Frith, 2006).

Executive functions refer to a wide range of mental skills, and can be described as the “ability to maintain an appropriate problem-solving set for the attainment of a future goal” (Pennington & Ozonoff, 1996). Deficits in flexibility, fluency and response selection/monitoring are especially common in PDDs (Happé et al., 2006; Kleinhans et al., 2005). Deficits in inhibition, planning and self-monitoring are also often reported (Robinson et al., 2009).

Visual processing, however, is often relatively intact (Ghaziuddin & Mountain-Kimchi, 2004; Joseph et al., 2009; Kaufman, 1994; Minshew et al., 1997; Samson et al., 2012; Williams et al., 2006). Specific difficulties in using vision among those with PDD have been reported, but contradictory results have also been published (Simmons et al.,
Minshew et al. (1997) studied neuropsychological functioning of 33 non-retarded adolescents and young adults with PDD. Those authors reported significant impairments of motor skills, complex language, complex memory and reasoning domains, but they also reported intact or superior performance for the attention, simple memory, simple language and visual-spatial domains. Williams and colleagues (2006) replicated the study with 56 non-retarded children with PDD. Both studies included matched control groups (Minshew et al., 1997; Williams et al., 2006). Results from both studies provided evidence that non-retarded PDD patients are characterized by selective impairment in higher-order abilities but had intact simpler basic abilities in these same domains.

### 1.8.3 Comparisons of neurocognition between SCH and PDD

Only a few comparison studies have focused on neurocognition in children and adolescent populations despite the many overlapping symptoms in SCH and PDDs. A study by Asarnow and colleagues (1987) compared cognitive functioning as measured by Wechsler Intelligence Scale for Children (WISC) between 23 autistic children (21 male and two female) with a mean age of 10.4 years (SD = 2.4) and 24 SCH children (17 male and 6 female) with mean age 10.1 years (SD = 1.8) with normal intelligence. Children with autism scored significantly lower on the Comprehension subtest than did children who had SCH, but children with SCH showed significantly lower scores on the Block Design, Object Assembly, Coding and Arithmetic subtests.

Schneider and Asarnow (1987) studied 15 children with PDD (14 male and 1 female), 11 children with SCH (8 male and 3 female) and 28 normal controls (22 male and 6 female), all participants had normal intelligence. Ages of the children varied between seven years 10 months and 14 years four months. They reported that the children with PDDs and those with SCH had similar problems in processing speed and executive functions. These authors also reported that PDD and SCH group performances in the Wechsler Coding subtest and visual search, as measured by Rey’s Tangled Line Test were poor for both groups. Neither group showed impairment in visuospatial functions. Wechsler Coding subtest and visual search and Rey’s Tangled Line Test, both require sustained attention and visuo-motor co-ordination. Children with PDDs showed significantly more impairment in verbal functioning than did those with SCH.
Bölte and colleagues (2002) used the WISC-III (Wechsler, 1991) and Wechsler Adult Intelligence Scale third edition (WAIS-III; Wechsler, 1997) to study adolescents with PDD or with SCH. The mean age was 16.8 years for the PDD group and 16.6 years (SD = 1.5) for the SCH group. Both groups consisted of 11 male and nine female individuals of whom 13 in both groups had IQ scores of over 70. There was no control group in this study. The patient groups showed no significant differences on any single Wechsler subscale, but the pattern of performance profiles seemed to differ between groups. For example, the PDD group showed peak performance for the Object Assembly, Similarities, and Information subtests, but had the lowest scores on the Picture Arrangement subtest, Digit Symbol and Comprehension. The SCH group on the other hand showed a more even pattern between the subtests, and scored highest on the Object Assembly and Digit Span subtests, and lowest on the Picture Arrangement and Digit Symbol (Coding) subtests. The largest differences between these two groups were in Comprehension and Similarities.

These comparisons show that there are differences in cognitive profiles between SCH and PDD. Findings suggest that children and adolescents with SCH may be relatively more impaired at visual processing than those with PDDs, whereas children and adolescents with PDDs may be relatively more impaired at higher order verbal processing. Adolescents with SCH may have more general neurocognitive difficulties, whereas adolescents with PDD have selective impairment of higher-order abilities.

1.9 Social cognition

Social cognition is an umbrella term for processes that make social interaction possible between individuals of the same species (Frith & Frith, 2007). Theory of mind (ToM) and emotional processing are functions that belonging to social cognition. Social perception and knowledge and attribution bias are related functions under the term social cognition (Green, 2008).

In study IV, we compared ToM and affect recognition components of social cognition that are quite widely studied among these patient groups.
1.9.1 Theory of Mind

The theory of mind (ToM), or mentalizing, is the ability of a person to predict and explain the behavior of other humans in terms of their mental states. It was first described by Premack and Woodruff (1978). ToM can be seen as a sum of many developmental skills that are essential to understand another’s mind. For example, understanding the causes of emotions, deception and understanding metaphor and sarcasm (Baron-Cohen, 1998). Joint attention, imitation, the ability to track a speaker’s intention during learning and decoding of words and pretend-play are also a part of the ToM system (Korkmaz, 2011).

ToM is a developmental skill that fully develops only in human beings (Korkmaz, 2011). A child whose development is normal begins simultaneously to take into account the real situation and the pretend version of the same situation at the age 18–24 months. Until three-years age a child normally learns to use semantic terms for mental states that include others (know, think, and pretend). A four-year old child understands that beliefs and desires are private and changeable and do not depend on an external state of reality changing. Normal children will pass the first-order ToM test at three to four years of age. Second-order tasks in which a person needs to understand what two people think sequentially can usually be passed by normal children at the age six-years.

1.9.2 Deficits in ToM in SCH

Frith (1994) posited that many clinical symptoms and signs such as delusions, auditory hallucinations and negative symptoms, observed in patients with SCH could be attributed to problems in ToM. There is currently no consensus on whether problems observed in social cognition are the result of neurodevelopmental impairment or neurodegenerative process in SCH however (Ozguven et al., 2010).

ToM problems are widely reported in SCH, such as in first-degree unaffected relatives of SCH patients (Bora & Pantelis, 2013), first-episode patients in the early stage of SCH (Bora & Pantelis, 2013; Koelkebeck et al., 2010), chronic patients, and also those patients in the remission phase of the illness (Bora et al., 2009; Sprong et al., 2007).
1.9.3 Deficits in ToM in PDD

Impairments in ToM were first related to autism by Baron-Cohen and colleagues (1985). They found out that 80% (16/20) of autistic children failed to predict correctly beliefs of others, whereas 85% (23/27) of normal children and 86% (12/14) of children with Down’s syndrome were able to do so. Deficits in ToM have been proposed to be a core deficit in PDD.

Both first-order and second-order ToM tasks can be easy for people with higher-functioning PDDs, whereas more advanced tasks tend to be problematical (Bowler, 1992; Ozonoff et al., 1991). It is argued that individuals with PDD may learn ToM skills explicitly, but not implicitly. Often social problems are more evident in real life, than in test situations. An individual with PDD has time to react in a test situation, but in real life situation quick responses are required and that causes problems in ToM testing (Frith, 2004).

1.9.4 Comparisons of ToM in SCH and PDD

Only a few studies have compared ToM performance of children and adolescents with SCH and PDD. A study by Pilowsky and colleagues (2000) compared the ToM performance of children and adolescents with HFA to the ToM performance of those with SCH. The study also found that 58% (7/12) of youngsters with autism and 67% (8/12) of those with SCH passed the “false belief task”, which was considered the most demanding one. Moreover, patients with SCH performed better at the deception task than those with autism, whereas no difference was found between SCH and PDD groups in other ToM tasks.

Of investigations on adults, the study by Lugnegård and others (2013) included 89 adult patients with SCH or AS and a non-clinical control group. Overall, the SCH group had similar problems in the ToM tests as the AS group. Adult patients with AS or with SCH performed poorly in ToM tests and also in other studies compared to healthy controls (Chung et al., 2014; Craig et al., 2004; Murphy, 2006). However, Ozguven and others (2010) reported that in general, adult patients with AS had worse ToM performance scores than patients with SCH. Their results showed that SCH patients had impaired second-order, but unimpaired first-order ToM performance. There is, however,
a wide range in the performance of AS patients as some performing better than others in
the ToM test (Murphy, 2006).

There is also considerable heterogeneity in the test methods used to assess ToM. All
previously mentioned studies used different assessment tools for ToM testing, some of
them used verbal tests only. There is currently no consensus on the optimum battery of
test for ToM, which may reflect the fact that the definition of ToM is quite broad.

1.9.5 Facial affect recognition

Facial affect recognition is the ability to recognize and discriminate between emotions
in the facial expressions of others (Ekman, 1972). This ability is important for
successful interaction with others and to participate actively in the social environment
(Morris et al., 2009). It is also vital for the development of the perceptual components
of ToM (Korkmaz, 2011). Furthermore, affect recognition can also be based on the
evaluation of gestures or vocalization.

1.9.6 Deficits in affect recognition in SCH

Impaired facial affect recognition is a prominent feature in SCH (Kohler et al., 2000;
Morris et al., 2009) and some have suggested that this deficit could be a trait marker,
since it also occurs in first-episode psychosis (Edwards et al., 2001). There are only a
few studies about affect recognition deficits in SCH children and adolescents in
existence. Both children and adults with SCH have showed deficits in affect recognition
compared to healthy controls (Habel et al., 2006; Seiferth et al., 2009).

1.9.7 Deficits in affect recognition in PDD

Deficits in facial affect recognition were investigated in retarded autistic children
(Hobson, 1986). Children with autism in that study had significant problems selecting
the appropriate facial expression to match gestures, vocalizations and emotional
contexts. Recently Wright et al. (2008) reported that emotion recognition may be
undisturbed in patients with higher functioning PDDs. A recent review article suggested
that mixed results in facial emotion recognition studies among PDDs could have
resulted from a compensatory mechanism such as verbal mediation or feature-based
learning, which individuals with PDD can use. Another explanation is that deficits in
facial emotion recognition in high-functioning individuals do emerge but only when
facial-emotion processing is ambiguous (Harms et al., 2010; Kuusikko et al., 2009). In their study Kuusikko et al. (2009) found that while in upper-facial basic emotion recognition the ASD group scored lower than the controls, the older ASD group performed better than the younger ASD group.

### 1.9.8 Comparisons of affect recognition in SCH and PDD

Children with autism exhibit significantly more problems in interpreting emotional meanings in speech than do those with SCH (Van Lancker et al., 1989). Another study (Bölte & Poustka, 2003) also explored differences in facial affect recognition between SCH and PDD. Again, adolescents diagnosed with autism performed significantly worse than did those with SCH.

Results of affect recognition in SCH and PDD patients are more consistent in adults and both groups seem to share some deficits. Thirty adult patients with diagnosed autism or SCH were studied (Sasson et al., 2007) and it was found that both clinical groups had more abnormalities in visual scanning in social situations compared to a control group (Sasson et al., 2007). In a large study of 80 adult male patients, those with SCH or HFA were compared to a control group (Couture, 2010). Both the SCH group and the HFA group had more problems in social cognition tasks compared to the controls, but the clinical groups did not differ from each other. Four different dimensions were used for the evaluation. Two dimensions measured emotion perception, one social judgment and one ToM. When the SCH group was divided into subgroups the SCH group with negative symptoms had more similarities in their performance with the AS group compared to the group with positive symptoms (Couture, 2010).

These findings suggest that emotion detection deficits could be part of the endophenotype of autism. It also seems that though social cognition in SCH is less impaired than in autism, it is not intact.
Although neurocognition and social cognition are separate domains of cognition, they are closely related (Sergi et al., 2007). Poor neurocognition usually predicts problems in social cognition, but it is also common for a person to have deficits in social cognition and also have intact neurocognition (Fanning, et al., 2012). However, facial emotion recognitions and expressions in addition to executive functions are essential for development of ToM (Korkmaz, 2011). Social cognition in SCH typically associate more strongly with poor community functioning, including problems in independent living and social or work functioning when compared to problems in neurocognition (Fett et al., 2011).

These two disorders seem to co-occur and share many common features, therefore we made a comprehensive study about development and what features these conditions share with each other and what features differ. We are not aware of any previous published studies on adolescents with SCH and comorbid PDD.
2 AIMS OF THE STUDY

2.1 The main aims of the thesis

This research investigated adolescent SCH patients and some of these patients had comorbid PDD. The main aim was to investigate the comorbidity of SCH and PDD and the overlap of clinical and developmental symptoms. The differences between neuropsychological profiles across selected domains of the SCH and PDD groups were also studied.

2.2 Specific aims of the studies

Study I assessed whether there was comorbid PDD in adolescent patients with SCH. The aim was to report those concurrent clinical features that are usually referred to as PDD among adolescents with SCH.

Study II evaluated catatonic features among adolescents with SCH and compared the nature and numbers of those features between adolescents suffering from SCH alone with those SCH patients with comorbid PDD. A comparison was also made between the profiles of catatonia-like features of SCH patients to those described earlier for persons with ASD without SCH.

Study III assessed the delays in developmental skills in adolescents who were suffering from SCH with or without comorbid PDD. Compared the ages of SCH patients with PDD with those of SCH alone when their respective parents/caregivers first became worried about their children’s’ development.

Study IV investigated neurocognition and social cognition skills (ToM and emotion recognition) in adolescent SCH patients with or without comorbid PDD and in adolescents with PDD only. Comparisons were made between all three groups.
3 PARTICIPANTS AND METHODS

3.1 Participants with SCH (Studies I-IV)

The data were collected from the Hospital District of Helsinki and Uusimaa, which is located in Southern Finland and comprises approximately 1.4 million inhabitants of whom ca. 82 500 were 13- to 17-year-old adolescents between the years 2009 and 2011. During the study period, the hospital district ran three rehabilitation units for adolescents with SCH. The study comprised a consecutive sample of patients (n = 18, 7 males, 11 females) and their families from all three rehabilitation units. The mean age of the participants at recruitment was 15.6 years, SD 1.4 years, (range 13–17 years, Studies I-III). The mean age of the participants was 16.2 years (SD 1.5 years, range 13.3–18.0 years) at the time the psychological tests (Study IV) were conducted. The diagnosis of SCH was based on an assessment according to the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL) for DSM-IV (Kaufman et al., 1997), and was performed by a clinical psychiatrist. Four patients had COS, whereas among the other 14, the onset of the disorder occurred at age 13 or later in life. Of the 18 participants, 17 scored ≥ 70 IQ (mean 93, SD 16) in a standard psychological assessment (WISC-III/WAIS-III; Wechsler, 1991; Wechsler, 1997) which was performed during or before the study period. All participants had a primary IQ > 70 based on life chart documents. Of the 18 SCH participants, birth records were available for 16, records from well-baby clinics for 15, and school health care reports for 17. One adolescent had suffered from epilepsy in early childhood, but was seizure-free and without antiepileptic medication during the study period. A non-contrast brain MRI was performed and evaluated by a clinical radiologist. The result was normal in all cases.

3.2 Participants with PDD only (in Study IV)

Fifteen adolescents with PDD only were recruited either from the Department of Child Neurology, Hospital for Children and Adolescents, Helsinki University Central Hospital (1 male, and 5 females), or the Department of Adolescent psychiatry, Tampere University Hospital (6 males and 3 females) between 2011 and 2013. They all had primary IQ > 70. The mean age at recruitment was 16.1 years (SD 1.6, range 13.3–
The Autism Diagnostic Interview–Revised (ADI-R; Lord et al., 1994; Rutter et al., 2003) or The Developmental, Dimensional and Diagnostic Interview (3di; Skuse et al., 2004) were used in clinical diagnostic assessment procedure. Exclusion criteria included a diagnosis of SCH and other severe psychiatric disorders. A psychiatrist and child neurologist specialized with neuropsychiatric disorders verified the diagnoses according to the DSM-IV (American Psychiatric Association, 1994). The patients with PDD only were age- (±6 months) and gender-matched with those with SCH at the time of psychological assessment.

3.3 The Diagnostic Interview for Social and Communication Disorders

The information from the Diagnostic Interview for Social and Communication Disorders (DISCO-11) was used in Studies I-III. Interviews with parents of all SCH patients were given. The DISCO version-11 is a semi-structured interview that was developed by Lorna Wing and Judith Gould in England (www.autism.org.uk) to be given to parents or to other primary caregivers (Wing, 2006). The interview takes two–three hours and it contains 387 questions about current skills, development of these skills and atypical behavior (e.g. repetitive stereotyped activities, emotions, maladaptive behavior and psychiatric disorders and forensic problems) during the lifespan of the primary caregivers’ charges. In the DISCO, the average ages when a normal child is expected to achieve developmental steps, have been adopted from the Vineland Adaptive Behavior Scales (Sparrow et al., 1984). The DISCO included a question about the child’s age the first time that the parents/caregivers became worried about their child’s development.

The DISCO is constructed for both clinical and research use to assess ASD in individuals of all ages and all levels of abilities. A computerized algorithm has been developed for assessing DISCO for research purposes. An algorithm is included for different diagnostic categories. We used ICD-10 criteria for assessing autism, AS, atypical autism onset of age and/or atypical symptoms for AS (WHO, 1992). ICD-10 algorithm diagnoses in DISCO are equivalent to those in DSM-IV. ICD-10 Childhood autism is equivalent to DSM-IV Autistic disorder, ICD-10 Asperger syndrome is
equivalent to DSM-IV Asperger’s disorder and ICD-10 Atypical autism is equivalent to DSM-IV PDD-NOS. DISCO has good inter-rater reliability (Wing et al., 2002) and high agreement has also been shown between DISCO and ADI-R classification (Nygren et al., 2009).

The interview is structured to collect information about the current situation (“current”) in addition to information about development and previous (“ever”) behavior. If a rating of recent onset of atypical behavior is made according to the manual it cannot be indicated. The reason is that some behaviors could have been present for some time in the past, which would lead to bias created by double counting as both “ever” and “current” indicate that the behavior is present in both situations. In the present study an aim was to compare behavior and skills in childhood with those in adolescence, because PDD is already clearly present in childhood, before the onset of puberty. For this reason we adapted Studies I-II by splitting information into childhood- (“ever”) and adolescence-sections (“current”). If the behavior was present before 10-years, it was scored “ever” and if the behavior was present at or after 10-years age it was scored “current”. Behavior disappearing after the age 10 was scored as “ever”. A similar adaptation was used by Hallerbäck et al. (2012), who scored earlier behaviors in childhood only as “ever” and current behavior as “current”.

Another adaptation of the DISCO-11 was made in Study II. In the original DISCO manual, the items, which are present are divided into moderate or marked according to their severity. However, in line with the study by Wing and Shah (2006), this was not done in Study II. Instead each catatonic item in Study II was defined as either absent or present. Moreover, the catatonic features in Study II were evaluated as the following: lifetime features, features existing before the age of 10 (=childhood catatonic features) and features existing at the age of 10 or later in life (=adolescence catatonic features).

The author (P.W.) was trained in the administration of the DISCO by the originators and she carried out all the interviews.
3.4 The Wechsler Intelligence Scale for Children -3rd version

The WISC-III is an individually administered intelligence test for children between the ages of 6 and 16 (Wechsler, 1991). The test includes verbal subtests: Information, Similarities, Arithmetic, Vocabulary, and Comprehension and nonverbal subtests: Picture Completion, Coding, Picture Arrangement, Block Design, and Object Assembly.

We used the following eight subtests of the test in Study IV: Information, Similarities, Arithmetic, Comprehension, Picture Completion, Coding B, Block Design and Object Assembly.

There were missing values for three participants with SCH: for one of these participants the Object Assembly subtest was missing, another participant was not assessed by the WISC-III, the third SCH participant was assessed by the Wechsler Adult Intelligent Scale -3rd version (WAIS-III; Wechsler, 1997) instead of the WISC-III and the fourth patient who had PDD only had missing data for the Comprehension subtest.

3.5 ToM and Affect recognition subtests in NEPSY-II

NEPSY-II (Korkman et al., 2008; Kemp & Korkman, 2010) is a comprehensive, co-normed, and multidomain neuropsychological battery designed for assessing neurocognitive abilities in 3-16 year-old children and adolescents. We used two subtests of the NEPSY-II for evaluating social cognition in Study IV: ToM and Affect recognition.

The ToM subtest consists of two parts: one with verbal items (max. score 17), and the other part with contextual items (max. score 8). Assessment of the verbal items requires the participant to either hear verbal descriptions or see pictorial descriptions of social situations and then answer questions about those situations. The participants’ understanding of the point of view of the index character in addition to figurative language were evaluated. In contextual items, the participant sees pictures that depicts a social context and then selects a photo that shows the appropriate affect for the index character. The participant must recognize emotions linked to social situations and cues.
The affect recognition test assesses the person’s ability to recognize emotional expression (happiness, sadness, anger, fear, disgust, and a neutral emotional state) in photographs of children’s faces (max. score 45). Participants must match and recognize faces expressing the same feeling. One participant with SCH was unable to complete this test.

3.6 Data Analysis

Study I data was descriptive and was analyzed manually. The data in Studies II-IV were analyzed using IBM SPSS statistics for Macintosh, version 21.0. (Argyrous, 2011; IBM Corp., 2012).

3.6.1 Study II

The Mann-Whitney U-test, Likelihood ratio chi-square test, and the Fisher’s exact test were used to compare the groups. The Wilcoxon signed rank test for within group comparisons was used. The findings were considered significant when p-values < 0.05 were obtained. The magnitude of the effect size (phi coefficient) was interpreted as follows: 0 to 0.10, negligible association; 0.10 to 0.20, weak association; 0.20 to 0.40, moderate association; 0.40 to 0.60, relatively strong association; 0.60 to 0.80, strong association; and 0.80 to 1.00, very strong association (Rea & Parker, 1992).

3.6.2 Study III

Fisher’s exact test, the Likelihood Chi Square test, Independent t-test and Mann Whitney U-test were used to compare the groups. The findings were considered significant when p < 0.05. Bonferroni correction was not used to control for type I errors due to the multiple comparisons, as it has been criticized for dramatically increasing the risk of type II errors (Moran, 2003; Nakagawa, 2004; Perneger, 1998). Instead, effect sizes are reported. The magnitude of the effect size was interpreted as follows: 0 to under 0.10, negligible association; 0.10 to under 0.20, weak association; 0.20 to under 0.40, moderate association; 0.40 to under 0.60, relatively strong association; 0.60 to under 0.80, strong association; and 0.80 to 1.00, very strong association (Rea & Parker, 1992).
3.6.3 Study IV

The published norms of the tests extend only up to the age of 16 years, thus all comparisons involved raw scores. Data was analyzed using permutational (nonparametric) MANCOVA (eg. Anderson, 2001) with gender and age as covariates. The results of permutational MANCOVA were further examined using individual permutational ANCOVA as proposed by Manly (2007). A correction for multiple comparisons was done using False Discovery Rate (FDR; Benjamini & Hochberg, 1995). The post-hoc tests were carried out by doing all possible pairwise comparisons between groups using independent samples t-tests with FDR correction. The test statistics of permutation tests are calculated precisely as standard parametric tests but the p-values are calculated based on sample-specific permutation distribution of that statistic which doesn’t require any distributional assumptions. All permutational analyses were analyzed using R version 3.0.2 statistical environment (R Core Team, 2013), other analyses using IBM SPSS version 21.0 (mac) (Argyrous, 2011). The NEPSY-II raw scores were analyzed using ANCOVA only because MANOVA is most powerful when the variables correlate with each other. In our sample, the NEPSY-II raw scores showed no significant correlation with each other. All correlations (Pearson) remained below 0.18. For all comparisons, effect sizes were calculated using partial eta squared where values around 0.02 are considered small, values around 0.13 are considered medium and values around 0.26 are considered large (Cohen, 1992).

Differences in age and IQ between the three groups were tested with Kruskal-Wallis and the difference in gender with Chi-square test. The norms used in WISC were not age appropriate in all cases (norms in WISC only extend up to 16), but as the age in the groups was similar, the group comparison should be valid.
3.7 Ethics

All SCH participants and their parents/guardians in Studies I-IV provided their written informed consent after receiving verbal and written information about the respective study. Each study plan was evaluated by the ethics committee of the Helsinki and Uusimaa Hospital Districts. The permissions to conduct the studies were granted by the pertinent institutional authorities of the Helsinki University Central Hospital and Hyvinkää Hospital Area.

Tampere University Hospital also granted their permission to conduct the study with reference to patients with PDD only in Study IV who lived in the Tampere area.
4 RESULTS

The summary of the main results are presented by study. More detailed results are available in the original published articles.

4.1 Study I: SCH and comorbid PDD in adolescents and current features in SCH that resembles symptoms in AS

Forty-four percent (n = 8) of adolescents who suffered from SCH fulfilled the diagnosis of at least some PDDs in childhood. Table 5 shows that two of them had childhood autism (F84.0), three had atypical autism (F84.1) in childhood and three fulfilled the criteria for AS (F84.5). Of the three subjects that had atypical autism, two (12, 14) had the onset after three years of age and all three had atypical symptomatology.

Table 5. Retrospective childhood PDD diagnosis of adolescents with SCH.

<table>
<thead>
<tr>
<th>Subject number</th>
<th>Communication</th>
<th>Reciprocal social interaction</th>
<th>Restricted, stereotyped, repetitive behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Childhood</td>
<td>Adolescence</td>
<td>Childhood</td>
</tr>
<tr>
<td>F84.0 Childhood autism</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>F84.1 Atypical autism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>12</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F84.5 Asperger's disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>No PDD in childhood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>18</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>
None of the three subjects who fulfilled the diagnostic criteria for AS had been diagnosed in childhood, although in one case there was a suspicion of PDD at the age of 10. One patient with childhood autism had got the PDD-diagnosis before the onset of psychotic symptoms, whereas the other patient was diagnosed with selective mutism at the age of six. The three subjects with atypical autism did not have PDD-diagnosis in childhood.

Article I, Table 1 shows that 10 out of 18 patients fulfilled the required symptom criteria for AS after 10 years of age, whereas only two of them fulfilled the entire criteria for AS of origins in early childhood. One patient had AS in childhood and PDD that was unspecified after 10 years of age. Six of those patients who did not have any PDD in childhood fulfilled the AS criteria in adulthood. All SCH subjects in adolescence had one or more of the core symptoms of PDD. All participants had treatment with antipsychotic medicines, which in most cases involved the modern serotonin–dopamine antagonists (e.g. risperidone or clozapine). The mean duration of antipsychotic medication was 1.2 years (SD 1.2, range 0–5). There were four adolescents who had the onset of psychotic symptoms of SCH before or at 12 years of age. One of them had childhood autism, one had AS, one had atypical autism and the fourth adolescent had no comorbid PDD. More detailed background information is presented in Table 6.
Table 6. Background information on the adolescents with SCH with and without comorbid PDD.

<table>
<thead>
<tr>
<th>Subject number</th>
<th>F84.0 Childhood autism</th>
<th>F84.1 Atypical autism</th>
<th>F84.5 Asperger's disorder</th>
<th>No PDD in childhood</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>2</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>8</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>12</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>9</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Started school in normal class x x x x x x x x x x x x x x x
Received special education in childhood x x x x
Received speech therapy x x x x
Development of independent sitting was delayed x x x x x x x x
Learned walk late x
Had poor coordination in childhood x x x x
Had poor coordination in adolescence x x x x x x x x

4.2 Study II: Catatonic features among those adolescents with SCH with or without comorbid PDD

All 18 adolescents with SCH had showed some catatonic features in their lifetimes (see Table 7). Fourteen of them (77.8%) had already manifested these features before the age of 10. The most prevalent lifetime catatonic features were “lacks facial expression”, “lack of cooperation”, “odd intonation”, and “poor eye contact” followed by “blank look in eyes” and “destructive behavior”.

56
Table 7. The 28 catatonic features evaluated in childhood, adolescents and lifetime in patients with SCH with or without comorbid PDD.

<table>
<thead>
<tr>
<th>Movement</th>
<th>Speech and vocalization</th>
<th>Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odd gait</td>
<td>Immediate echolalia</td>
<td>Poor eye contact</td>
</tr>
<tr>
<td>Poor coordination</td>
<td>Delayed echolalia</td>
<td>Shouts for no reason</td>
</tr>
<tr>
<td>Odd hand postures</td>
<td>Odd intonation</td>
<td>Aggressive for no reason</td>
</tr>
<tr>
<td>Runs in circles</td>
<td>Shrieks for no reason</td>
<td>Lack of cooperation</td>
</tr>
<tr>
<td>Rocks while sitting</td>
<td>Laughs for no reason</td>
<td>Destructive</td>
</tr>
<tr>
<td>Complex body movements</td>
<td></td>
<td>Strips in public</td>
</tr>
<tr>
<td>Walks on tiptoe</td>
<td></td>
<td>Inappropriate personal habits</td>
</tr>
<tr>
<td>Grimaces</td>
<td></td>
<td>Hyperactive</td>
</tr>
<tr>
<td>Lacks facial expression</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The number of catatonic features increased significantly after the transition from childhood to adolescence (in childhood: mean 4.1, SD 4.4, median 3, range 0–14, vs. in adolescence: mean 8.9, SD 3.1, median 9, range 4–15; Wilcoxon rank signed test, z = -3.249, p = 0.001).

The childhood, adolescence and lifetime prevalence of 28 catatonic features are also presented in Article II Table 1.

Table 8. Numbers and total numbers of different catatonic features in childhood, adolescence and lifetime in SCH patients with or without comorbid PDD.

<table>
<thead>
<tr>
<th>Number of catatonic features/person</th>
<th>Schizophrenia only</th>
<th>Schizophrenia and comorbid PDD</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>SD</td>
<td>range</td>
</tr>
<tr>
<td>In childhood</td>
<td>1.50</td>
<td>1.72</td>
<td>0–5</td>
</tr>
<tr>
<td>In adolescence</td>
<td>8.50</td>
<td>2.95</td>
<td>4–13</td>
</tr>
<tr>
<td>Lifetime</td>
<td>8.80</td>
<td>2.94</td>
<td>4–14</td>
</tr>
</tbody>
</table>

Amount of different catatonic features in whole group

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenia only</th>
<th>Schizophrenia and comorbid PDD</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>In childhood</td>
<td>11</td>
<td>22</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>In adolescence</td>
<td>19</td>
<td>22</td>
<td>p=0.04</td>
</tr>
<tr>
<td>Lifetime</td>
<td>21</td>
<td>24</td>
<td>NS</td>
</tr>
</tbody>
</table>
As seen in Table 8 the numbers of catatonic features in childhood were significantly higher among the patients with a comorbid PDD compared to those without one. Nevertheless, during adolescence and the number of catatonic features throughout the whole lifetime, there was no significant difference between the two groups. The numbers of catatonic features increased significantly among those SCH adolescents without a comorbid PDD during the transition from childhood to adolescence, but not among those with a comorbid PDD.

Of the 28 catatonic features studied, those adolescents with SCH and a comorbid PDD had significantly more total features in childhood and in adolescence than those adolescents with SCH only. There was no significant difference between these two groups for the total number of lifetime features.

Comparisons of the frequencies of 28 catatonic features between these two groups in childhood show five specific features seen in Article II Table 2: “lacks facial expression”, “delayed echolalia”, “odd intonation”, “destructive” and “strips in public” occurred significantly more often among the patients with a comorbid PDD. In adolescence there was only one catatonic feature, “grimaces”, occurred significantly more often among the patients with a comorbid PDD.

4.3 Study III: Delays in developmental skills among those adolescents with SCH with and without comorbid PDD

Delays in developmental skills of adolescent SCH patients were studied. In this study 43 developmental items taken from 17 developmental areas (see Table 9) from DISCO-11 were analyzed. All adolescents with SCH exhibited some developmental delays. The median number of skills with a delay was three for all patients. The mean age of the adolescents when, for the first time, their parents or guardians became worried that something might be wrong with their child’s development was 99.7 months (8.3 years) (SD 65.1, range 12–204).
Table 9. 17 developmental areas studied in adolescents with SCH with or without comorbid PDD.

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenia with comorbid PDD</th>
<th>Schizophrenia only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>SD</td>
</tr>
<tr>
<td>The mean age (months) of the adolescent when parents became worried</td>
<td>129.6</td>
<td>61.3</td>
</tr>
<tr>
<td>The number of developmental skills delayed</td>
<td>2.3</td>
<td>1.5</td>
</tr>
</tbody>
</table>

All the delays in developmental skills are presented in Article III Table 1. The most frequent delays were in “reading their first book”, “independent sitting”, “riding a tricycle”, “cooperative play”, and “role play with their age peers”, followed by “riding a bicycle”, “tying their shoelaces”, “expressing meaningful words”, “spontaneously joining in with their age peers”, “parallel play and drawing recognizable objects or persons”.

Table 10. The mean age of SCH children when their parents first became worried about children’s development and the individual numbers and totals of delayed developmental skills of adolescents with SCH with and without comorbid PDD.

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenia with comorbid PDD</th>
<th>Schizophrenia only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>SD</td>
</tr>
<tr>
<td>Total amount of specific skills delayed</td>
<td>12</td>
<td>42</td>
</tr>
</tbody>
</table>

59
Parents of SCH adolescents with no comorbiditidy reported they became worried for the first time about their child’s development at a significantly later age than parents of adolescents with comorbid PDD (Table 10).

Adolescents without comorbidity had significantly fewer delays in specific developmental skills than adolescents with comorbidity. Table 1 in Article III reveals that the comorbid group had delays significantly more often for three specific skills, which were: cooperative play, role play with their age peers and reading their first book, than adolescents without comorbidity. The effect sizes showed either relatively strong or strong associations.

As seen in Table 10 adolescents without comorbidity exhibited significantly lower total amounts of different developmental delays than adolescents with comorbid PDD.

### 4.4 Study IV: Neurocognition and social cognition among those adolescents with SCH, a PDD and both disorders

The SCH group without comorbidity performed significantly worse in neurocognitive subtests in Picture Completion than did the SCH group with comorbid PDD and adolescents with PDD only. The SCH group without comorbidity performed significantly worse at Object Assembly than did the group with PDD only. The performance of the SCH group without comorbidity and the SCH group with comorbid PDD group was marginally poorer at Coding B testing than that of the group with PDD only. Other pairwise comparisons were non-significant (see Table 11).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Schizophrenia</th>
<th>Schizophrenia + PDD</th>
<th>PDD</th>
<th>F</th>
<th>p</th>
<th>p-values (fdr)</th>
<th>partial η²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurocognition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information</td>
<td>20.43 (1.45)</td>
<td>21.03 (1.59)</td>
<td>21.78 (1.03)</td>
<td></td>
<td></td>
<td>F(2,24) = 6.52</td>
<td>0.005</td>
</tr>
<tr>
<td>Similarities</td>
<td>22.08 (1.53)</td>
<td>20.13 (1.68)</td>
<td>23.23 (1.09)</td>
<td></td>
<td></td>
<td>F(2,24) = 6.52</td>
<td>0.005</td>
</tr>
<tr>
<td>Arithmetics</td>
<td>20.99 (1.08)</td>
<td>17.76 (1.19)</td>
<td>20.03 (0.77)</td>
<td></td>
<td></td>
<td>F(2,24) = 6.52</td>
<td>0.005</td>
</tr>
<tr>
<td>Comprehension</td>
<td>24.75 (1.73)</td>
<td>22.39 (1.89)</td>
<td>23.55 (1.23)</td>
<td></td>
<td></td>
<td>F(2,24) = 6.52</td>
<td>0.005</td>
</tr>
<tr>
<td>Picture Completion</td>
<td>19.15 (0.99)</td>
<td>23.86 (1.09)</td>
<td>23.06 (0.71)</td>
<td></td>
<td></td>
<td>F(2,24) = 6.52</td>
<td>0.005</td>
</tr>
<tr>
<td>Coding B</td>
<td>49.61 (5.42)</td>
<td>45.72 (5.94)</td>
<td>63.12 (3.86)</td>
<td></td>
<td></td>
<td>F(2,24) = 6.52</td>
<td>0.005</td>
</tr>
<tr>
<td>Block Design</td>
<td>47.21 (3.35)</td>
<td>49.97 (3.68)</td>
<td>54.45 (2.39)</td>
<td></td>
<td></td>
<td>F(2,24) = 6.52</td>
<td>0.005</td>
</tr>
<tr>
<td>Object Assembly</td>
<td>26.19 (2.12)</td>
<td>32.74 (2.33)</td>
<td>34.26 (1.51)</td>
<td></td>
<td></td>
<td>F(2,24) = 6.52</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Table 11. WISC-III subtests' raw scores (mean, SD) and the differences in scores between the three groups controlling for age and gender.
There were significant differences in the NEPSY-II ToM verbal test results of the social cognition subtests (see Figure 1). The SCH group without comorbidity performed significantly worse than did the group with PDD only. The groups did not differ for the other two tests that measured social cognition.

![Figure 1. Mean T-scores (±SEM) on social cognition tasks of 15 adolescents with PDD only (PDD), 8 with SCH and a comorbid PDD (SCH + PDD), and 9 adolescents with SCH (SCH).](image)

* p< 0.05

SEM = standard error of mean
5 DISCUSSION

The purpose of this research was to study adolescent patients with SCH. The primary aim was to assess possible comorbidity of SCH with PDD. Eight adolescents out of a total of 18 (44%) patients with SCH fulfilled the diagnostic criteria for a comorbidity of some of the PDDs in childhood in our sample. In addition, all 18 SCH patients had one or more symptoms of PDDs in adolescence. These principal results are in line with the previous findings, which show that these disorders can occur together and they also share similar symptoms.

A secondary aim was to compare the nature and the occurrence of delays in developmental skills and catatonic features among two groups. The two groups in this study were adolescents with SCH and comorbid PDD and adolescents with SCH only. We also compared neurocognition and social cognition between three groups of adolescents, namely: those with SCH with and without comorbid PDD and adolescents with PDD only.

Some evidence was found that suggest that those SCH adolescents with comorbid PDD may have the following characteristics: earlier onset of symptoms, more numerous and larger variety of catatonic features, more delays in development skills and different profiles in their neurocognitive abilities and disabilities compared to SCH adolescents without comorbidity. We are not aware of published studies in which developmental skills, catatonic features or neurocognition and social cognition have been compared between these patient groups.

5.1 Comorbidity of SCH and PDD among adolescents

Forty four percent (8/18) of adolescents with SCH in Study I had a diagnosis of PDD in childhood when assessed retrospectively. This result is in line with previous findings for COS in which 25–50% of SCH patients were found to have PDD preceding the onset of SCH (Hallerbäck et al., 2012; Rapoport et al., 2009; Sporn et al., 2004). Table 2 of Article I shows that two SCH patients had typical AS which had originated in early childhood. One other SCH patient suffered from AS, which had developed into an unspecified PDD because the diagnostic criteria for reciprocal social interaction were no
longer met for that patient after 10 years of age. Two patients had childhood autism and three other patients had atypical autism in childhood. Children with autistic disorder can also have normal IQ scores (Fernell & Gillberg, 2010). In our sample all adolescents had primary IQs of over 70. The reason why two adolescents fulfilled the criterion for childhood autism was the delay in their language development. Four adolescents experienced the onset of psychotic symptoms before or at 12 years of age. One of these four had childhood autism, one had AS and one had atypical autism and the fourth did not have comorbid PDD.

However, the correct diagnosis of PDD in childhood was not obtained for most of the participants in Study I before the onset of psychotic symptoms and the diagnosis of SCH in adolescence. Most of these patients had been examined for developmental problems or had received special education in childhood, but they had not received a comprehensive assessment for comorbidities. None of the three subjects who fulfilled the diagnostic criteria for AS had got the diagnosis in childhood, although in one case there was a suspicion of PDD at the age of 10. Often children with AS are not diagnosed until 11 years or sometimes even later (Cederlund & Gillberg, 2004; Frith, 2004; Howlin & Asgharian, 1999). More education is clearly needed for pediatric and child psychiatric services to be able to make an earlier diagnosis of PDD in children.

It has been reported by other studies that COS patients with PDD do not differ from SCH-only groups with respect to age of onset of psychotic symptoms, IQ, level of functioning or other demographic parameters (Rapoport et al., 2009; Sporn et al., 2004). Some children may adapt quite well to their deficits caused by PDD but may develop florid psychotic symptoms during adolescence (Gillberg et al., 1986). Sometimes the symptoms of PDD, especially among those of high-functioning patients, are difficult to notice because the patients manage to compensate for their deficits and seem to manage quite well. Sometimes the existence of AS is hidden because of a good environmental support (Frith, 2004). The result showed that ASD was correctly diagnosed in only about 60% of school-aged children who “really” had ASD in a population study of children of five to nine years of age that was conducted in the UK (Baron-Cohen et al., 2009). The prognosis for EOS is often poor (Clemmensen et al., 2012; Hallerbäck et al., 2012; Rapoport et al., 2009) and PDDs tend to be lifelong conditions, which in the long run facilitate adverse impacts of comorbidities on global functioning. Therefore, it is
important to pay attention to both diagnoses when planning treatment for these adolescents.

At present it seems that although patients with SCH often have PDD in childhood, the development of SCH in subjects with PDD is quite rare. Nosological confusion and possible referral bias generate conflicting evidence regarding the frequency of SCH in patients with PDD (Skokauskas & Gallagher, 2010). Reports show that 0–3% of adult patients with PDD have comorbid SCH (Abdallah et al., 2011; Hutton et al., 2008; Mattila et al., 2010; Stahlberg et al., 2004). Even Hans Asperger had mentioned in his classic study that among his 200 ASD patients, only one developed comorbid SCH (Asperger, 1944). There is also the possibility that patients with PDD can be mistakenly diagnosed with SCH. For example, the symptoms of depression among higher-functioning PDD children may especially resemble psychotic symptoms (Ghaziuddin et al., 1995; Sullivan et al., 2013). It is known that young adults with AS are at high risk for depression and anxiety disorders (Lugnegård et al., 2011).

There is also a risk of making a diagnosis of developmental disorder based only on current symptoms. More than half 56% (10/18) of the adolescents with SCH in Study I showed current symptoms that were consistent with AS. However, only three of them had AS in childhood. Nowadays, documentaries and other programs about AS have been widely aired by the media and these have raised public awareness about the condition. Therefore, psychiatrists and psychologists treating and assessing adolescents frequently meet patients and their families who report symptoms that resemble those of AS. In such cases, a wide diagnostic assessment including detailed developmental anamnesis in addition to structured psychiatric interviews combined with sound clinical judgments are needed to avoid a false positive diagnosis of AS instead of other conditions such as SCH.
It has been proposed that Multiple Complex Developmental Disorder (MCDD) forms a bridge between PDD and SCH (Rapoport et al., 2009). MCDD is described by severe early onset deficits in social relationships, thought disorder and affect regulation. It is characterized as a subtype of PDD-NOS (Sprong et al., 2008) or a distinct syndrome different from PDD (De Bruin et al., 2007). Although the structure of DISCO-interview does not allow for direct questions to discern symptoms between those described in MCDD, our findings of PDD and SCH do suggest a resemblance to these described in MCDD.

5.2 Similarities and differences in symptoms of SCH and PDD

PDDs share a core triad of abnormalities: (1) qualitative impairments in reciprocal social interactions, (2) qualitative impairments in verbal and non-verbal communication and (3) restricted social imagination with repetitive and stereotyped patterns of interests and behavior (Lugnegård et al., 2011). All 18 patients with SCH had one or more symptoms of PDDs in adolescence. As many as 16 out of 18 patients (89%) had qualitative abnormality in reciprocal social interaction during adolescence, which was most often expressed in a failure to develop peer relationships and a lack of shared enjoyment. Moreover, 16 out of 18 patients in adolescence had qualitative impairments in communication. An especially prevalent impairment was the relative failure to initiate or sustain reciprocal conversation followed by stereotyped, repetitive or idiosyncratic language in addition to abnormal content of speech and repetitive themes. All these features are common to both PDD and SCH (Ghaziuddin, 2005). Fourteen out of 18 adolescents had restrictive, repetitive and stereotyped patterns of behavior, interests or activities. This included the need for perfection and items such as “arranging objects”, “eats only few foods”, “amasses facts”, and/or “watches the same videos”. Many of the adolescents had these repetitive activities especially at the onset of treatment in hospital although only two of them were diagnosed with obsessive–compulsive disorder. Thus, they might have indicated either the schizophrenic process or in other cases, the PDD trait. According to a recent study, however, adults with AS and adults with schizophrenic psychosis reported higher levels of autistic traits than controls in a self-report questionnaire (Lugnegård et al., 2014). On the other hand, the
features of autism are also quite common in the general population (Lugnegård et al., 2014).

There is a clear overlap between the symptoms of PDD and the negative symptoms of SCH. Many subjects with autism have poor social relatedness, anhedonia, flat or constricted affect or the ability to show emotions, poor use of gestures and diminished eye contact, alogia or poor speech, and the presence of stereotypic behaviors and mannerisms (Ghaziuddin, 2005). There is no clear consensus about the qualitative nature of single symptoms that might differentiate schizophrenic symptoms from those characteristic of PDD (Hallerbäck et al., 2012; Raja & Azzoni, 2009; Raja & Azzoni, 2010).

Positive symptoms seen in SCH are not typical for PDD. In his original paper on “Autistic psychopathy in childhood” in 1944 Asperger noted: “While the schizophrenic patient seems to show progressive loss of contact, the children we are discussing lack contact from the start”, and in comments on differential diagnosis: “against this diagnosis (SCH) speaks the fact that there is no sign of progressive deterioration, no characteristic acute onset of alarming florid symptoms (severe anxiety and hallucinations), nor there are any delusions” (Asperger, 1944). These guidelines seem to be valid even nowadays.

5.3 Motor problems as a side effects of the medical treatment

Motor clumsiness is often present in AS according to the ICD-10 classification, although it is not included in the actual diagnostic criteria (WHO, 1992). Two out of three subjects with AS in our sample presented this feature in childhood. Of the SCH adolescents four presented clumsiness in childhood and it continued into adolescence. Three of them also belonged to the PDD comorbidity group. An additional five patients first started experiencing clumsiness or problems with motor control upon entering adolescence. None of these patients had PDD in childhood. This clearly happened for three of these five SCH only patients after the administration of antipsychotic medication, whereas in other two the potential temporal connection with medication could not be verified in patient charts. Moreover, many patients had been prescribed several antipsychotic medications, which were often used in combination with each
other or with some other classes of psychotropic medications. The overall duration of antipsychotic medication treatment was quite short (mean 1.2 years) however. According to some preliminary findings (Raja & Azzoni, 2010), patients with comorbid PDD and SCH develop motor side effects of antipsychotic medicines more frequently than patients affected by SCH only. Another group of authors had previously reported a high prevalence of spontaneous acathisia in AS-adults without a history of antipsychotic medication (Tuisku et al., 2004), which had possibly rendered them vulnerable to the motor functioning impairment side effects of dopamine antagonists.

In some case reports of adults with both AS and SCH (Raja & Azzoni, 2009), antipsychotic medication improved psychotic symptoms, but contrary to what is generally observed in SCH, global functioning did not change significantly. It has been long known that the core symptoms of PDD-patients respond poorly to medication (Ghaziuddin, 2005).

The DISCO is designed primarily for the detection of qualitative abnormalities in development. Therefore, it is not an optimal tool for the assessment of side effects of medications, e.g. increase of acathisia or worsening of motor functions during treatment. An adequate follow-up of adolescents in our sample is required to see which symptoms are best ameliorated in EOS with or without PDD.

5.4 Changes in diagnostic classifications

There are no restrictions for the comorbidity of Autism spectrum disorder and SCH in DSM-5 (American Psychiatric Association, 2013). Earlier diagnostic classifications used varying approaches to dealing with this comorbidity. The diagnostic criteria for SCH in DSM-IV-TR-classification (American Psychiatric Association, 2000) states that “if there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of SCH is made only if prominent delusions or hallucinations are also present for at least a month”. Raja and Azzoni (2010) pointed out that the DSM-IV-TR implicitly assumes that a diagnostic criteria for SCH other than delusions or hallucinations, may be already met by patients with AS. Similarly, there is no restriction for comorbidity of SCH in diagnostic criteria for autistic disorder in DSM-IV. AS criterion “F” states that “criteria are not met for another specific Pervasive
Developmental Disorder or Schizophrenia”. However, a passage in the text states “the diagnoses of Asperger’s disorder and Schizophrenia may coexist if the onset of the Asperger’s disorder clearly preceded the onset of Schizophrenia”.

A meta-analysis of 14 studies on how the DSM-5 impacts upon autism diagnosis, found that DSM-5 will probably decrease the number of individuals diagnosed with PDD particularly the PDD-NOS subgroup (Kulage et al., 2014). However, no significant decrease under DSM-5 was expected for individuals with Autism spectrum disorder compared to those who formerly met the diagnosis for AS according the DSM-IV-TR criteria. There is also a new diagnosis in DSM-5, 315.39 Social (Pragmatic) Communication Disorder, which differs from Autism spectrum disorder with respect to the following: a lack of restricted/repetitive patterns of behavior, interest, and activities during the early development. Some patients who would earlier have been diagnosed with PDD-NOS may now fulfill the diagnostic criteria for Social (Pragmatic) Communication Disorder.

There is no statement about comorbid PDD in the ICD-10 criteria (WHO, 1992) for SCH. However, it is mentioned in the criteria for childhood autism and AS that the clinical picture is not attributable to SCH.

There have been age limits in place for early language development for PDDs. The requirement for AS is that single words are used by two years of age and communicative phrases by the age of three years. The use of these age limits as cut-off points have been criticized, because these guidelines do not necessarily mean that language acquisition is typical. If communicative phrases are used by three years of age it does not necessarily mean that language understanding is good (Frith, 2004). These age requirements are not stipulated in the diagnostic criteria for Autism spectrum disorder in DSM-5.

In the Study I, the PDD diagnosis was made using ICD-10 classification, which currently is the standard classification used in Finland. A new version, ICD-11, is expected to be published in the near future, however. As the ICD-classification has always been very similar to the DSM-classification it is likely that major revisions expected in the version ICD-11 concerning the classification of PDD will be in line with DSM-5 descriptions.
5.5 Catatonic features

All 18 adolescents with SCH in Study II presented many lifetime catatonic features. This finding is in line with those of previous studies (Green et al., 1992; Thakur et al., 2003), where children and adolescents with schizophrenic and psychotic disorders showed signs of catatonia. Catatonic features in childhood we found in our sample were more prevalent among those adolescent SCH patients that had a comorbid PDD than those with SCH alone. The difference between these two groups however was no longer apparent in adolescence.

Catatonia and SCH had a common history that reached back to Kraepelins description from 1893 to recent years. However, from 1970 onwards SCH and PDD have been regarded as different conditions and catatonia remained a feature of SCH but not of PDD. Questions about the connection between PDD and catatonia have emerged however. Recently, DSM-5 has distinguished catatonia from SCH and regards catatonia as a more diverse entity. The classification of catatonia in DSM-5 can now be associated either with another mental disorder that emerges as part another medical condition, or remain unspecific (American Psychiatric Association, 2013). Both the duration and the number of symptoms required for diagnosis varied in earlier classifications of catatonia. Several different rating scales for catatonia exist, validated in different patient populations and with different items included (Sienaert et al., 2011).

In the Study II we chose 28 specific catatonic items from the DISCO-interview on the base of earlier study by Wing and Shah (2006). In their study Wing and Shah (2006) studied catatonia-like features in 200 children and adults with ASD. Those authors chose these items on the bases of clinical similarities between catatonia-like behavior and the unusual patterns of movement, speech, and behavior found in persons with ASD. These features are typically present in early childhood and they have a tendency to become less marked with increasing age, especially in more able persons with ASD (Wing & Shah, 2006). The number of catatonic features in our Study (II) did not significantly change in transition from childhood to adolescence among the SCH patients with a comorbid PDD. However, we found the number of catatonic features increased significantly in the transition from childhood to adolescence among those SCH adolescents without comorbid PDD. In the future, it would be interesting to study whether this difference reflects the onset and impact of the SCH process, although other
factors, such as antipsychotic medication, may also have contributed to this result.

More detailed analysis revealed that during childhood, five specific catatonic items occurred with a higher prevalence in SCH patients with a comorbid PDD than those without comorbidity. The five items were the following: “lacks facial expression”, “delayed echolalia”, “odd intonation”, “destructive behavior” and “strips in public”. However, the items “lacks facial expression” and “stripping in public” can be regarded as qualitative impairments in reciprocal social interactions, whereas “delayed echolalia” and “odd intonation” can be regarded as qualitative impairments of verbal and non-verbal communication.

This finding leads, at least partially, to a circular argument. “Lacks facial expression” and “stripping in public” can be regarded as qualitative impairments in reciprocal social interactions and “delayed echolalia” and “odd intonation” as qualitative impairments of verbal and non-verbal communication. Patients with PDDs also exhibit repetitive and stereotyped patterns of behavior, and when those are prevented the patient may get very anxious and sometimes even destructive. Wing and Shah (2006) suggested there is an overlap between catatonic features and the core symptoms of PDDs. Some risk factors have been suggested for catatonia in PDD. Stressful life events often precede catatonic symptoms in PDD (Hare & Malone, 2004) and those individuals who have impaired language and passivity in social interaction are more likely to have catatonic features (Wing & Shah, 2000). It has been suggested that the key issue in diagnosing catatonia in autism is the emergence of the “new” symptoms or a “change” in the type and pattern of premorbid functioning (Ghaziuddin et al., 2005).

More than three-quarters of all our SCH adolescents had four catatonic features in common during their lifetime: “lacks facial expression”, “odd intonation”, “poor eye contact” and “lack of cooperation”, but none of them exhibited any features from the “visual fascination” subgroup. Wing and Shah (2006) reported that more than three-quarters of their patients with ASD shared also these same four catatonic features plus the feature called “delayed echolalia”. Those authors also reported that the frequencies of features in the “visual fascination” subgroup were very low. Given the fact that the authors had a sample of 200 ASD persons of whom only 72 individuals had IQs in the average or superior range, it is interesting to note this overlap between their and our results. In case studies, those PDD patients with higher intelligence manifested fewer
catatonic features (Shorter & Wachtel, 2013). However Wing & Shah (2000) reported that there were no significant differences between those PDD patients who showed catatonic symptoms and a control group for age, IQ, history of seizure disorder or diagnostic subgroup of autism.

Wing and Shah (2000) studied 506 referrals to a specialist clinic for ASD and reported that 17% of patients aged 15 or older met the criteria for catatonia. The risk of developing clinical catatonia has been noted to be about the same in persons with autism as in those suffering from affective and psychotic disorders (Kakooza-Mwesige et al., 2008). Children with ASD, however, seem to have a higher risk for catatonic features than children with learning disabilities or language impairment (Wing & Shah, 2006). Sometimes PDD has not been recognized until the appearance of the first catatonic symptoms. Early recognition of catatonia is important in patients with PDD because of psychological and medical treatment (Shah & Wing, 2006).

There has been discussion about the associations between catatonia, autism and SCH. Dhossche (2004) proposed that autism could be an early expression of catatonia because of a common genetic etiology. Genetic studies also show an overlap between PDD and SCH (Rapoport et al., 2009). It has been suggested that autism, catatonia and psychoses in children are different manifestations of a single underlying form of brain pathology (Shorter & Wachtel, 2013). These three diagnoses had all been routinely applied to children and adolescents in the 1920s. Nowadays these three diagnoses are considered to be independent disease entities. After evaluating both historical case vignettes and modern cases, Shorter and Wachtel (2013) proposed that these three illnesses may form what they called an “iron triangle”.

5.6 Developmental delays
A total of 43 developmental skills and possible delays in their acquisition were assessed in Study III. The median number of skills with a delay was three for all the SCH adolescents.

All 18 adolescents with SCH in our study exhibited some developmental delays, which was in line with our hypothesis. The most prevalent developmental delays were in the areas of gross and fine motor development, speech development, social
interaction and play. These results are in agreement with those of earlier studies that found early delays in the development of certain skills among those who later manifested AOS (Cannon et al., 2002; Isohanni et al., 2000; Jones et al., 1994; Walker & Lewine, 1990). However, children who are diagnosed with either COS or EOS are reported to have more frequent and more severe problems in language/speech, social skills and motor development with a more insidious onset than those who have AOS (Alaghband-Rad et al., 1995; Jones et al., 1994; Nicolson et al., 2000; Vourdas et al., 2003).

We also hypothesized that the nature and number of developmental delays would be much the same among SCH adolescents with and without a comorbid PDD. Contrary to our hypothesis, however, the median number of delays in developmental skills was significantly higher among adolescents with SCH and a comorbid PDD than among those with SCH alone. We found that those patients with both disorders exhibited a significantly larger variety of developmental delays than did those suffering from SCH alone.

All adolescents in our study had an IQ in the normal range. Children with PDD have been reported to have more impaired daily living skills and self-help skills compared to children with non-autistic developmental delays and that this difference can emerge by two years of age (Paul et al., 2014). A significant discrepancy between overall cognitive ability and adaptive functioning that favored IQ scores over real-life skills was typical for PDD (Bölte & Poustka, 2002). In childhood autism abnormal or impaired development is evident before the age of three years according to diagnostic criteria and problems may occur in areas of self-help skills, adaptive behavior and curiosity about the environment. Motor milestones may be somewhat delayed and motor clumsiness is usual. It seems that comorbid PDD is associated with a greater variety and higher numbers of developmental delays in adolescents with SCH.

Only three developmental skills were significantly more delayed among our SCH patients with PDD comorbidity than among patients with SCH alone. These three skills were “cooperative play”, “role-play with their age peers”, and “reading their first book”. Cooperative play and role play with their age peers are known to be typical of children with PDDs, due to their serious deficits in the development of the imagination and social interaction, thus deficiencies in these are considered as core abnormalities of the
disorder group (Lugnegård et al., 2011). A study found that those children at the age seven who were later to develop SCH were reported to have more social maladjustments than controls (Done et al., 1994). Overreactivity, hostility and inconsequential behavior were common especially among boys. It seems that social problems in PDD present earlier and some development is delayed, whereas development of social skills is not necessary delayed in those who are developing SCH but instead may have qualitative abnormality that causes problems in social interaction.

Those children who later develop SCH are reported to have more internalization problems, overreactivity at the age of seven and anxiety before 15 years of age (Cannon et al., 2002; Done et al., 1994; Jones et al., 1994).

Deficits in reading comprehension are common among individuals with ASD with normal intelligence (Åsberg et al., 2008). A cognitive style of weak central coherence that is typical for PDD has been proposed to affect the ability to give global context-appropriate answers (Happé, 1994). Children with PDD and normal intelligence show discrepancies between actual academic achievement levels and levels predicted by their intellectual ability (Estes et al., 2011). More overall deficits in academic achievement have been reported among those who later develop SCH compared to controls, but these differences were quite small and statistically non-significant (Dickson et al., 2012).

The mean age of the adolescents at which, their parents first became worried that something might be wrong with their child’s development was significantly lower among SCH adolescents with a comorbid PDD than among those with SCH alone. This difference between our two groups probably stems from the fact that the number of developmental delays was significantly higher among those with both disorders than among those with SCH alone. Our finding is in line with a recent study that found that parents whose children suffered from ASDs became worried about their child’s development significantly earlier than did parents whose children suffered from other kinds of developmental problems (Veness et al., 2012). However, unlike the results of De Giacomo and Fombonne (1998), the parents of only two adolescents in our study reported worries before their children reached the age of two.
Despite the overlap between the results of genetic and neuroimaging studies and between the symptoms of SCH and PDDs, the developmental profiles of adolescents with both SCH and PDDs appear to differ substantially from those with SCH alone. We are not aware of any earlier published studies in which a direct comparison of developmental delays in patients with SCH alone or SCH and PDD combined have been made.

5.7 Neurocognition and social cognition

We compared the adolescent group with SCH only, the comorbid group with PDD and an additional a separate group of adolescents with PDD only, in Study IV. We hypothesized that problems found in adolescents with both disorders would be more severe than in adolescents with isolated disorders. The author is unaware of any previously published studies that compared these three diagnostic groups of adolescents.

All three groups exhibited different profiles in their neurocognitive abilities and disabilities. Adolescents with SCH only performed worse than did those with PDD only in three neurocognitive non-verbal tests in WISC-III that required visual and perceptual organization skills. On the other hand, adolescents with SCH only as well as those with both disorders experienced more problems with processing speed than did adolescents with PDD only. Adolescents suffering from SCH only experienced more difficulty with verbal ToM tasks than adolescents with PDD only. Contrary to our hypothesis, the comorbid group with PDD did not show more severe symptoms.

Those neurocognitive subtests that showed differences between the groups required perceptual organization, visuo-motor co-ordination, attention and short-term visual memory, long-term memory, mental processing speed and motor co-ordination (Kaufman, 1994). Our results agree with those of several other researcher groups who reported spare visual processing for PDDs and also found that adolescents with AS performed better than those with SCH in subtests that required perceptual organization (Ghaziuddin & Mountain-Kimchi, 2004; Joseph et al., 2009; Kaufman, 1994; Minshew et al., 1997; Samson et al., 2012; Williams et al., 2006). The tendency to process details instead of the “big picture”, known as the weak central coherence, may prove helpful
for those with PDD in this kind of performance test where main purpose is to focus on a missing part of the picture or some detail. However, it has also been reported that focusing on details was similar in PDD patients and their controls (Planche & Lemonnier, 2011).

Adolescents with SCH only performed significantly worse than adolescents with PDD only in subtests that required perceptual organization, mental processing speed and motor co-ordination, a finding that was in line with those of Asarnow et al. (1987) and Kaufman (1994). Our finding is also in line with the previous longitudinal studies which reported that children who later developed SCH performed significantly worse in subtests that required perceptual organization, mental processing speed and motor co-ordination and they also had significantly lower total IQ scores than those who remained healthy (Stirling et al., 2003, Sørensen et al., 2010).

We found that adolescents with SCH only performed worse than did those with PDD only in subtest that required sustained attention, short-term visual memory, mental processing speed and visuomotor co-ordination. This finding is in line with the generally held view that slow information processing is a central feature of the cognitive impairment observed in SCH (Asarnow et al., 1987; Dickinson et al., 2007). It should be noted however that the difference was only marginal after the type 1 error correction. Our findings are also supported by previous study data that reported young individuals who later developed SCH had a greater deficit in test performances that required information processing speed than healthy controls and unaffected siblings (Nienadam et al., 2003; Sørensen, 2006). However, a study by Schneider & Asarnow (1987) found the performance of patients with SCH and of those with PDDs had no significant differences in this type of test. There are also findings that indicated that children with PDDs and high intelligence may perform poorly in this kind of test (Ehlers et al., 1997; Siegel et al., 1996).

To our surprise we found that adolescents with SCH and comorbid PDD performed as well as those adolescents with PDD only, and better than adolescents with SCH alone in subtests that involved visual processing. The tendency to process details instead of the big picture in the comorbid group is helpful because the PDD-related tendencies may have improved SCH-related problems in the same individuals. However, in another test that assessed perceptual organizational abilities but did not necessarily focus on
details, the scores of adolescents with comorbidity were intermediate between PDD only and SCH groups. Nevertheless, adolescents with SCH and comorbid PDD obtained the lowest scores for a subtest that measured processing speed although it showed no differences from the performance of adolescents with SCH. It seems that the PDD was not an ameliorating factor for this task.

The only significant difference occurred in the ToM verbal items that measured social cognition. Surprisingly, adolescents with SCH only showed more difficulty in this task than did adolescents with PDD only, whereas adolescents with comorbidity were intermediate between these two groups. The NEPSY-II verbal ToM items included first- and second-order false-belief tasks and metaphors. Some questions appeared in the form of a lengthy verbal story. Problems in neurocognition (attention, short-term memory, and information processing) may affect SCH patients’ levels of performance in this subtest. However the performance of the adolescents with SCH showed no difference from that of other patient groups for the Arithmetic subtest, which measures the same abilities. Nor did we find differences for any verbal subtests. It seems that neurocognitive impairments could not explain this finding in social cognition.

No differences were found between the groups for NEPSY-II visual ToM items and Emotion recognition subtest scoring. We cannot make reliable inferences about the normality of the performance due to the lack of a control group. There is, however, some evidence that individuals with PDD may not have significant problems in all ToM tasks (Korkman et al., 2008). The development of the NEPSY-II involved the study of different diagnostic groups, and also in a clinical subpopulation of children with AS, and reported that 26.3% of the AS group experienced significant problems in ToM tasks (verbal and visual together), compared to 10.5% in the control group (Korkman et al., 2008). This disparity suggests that many children with AS may perform quite well at doing NEPSY-II ToM tasks. Both first-order and second-order ToM tasks can be easy for high-functioning persons with PDDs as suggested earlier, but more advanced tasks tend to reveal problems (Bowler, 1992; Ozonoff et al., 1991). It has also been argued that individuals with AS can perform well in ToM tests with their explicit verbal ability and if they have enough time to think of answers, but in real life social situations deficits are more evident (Frith, 2004).
5.8 Study strengths and limitations

The strengths of this study include the recruitment of patients on a consecutive basis from inpatient units in a geographically defined area. Structured instruments with good psychometric properties were used in combination with primary documents from early childhood, which are readily available in Finland. The basic diagnostic procedures in Finland have proven to be reliable (Isohanni et al., 1997). Delays in developmental skills were evaluated more widely in our study than in earlier studies.

Nevertheless, the study has its obvious limitations. One must bear in mind that the parents were asked to recall the childhood behavior of their already adolescent offspring. Consequently, such data do not necessarily reflect actual behaviors, but subjective memories. These results should therefore be regarded as preliminary.

COS and EOS are less common than AOS and, unfortunately, the sample remained small. This small sample size limits the generalizability of our findings. Moreover, the current study may have been underpowered to detect the smaller statistical group differences that could have been detected in a larger sample.

The majority of adolescents in this study were girls, which is not typical for EOS, or for PDD. Further, this study lacked a healthy control group. It is also clear that more research is needed to clarify the boundaries between SCH and Autism spectrum disorder.

5.9 Methodological considerations

DISCO was mainly developed for diagnostic purposes, and there is actually no option in the algorithm to detect the deterioration of various functions or features. We obtained a detailed and operationalized qualitative description of various behavioral patterns in SCH and PDD patients during the early school years and during adolescence. Our adaptation of the DISCO-interview by splitting it into childhood- and adolescence-arms has not yet been validated elsewhere. The adaption is, however, in accordance with the original structure of this diagnostic instrument and that used in a recent study by Hallerbäck et al. (2012), which was similar. In addition, the average developmental ages in the DISCO when the child should learn some developmental skills, have been taken from the Vineland Adaptive Behavior scale, and Finnish norms are lacking.
We used WISC-III and NEPSY-II subtest raw scores for comparisons between the groups in Study IV. The reason for this choice of instruments was that these tests have standardized scores for up to 16 years of age, but not for older individuals and in our study group some of the adolescents were over 16 years. The use of raw scores and age as a covariant allowed us to compare the relational difference in the scores between the groups. We decided to use same test for all these adolescents, instead of using an adult version of Wechsler test for older adolescents, because to do otherwise would have rendered the performances in the subtests to be incomparable between the different test versions.

There are many tests available for assessing social cognition, but only few are standardized. The problem is also that different studies use different tests to assess the same domains of social cognition. It is difficult to compare results of different studies with such a diversity of tests. We chose to use the NEPSY-II task for ToM because this is the first standardized ToM test in Finnish. Our results for social cognition obtained a maximum raw score of 17 for the verbal ToM test and the mean scores of adolescents with SCH alone and PDD only were over 15 raw score points. However, with 16/17 raw scores for verbal ToM task an adolescent within the age group 16 years six months gets one standard point, which defines very poor performance.

5.10 Future directions

Systematic studies in SCH patients that address the overlap of criteria of MCDD, impaired social behavior and the presence of thought disorder in particular, and information obtained from DISCO-interview are warranted in the future. This might clarify the nosological confusion between the differences and similarities between SCH and PDD spectrum disorders that still prevail today. More rigid follow-up of motor side effects of antipsychotic medicines using structured instruments designed for this purpose such as Barnes acathisia scale, are needed. An adequate follow-up of adolescents of our sample is required to evaluate, which symptoms are best ameliorated in EOS with or without PDD.

Further, studies with follow-ups from childhood to adulthood are needed to investigate whether differences in the occurrence of clinical catatonia as conceptualized
in the DSM-5 between SCH patients with and without a comorbid PDD emerge. The same naturally applies to catatonia-like features and their waxing or waning or possible exacerbation into clinical catatonia. In addition, the impact of PDDs manifests as more frequent and earlier-onset developmental delays, which must be studied from a developmental perspective. Shedding more light on these differences will require additional studies that compare our current group of patients with PDD patients without SCH. In the future it would also be interesting to study differences between our group of adolescents with SCH and those who are destined to develop AOS and compare delays in their respective development. Then we could say whether or not there are more severe and a broader range of developmental delays in EOS than AOS.

It is clear that more research is needed to clarify the boundaries between SCH and ASD. Studying the potential neurocognitive phenotypes with larger patient samples could shed light on these intriguing issues. Larger sample sizes of studies would also facilitate making valid comparisons between the performances of girls and boys.

### 5.11 Conclusions

The findings from this thesis show that adolescents with SCH can have comorbid PDD, and usually in clinical work these cases with dual diagnoses are not always easy to recognize. Our results are in line with previous findings for COS and AOS patients in comorbidity with PDD. Earlier diagnostic classifications, before DSM-5, had variable approaches for defining comorbidity of SCH and PDD. Because of that, these two disorders may not have been diagnosed together in the past, even if it would have been necessary to do so. It seems that patients with a primary diagnosis of SCH and a subsequent comorbidity of PDD are more usual than patients with a primary diagnosis of PDD and a subsequent comorbidity of SCH. As seen in our Study I, adolescents with SCH often have symptoms consistent with AS, although only few of them have fulfilled the diagnostic criteria in their childhood, which is a prerequisite for the diagnosis of AS. Many of the behavioral symptoms that resemble symptoms of AS, such as negativity and difficulties in reciprocal social interaction especially with adults are often typical behavior in adolescence. There is a risk for misdiagnosis of adolescents with autistic symptoms if a detailed longitudinal anamnesis is not obtained. The current findings
highlight the importance for pediatricians, psychologists and primary health care to acquire more knowledge about the nature of these disorders, so that reliable diagnoses, treatment and rehabilitation can be offered to patients.

Our Study II found that adolescents with SCH and comorbid PDD show many catatonic features in childhood, whereas those without comorbidity seem to develop these features first in adolescence. Catatonic features exhibited by adolescents with SCH alone resemble those described in persons suffering from PDDs without SCH. Whether this reflects the onset and impact of the SCH process remains unsolved. The presence of comorbid PDD may alter the profile of symptoms in adolescents with SCH to earlier and wider ranging catatonic features than would exhibit in SCH only. There has been some divergence in earlier results concerning the prevalence of catatonia, because unanimous criteria for catatonia have been lacking. Catatonic symptoms appear to vary widely and they also appear to differ between childhood, adolescence and adulthood.

Developmental delays were also frequent in adolescents suffering from SCH. Patients with SCH and a comorbid PDD showed significantly greater numbers and a wider range of developmental delays than patients with SCH alone. Parents of those children with comorbidity became concerned about their children’s development when their children were at younger age than the parents of children who had SCH alone. It seems that comorbidity brings a wider range of developmental delays into the clinical picture of SCH. Past studies on the developmental delays in these patient groups have often only evaluated delays in motor or language skills. Our evaluation of delays in Study III was more comprehensive than those of those earlier studies.

Finally, the adolescents with SCH alone, or with PDD as a comorbidity and those with PDD only had differing profiles in their neurocognitive abilities and disabilities upon testing. The comorbid group seemed to display a combination of the visual strengths and characteristic style of PDD with the slow processing speed of SCH in their neurocognitive profile. Adolescents who were suffering from SCH experienced more difficulty with verbal ToM tasks, which is a finding that neurocognitive impairments could not explain.
Adolescence is the developmental stage that favors the clinical expression of psychotic symptoms (Raja & Azzoni, 2010). Catatonia has been proposed to be fully expressed in adolescence in patients with PDD (Wing & Shah, 2000). There are some developmental attributes during adolescence that exposes the individuals to clinical expressions of different symptoms. For this reason, making reliable diagnoses of SCH, PDD or catatonia at this age is especially demanding, and developmental information about changes and new symptoms is essential. There may also be differences in how symptoms of PDD or SCH are presented between males and females. Our small sample size made it impossible for us to compare profiles between genders with any statistical validity. This gender issue has often been missed in earlier studies as well. It is important to note that in our sample the proportion of females was higher compared to earlier studies.

The attempts to explain how PDD, SCH and catatonia are related to each other include concepts such as MCDD and an “iron triangle”. At present we lack information about the etiology of these disorders. In the light of current knowledge there is a possibility that subgroups such as the MCDD and the “iron triangle” may indeed exist and our results add to the understanding of the shared features.
6 REFERENCES


