

GIRLS WITH SOCIAL AND/OR ATTENTION IMPAIRMENTS

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To all the girls out there in need of recognition

ABSTRACT

Background: This study set out to increase knowledge about the clinical presentation, impairment level, associated problems, and screening/identification of girls coming to clinics with non-specified social and/or attention deficits. **Material and methods:** An in-depth case study of six girls presenting to clinicians with social deficits had showed that they all met criteria for autism, in spite of the fact that this diagnosis had not previously been considered. This led to the planning of a much bigger study including in-depth assessment of one hundred girls referred for social and/or attention/academic problems and a matched group of sixty girls from the community. The clinical assessments were all performed by the author and a small group of paramedical colleagues, consisting of neuropsychologists, educationalists, physiotherapists, and a social worker. A new autism spectrum screening instrument (the ASSQ-REV, an expanded version of the well validated autism screening tool ASSQ) aimed at identifying girls with previously unrecognised features of autism was developed and tested among school age girls from the Clinic group, and among matched Clinic boys and Community girls. **Results:** The main results indicated that when girls present with impairing social and/or attention deficit problems, they usually (in more than ninety per cent of the cases) have autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD) or both. Community girls meet criteria for such disorders only in a few per cent of all cases. Parents had usually noticed deviant development or behavioural problems before child age three years, and 47% had consulted a professional before age four (without being adequately helped or understood). The mean child age for a main diagnosis of ASD or ADHD was 8.8 years and 13.0 years, respectively. Clinic girls with ASD usually have co-existing symptoms of ADHD, amounting to full clinical diagnostic status, and at least one of four Clinic girls with ADHD show autistic traits. The ASD and ADHD groups had the same high rates of psychiatric comorbidity, including oppositional defiant disorder, anxiety and/or depressive conditions as well as impairing sleep problems. In addition, they very often have mild-moderate motor control problems, amounting to impairing developmental coordination disorder in a large minority of all cases. Other frequently experienced consequences for school-age girls with ASD and/or ADHD are underachievement and bullying in school settings. Girls with ASD had more problems with global functioning and adaptive levels of daily living skills than girls with ADHD. The ASSQ-REV screening tool does not appear to work better than the ASSQ in identifying girls with ASD. However, certain individual items from the ASSQ-REV seem to work well in separating boys and girls with ASD. **Discussion:** Most girls with clinically relevant social and/or attention deficits (presenting at clinics before adult age) usually have ASD, ADHD or a combination of the two. Taking into account the early (or very early) onset of a variety of symptoms and the severe consequences of them, every girl assessed for such problems or “unexplained” low global functioning should promptly be worked up from the point of view of confirming or refuting diagnoses of these disorders. In addition, once the ASD and/or ADHD has been identified, it is essential to continue with a broad assessment battery including motor control tests, reading and writing tests, and interview and observation with a view to identifying co-existing psychiatric disorders such as oppositional defiant disorder, anxiety disorder, depressive states, obsessive-compulsive disorders and sleep disorder. The ASSQ-REV did not increase precision in targeting girls with ASD, but individual items from this instrument clearly separated girls with ASD from boys with ASD (and Community girls without psychiatric problems). These items should be considered for inclusion together with existing screening instruments for ASD and other neuropsychiatric disorders so that more girls with “hidden” neurodevelopmental impairment might be recognised at early school age at the very latest. A better understanding of girls’ neuropsychiatric symptoms is needed in health care and in school settings. **Key words:** Autism Spectrum Disorder (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), girls, psychiatric comorbidity, Developmental Coordination Disorder (DCD), Reading/Writing Disorder (RWD), school situation, Autism Spectrum Screening Questionnaire (ASSQ), ASSQ-REV

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LIST OF PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals I-V:

I. Kopp, S., and Gillberg, C. (1992). Girls with social deficits and learning problems: autism, atypical Asperger syndrome or a variant of these conditions. *European Child and Adolescent Psychiatry*, 1, 89-99.

II. Kopp, S., Berg-Kelly, K., and Gillberg, C. (in press). Girls with social and/or attention deficits: a descriptive study of 100 clinic attenders. *Journal of Attention Disorders*.

III. Kopp, S., Beckung, E., and Gillberg, C. (2010). Developmental coordination disorder and other motor control problems in girls with autism spectrum disorders and/or attention-deficit/hyperactivity disorder. *Research in Developmental Disabilities*, 31, 350-361.

IV. Åsberg, J., Kopp, S., Berg-Kelly, K., and Gillberg, C. (2010). Reading comprehension, word decoding and spelling in girls with autism spectrum disorders (ASD) or attention-deficit/hyperactivity disorder (AD/HD): performance and predictors. *International Journal of Language and Communication Disorders*, 45, 61-71.

V. Kopp, S., and Gillberg, C. (2010). The Autism Spectrum Screening Questionnaire (ASSQ) - Revised Extended Version (ASSQ-REV): an instrument for better capturing the autism phenotype in girls? Manuscript submitted for publication.

ABBREVIATIONS

ABC	Autistic Behavior Checklist
AD	Autistic Disorder
ADHD	Attention-Deficit/Hyperactivity Disorder
ADI-R	Autism Diagnostic Interview-Revised
ADOS-G	Autism Diagnostic Observation Schedule-Generic
APA	American Psychiatric Association
ASD	Autism Spectrum Disorder
ASSQ	Autism Spectrum Screening Questionnaire
ASSQ-GIRL	18 new screening items believed to tap into the autism phenotype in girls
ASSQ-REV	ASSQ + ASSQ-GIRL= ASSQ-Revised Extended Version
AUC	Area Under the Curve
CARS	Childhood Autism Rating Scale
CAPA	Child and Adolescent Psychiatric Assessment
CD	Conduct Disorder
CI	Confidence Interval
CNC	Child Neuropsychiatric Clinic
CTRS-R:L	Conners' Teachers' Rating Scale-Revised:Long Form
DCD	Developmental Coordination Disorder
DSRS	Birleson Depression Self-Rating Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
EB-test	Eva Beckung motor-test
EEG	Electroencephalogram
FTF	Five To Fifteen questionnaire
ESSENCE	Early Symptomatic Syndrome Eliciting Neurodevelopmental Clinical Examinations
GAF	Global Assesment of Functioning scale
ICD-10	International Classification of Diseases tenth revision
LD	Learning Disability
MNP	Motor-Neurological-Perceptual assessment
M-ABC	Movement-Assessment Battery for Children
MPA	Minor Physical Anomalies
MR	Mental Retardation
NOS	Not Otherwise Specified
ODD	Oppositional Defiant Disorder
OCD	Obsessive- Compulsive Disorder
OR	Odds Ratio
PDD	Pervasive Developmental Disorder
PDA	Pathological Demand Avoidance
PE	Physical Education
ROC	Receiver Operating Characteristic
RWD	Reading and/or Writing Disorders
SD	Standard Deviation
TD	Tourette's Disorder/Tic Disorder
VABS-DLS	Vineland Adapative Behaviour Scales-Daily Living Skills
WAIS-R	Wechsler Adult Intelligence Scale-Revised
WISC	Wechsler Intelligence Scale for Children
WPPSI-R	Wechsler Preschool and Primary Scale of Intelligence for Children- Revised

INTRODUCTION

Social and attention disorders, and other early childhood onset psychiatric problems

Autism spectrum disorders (ASDs), also referred to as pervasive developmental disorders (PDDs), attention-deficit/hyperactivity disorder (ADHD), and tic disorders (including Tourette disorder) can be among the most severe psychiatric disorders with onset in infancy or early childhood (Gillberg, 1995). These neuropsychiatric disorders are heterogeneous conditions with a strong genetic component. A range of developmental, behavioural, and emotional symptoms are present during childhood and adolescence, and combine in different constellations at different ages. Other, closely related, conditions are learning disability (LD), developmental coordination disorder (DCD), and reading and/or writing disorder (RWD) (see below).

For all these conditions, our current understanding is based primarily on results obtained in research on males. The fact that so much research in the field has focused on boys has been attributed to the estimated much higher population prevalence of developmental disorders, and, particularly, the much higher rate of clinic referrals in males. Nevertheless, even though some major authorities in the field – including Hans Asperger – concluded that some variants of early onset psychiatric/personality disorders almost exclusively occur in males, other influential figures – including Georges Gilles de la Tourette and Leo Kanner – acknowledged the existence of major and severely impairing problems (e.g. tic disorders, autism) in girls and women. The failure of neuropsychiatric research over the past century to truly take account of the prevalence, clinical presentation and outcome of disorders such as ADHD and ASD in females, is, in itself thought-provoking. Why is it, that, at the beginning of the 21st century, we know a lot about autism and attention disorders in males, but little, if anything, about these same disorders in females? Admittedly, research interest in females with ADHD has increased during the latest decade (Biederman et al., 1999; Sharp et al., 1999; Newcorn et al., 2001; Rucklidge & Tannock, 2001; Abikoff et al., 2002; Biederman, Mick, et al., 2002; Dalsgaard, Mortensen, Frydenberg & Thomsen, 2002; Hinshaw, 2002; Hinshaw, Carte, Sami, Treuting & Zupan, 2002; Biederman & Faraone, 2004; Quinn & Wigal, 2004; Yang, Jong, Chung & Chen, 2004; Graetz, Sawyer & Baghurst, 2005; Staller & Faraone, 2006; Biederman et al., 2006; Hinshaw, Owens, Sami & Fargeon, 2006; Bauermeister et al., 2007; Rucklidge, 2010), but the volume of published research is still very limited. In ASD, the situation is worse, and there are not even a handful of published papers that include a large number of girls or women with autism or related conditions.

ESSENCE - Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations

The acronym ESSENCE was recently coined by Gillberg (2010, in press) to refer to Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations. ESSENCE is introduced with a view to attracting attention to the reality of girls and boys presenting in clinical settings before the age of 3 (-5) years with symptoms of delay or deviance as regards (a) general development (b) communication and language (c) social interaction (d) motor coordination (e) attention (f) activity level (g) behaviour (h) mood, and/or persistent sleep/feeding. The symptoms usually signal an underlying syndrome (LD, ASD, ADHD, DCD, TD etc.), most of which are conceptualised as more or less discrete disorders in the Diagnostic Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association (APA), 2000), and in the International Classification of Diseases, Tenth Revision (ICD-10) (World Health Organisation (WHO) 1993). At the time of referral it may be difficult to determine which of these syndromes is the most “salient”, and what degree of “comorbidity”/overlap of disorders is involved. However, currently, clinics have tended to become more and more specialised, focusing on autism, LD, speech-language disorder *or* ADHD. If a child does not meet full criteria for autism at the “autism clinic”, the family may be left with the idea that “it is not autism”, therefore the girl’s or boy’s symptoms do not warrant autism intervention, and a “wait-and-see” attitude may be adopted. Alternatively, a speech-language disorder may be diagnosed at age 3 years by the

speech therapist at the specialised speech therapy clinic, speech therapy will be prescribed for years, and then, at school age, the child will be diagnosed with ASD, having-possibly-missed out on autism intervention for 3-4 years. A “diagnosis” of ESSENCE at age 3 years (-5) in both these instances would instead, hopefully, have led to an understanding that the girl or the boy, in all probability, has one or more of the named syndromes, interventions are warranted from the start for the symptoms that are the most prominent, and follow-up by a multidisciplinary team for many years will be needed. ESSENCE is not intended to replace more detailed diagnosis, rather the opposite, but to serve as an umbrella term for all the early onset neurodevelopmental syndromes that *always* require careful multidisciplinary assessment.

The ESSENCE way of thinking about early onset child symptoms is in line with my own clinical and research experience of an often much too long delay before getting an appropriate diagnosis and of the widespread co-occurrence of overlapping symptoms of ADHD in ASD cases, and of clear traits of ASD in ADHD cases – plus the frequent “comorbidity” of motor and/or vocal tics in both disorders. Such overlapping symptoms constitute a complex clinical picture and greatly confuse the diagnostic process in girls (as well as in boys) with early onset psychiatric disorders. When, in the 1990s, I set out to work on the project that is the backbone of this thesis, I therefore chose a comprehensive approach to assessment (including methods that would tap into both ASD, ADHD, TD, and other disorders), an approach that appears to have become more popular in later research (Frazier et al., 2001; Goldstein & Schwabach, 2004; Reiersen, Constantino, Volk & Todd, 2007).

Persistent multiple regulatory problems (RP), i.e. excessive crying, feeding and sleeping difficulties, from infancy to childhood are common in the ESSENCE groups of children and experienced neuropsychiatrists have long considered them to be an “alarm signal” for an underlying disorder. Recently, persistent RP have been shown to predict adverse social skills and poor adaptive behaviour in the preschool years (Schmid, Schreier, Meyer & Wolke, 2010). In my thesis, I have included screen and interview items that tap into RP.

In most girls and boys with ASD, ADHD or TD, co-occurring psychiatric or behavioural disorders seem to be the rule rather than the exception. This co-existence of disorder/overlap of symptoms is now often referred to as “comorbidity”. The existence of a “pure” ASD, ADHD or TD syndrome is rare both in clinics and general population (Robertson, 2000; Kadesjö & Gillberg, 2001; Simonoff et al., 2008). Already in the early 1980s, Gillberg (1983) published a study of the comorbidity of attention disorders with autism, depression, and conduct disorders. This area of comorbidity research in child psychiatry has evolved, rather belatedly, in an almost land-slide fashion during the last decade (Pliszka, 1998; Biederman et al., 1999; Lee & Ousley, 2006; Leyfer et al., 2006; Mikami, Hinshaw, Patterson & Lee, 2008; Quinn, 2008; Mattila et al. (in press)).

ASD

ASDs (or PDDs) are characterised by severe social interaction-communication deficits, and stereotyped repetitive behaviours, according to the DSM-IV (1994) (see page 13). ASD comprises the diagnostic categories autistic disorder, childhood disintegrative disorder, Asperger disorder and PDDNOS (atypical autism in the ICD-10, 1993) (plus Rett’s disorder, which clearly does not belong as a separate diagnostic category, given that it is a neurological disorder that often presents with autism).

Autism was probably first described by Jean Itard, who reported on both girls and boys with the condition already in the first decades of the nineteenth century (Carrey, 1995). However, it was not until the publication of papers by Leo Kanner and Hans Asperger, that the term “autism” was used to describe the disorders currently considered to be subsumed under the umbrella definition of ASD. The term ASD is taken to imply the existence of a continuum of more severe to moderate autistic symptomatology, rather than to specific categorical disorders, and several studies have failed to find support for the existing categorical nosology (Prior et al., 1998; Bölte & Poustka, 2001). The concept of an autism spectrum might also be taken to mean the dimensional existence of autistic traits in the general population, suggested by Gillberg (1992), and recently empirically supported by several groups (Constantino & Todd, 2003; Skuse,

Mandy & Scourfield, 2005; Baron-Cohen, Hoekstra, Knickmeyer & Wheelwright, 2006; Posserud, Lundervold & Gillberg, 2006).

Almost all of the very few early studies published of girls with ASD have focused on the low functioning group with IQs in the retarded range (Wing, 1981; Lord, Schopler & Revicki, 1982; Tsai & Beisler, 1983; Konstantareas, Homatidis & Busch, 1989). Ewa Ssuharewa (1926) first described autism in more “able” children (all boys), although she termed the condition “schizoid psychopathy”. Almost twenty years later, Hans Asperger (1944) published his paper on school-age boys, usually with “normal intelligence”, with what he referred to as “autistic psychopathy” (later to be called Asperger’s syndrome by Lorna Wing (1981), and operationalised for diagnosis by Gillberg and Gillberg (1989), see page 15). Supposedly, partly as a consequence of Asperger’s description of only male cases, and his utterance that “it is *fascinating to note* that the autistic children we have seen are almost exclusively boys“ (see Frith, 1991, p.84), and maybe because girls are not prone to Asperger’s “type of autism”, males, and not females, have been considered for a diagnosis of Asperger syndrome. However, from 1964 until her death in 2009 Sula Wolff reported on a group of girls and boys with an abnormal pattern of behaviour that she classified as schizoid personality disorder (Wolff, 1995). She also followed up a group of 33 girls with this condition, noting that, in the majority of cases, in adult age they were similar in style and functioning to males with the same diagnosis (Wolff & McGuire, 1995). These girls were said to be hard to bring up and to have severe adjustment problems at school. They also showed solitariness, rigidity of mental set, an unusual or odd style of communication, and they clearly resembled children given the diagnosis of Asperger’s syndrome.

The psychoanalytical literature also contains descriptions of girls who would probably have met criteria for ASD, albeit their conditions were differently labelled by the authors “benign psychosis” (Mahler, Ross & DeFries, 1949), “severe disturbance of ego-development” (Weil, 1953), and “borderline state” (Geleert, 1958). Francis Tustin (1981, 1986) is one of the few psychoanalysts who actually referred to autism in the case studies (including of girls) she published. Coming from a very different neurobiological perspective, Lauretta Bender published a longitudinal study of women diagnosed in childhood as suffering from “schizophrenia”. It is clear that some of these would have met current criteria for ASD (Bender & Grugett, 1956).

In the few existing comparative clinical studies on females and males with clinical symptoms of ASD, some show no significant gender differences after controlling for IQ (Volkmar, Szatmari & Sparrow, 1993; Holtmann, Bölte & Poustka, 2007), not even in younger children (Pilowsky, Yirmiya, Schulman & Dover, 1998). However McLennan, Lord, and Schopler (1993) reported that boys with ASD were more impaired than girls with ASD in terms of early social development (in a group of high-functioning clinic attenders). In contrast, females were described as having more severe social deficits during adolescence, particularly as regards peer relationships. Higher rates of restricted repetitive behaviours have been reported by Lord, Schopler and Revicki (1982) and Hartley and Sikora (2009) in younger boys compared to younger girls with ASD.

Comorbidity

Along with the features that define autism, children with ASD may have a wide range of co-existing psychiatric disorders (Gadow, DeVincent, Pomeroy & Azizian, 2004; Leyfer et al., 2006). However, only one small study, including 12 girls, to our knowledge, has reported specifically about the co-existing disorders in school-age girls with ASD (Mattila et al., (in press)), and a small group of girls has been included in some other studies (Frazier et al., 2001; Sturm, Fernell & Gillberg, 2004; Leyfer et al.; Kuusikko et al., 2008; Simonoff et al., 2008).

Adaptive “Daily Living Skills”

Apart from the core deficits and co-existing psychiatric symptoms, ASD has also been characterized by impairments in everyday tasks such as hygiene, eating, and dressing (Gillberg, 2002). Although no studies specifically on girls with autism have been reported, Lee and Park (2007) in their review of adaptive

behaviour studies, found significantly below average skills on the section Daily Living Skills of the Vineland Adaptive Behavior Scales (VABS) in a clinic group of males with Asperger syndrome.

ADHD

Alexander Crichton (1798) is believed to have been the first medical doctor to report on ADHD (see Palmer & Finger, 2003). He referred to “mental restlessness” and described a condition that much resembles the inattentive subtype of ADHD. The first modern systematic account of hyperactivity (restlessness) and sustained attention problems causing school failure even despite normal intellect in both girls (5) and boys (15), was published in the *Lancet* by Sir George Frederick Still (1902). He described a condition of “moral dyscontrol” and noted that some of the children were also mischievous, violent and not responding to punishment. Since then, the attitudes regarding the nature of the condition have been reflected in the various name changes this disorder has undergone over the years. From the 1970s, the DSM classification system has been used, initially with hyperactivity as the primary symptom, and later with a focus on attention and impulsivity (Douglas, 1972). ADHD is currently defined in the DSM-IV as age-inappropriate impairing symptoms of inattention, hyperactivity and impulsivity, and subdivided into three types, mainly inattentive, mainly hyperactive-impulsive, and combined (see page 16).

Today ADHD is regarded as one of the most common behavioural disorders in girls and boys in the general population, and the most common diagnosis in child psychiatric units, at least in the case of boys (Kopp & Gillberg, 2003; Merikangas et al., 2010). ADHD may be conceived of as the extreme end of a complex trait that is continuously distributed in the general population (Rowe & Rowe, 1997; Gomez, Harvey, Quick, Scharer & Harris, 1999). This dimensional character of the ADHD traits makes the approach to classification of “disorder” arbitrary. Recent authors have stressed the importance of functional impairment as cut-off - in addition to counting symptoms - for a diagnosis of ADHD to be made (Gordon et al., 2008).

Until quite recently, the literature on ADHD gave the impression that ADHD is an almost exclusively male problem; one study after another concentrated on boys only (Heptinstall & Taylor, 2002, p. 99). However, in contrast to the research field of ASD, awareness of the lack of knowledge about girls with ADHD has increased, starting with the first conference on sex differences in ADHD held in the US in 1994 (Arnold, 1996). Since then there has been an ongoing discussion about the appropriateness of the existing classification system for diagnosing girls with ADHD (Barkley, 1995; Gaub & Carlson, 1997; Quinn & Nadeau, 2002; Hudziak, Derks, Althoff, Rettew & Boomsma, 2005; Ohan & Johnston, 2005; Waschbusch & King, 2006), and about the great difference in sex-ratio between population studies and clinical studies (more even sex-ratio in population studies) (Gaub & Carlson, 1997; Ohan & Visser, 2009)

In the burgeoning research on ADHD in females five major findings have been stressed: (i) high rates of co-existing psychiatric problems in both the internalizing and disruptive spectrums, (ii) lower IQ, albeit in the average range, (iii) social interaction problems in relation to both peers and adults, (iv) increased risk for school failure, and (v) high rates of substance dependence.

Comorbidity

The comorbidity rates are high and quite similar between girls and boys with ADHD (Sharp et al., 1999; Biederman & Faraone, 2004). Boys have more co-existence of ODD and CD than girls with ADHD, although this is due to the gender and not to ADHD. Compared to boys, higher rates of depression and anxiety have been found in adolescent girls with ADHD (Biederman, Mick et al., 2002; Bauermeister et al., 2007) Again, this has been attributed to gender, and not ADHD. In a retrospective Danish study, more reactive attachment disorders were found in female clinic attenders treated with stimulants compared to males (Dahlsgaard, Hansen, Mortensen, Damm & Thomsen, 2001).

Cognitive ability

Nearly all studies on both girls and boys have found lower IQ in the ADHD group compared to controls. In some studies girls have been shown to perform worse than boys. However some researchers have attributed this to referral bias (James & Taylor, 1990; Gaub & Carlson, 1997).

Social interaction problems and self-esteem

Both girls and boys with ADHD suffer from peer relationship problems (deHaas, 1986; Greene et al., 2001; Cunningham & Boyle, 2002; Marton, Wiener, Rogers, Moore & Tannock, 2009). Some of the studies point towards the problem being greater in girls than boys, possibly due to the more demanding social interaction rules in girl friendships (Berry, Shaywitz & Shaywitz, 1985; Langlete Hage, 1999; Young, Heptinstall, Sonuga-Barke, Chadwick & Taylor, 2005). Compared to girls without ADHD, girls with ADHD have fewer friends, experience more peer-rejection, and are more often left out from play (Berry et al., 1985; Blachman & Hinshaw, 2002). One contributing factor to these findings might be the more prominent verbal aggressiveness observed in girls with ADHD compared to “normal” controls (Abikoff et al., 2002; Zalecki & Hinshaw, 2004).

Some studies report females with ADHD to be more vulnerable to experience low self-esteem, a higher degree of stress, and less control over their situation compared to males with the disorder (Arcia & Conners, 1998; Rucklidge & Tannock, 2001; Quinn & Wigal, 2004). In comparison to girls without ADHD the discrepancy is huge in these respects (Berry et al., 1985; Owens & Hoza, 2003).

School failure and bullying

The majority of studies on girls with ADHD have shown moderate to severe impairments in school achievements compared to girls without the disorder (Biederman et al., 1999; Doyle, Faraone, DuPre & Biederman, 2001; Hinshaw et al., 2002). As regards school failure, variable findings in females versus males have been reported by Sharp et al. (1999), Biederman, Mick et al. (2002), Rucklidge and Tannock (2001), Hartung et al. (2002), and Bauermeister et al. (2007). Lower educational levels in clinic referred women with ADHD compared to men with ADHD were reported by Arcia and Conners (1998). At least one study has demonstrated that when there are more severe learning problems, girls with ADHD get less help even than boys with less severe ADHD symptoms at school (Langlete Hage, 1999). This tallies with findings showing generally more teacher attention being paid to boys in school settings (Wernersson, 1977; Örn, 1990, 2002). Girls compared to boys with ADHD were also more likely to be the victim of bullying (Nøvik et al., 2006).

Substance use disorder

Increased rates of substance use disorder (SUD, which includes smoking cigarettes, drinking alcohol and taking drugs) in girls with ADHD has been noted by some researchers (Biederman et al., 1999), but this has not been confirmed by others (Rucklidge & Tannock, 2001). Girls with ADHD have also been found to have more SUD than boys with ADHD (Biedermann, Mick, et al., 2002). There is a similar elevated risk in both genders for SUD when having ADHD with co-existing conduct disorder (CD) (Molina, Bukstein & Lynch, 2002; Ribeiro, Jennen-Steinmetz, Schmidt & Becker, 2008).

Other factors, including barriers to detection, social adversity, and outcome

Szatmari, Offord, and Boyle (1989) have shown that different informants provide different information about the same girl or boy, and that it is therefore recommended that information about the child be obtained from at least two informants. In studies on boys with ADHD, teachers and parents differ to some extent, but not as much as they do in their ratings of girls with ADHD, for whom parents always estimate girls to have more problems than do teachers. This is one of the crucial diagnostic problems and it impedes referral and diagnosis in affected girls with ADHD (at least in cases where the parent has the “right opinion”) (McGee & Feehan, 1991; Magnusson, Smari, Gretarsdottir & Prandardottir, 1999; Newcorn et al., 2001; Hartung et al., 2002; Brewis & Smith, 2003).

Bussing, Zima, Gary and Garvan (2003) have shown that parents with higher socioeconomic level more often bring their children (girls as well as boys) for specialist assessment. James and Taylor (1990) found that in order to get a girl with ADHD assessed, parents need to be very active or well educated. Girls with more impairment, more additional diagnoses and lower IQ, are more likely to be assessed than are more capable girls with similar diagnosis. This, however, is not the case for boys. In families where boys and girls are equally affected by symptoms, the boys, not the girls, tend to be referred (Bussing, Zima, et al.

2003). Teachers tend to have a gender-based opinion about diagnoses: boys are more often believed to have ADHD when in fact they have ODD, and the opposite applies in girls (Jackson & King, 2004). Medical doctors more often give boys (not girls) an adequate diagnosis, even when the girls have a very similar report of symptoms (Gardner, Pajer, Kelleher, Hudson & Wasserman, 2002).

In both girls and boys some studies have shown more ADHD symptoms being reported in children of parents with lower levels of education (Huss, Hölling, Kurth & Schlack, 2008; Kadesjö et al., 2004; Rydell, 2010). Other adverse psychosocial factors including low socioeconomic level and family conflict have been shown to have a negative impact on the degree of reported ADHD symptoms in the child (Biederman, Faraone & Monuteaux, 2002).

In terms of outcome, the most recent studies of girls with ADHD have shown that the majority has poor adjustment in comparison to control girls without ADHD 5-8 years after the first assessment, with a higher risk of manifest disruptive behaviour, mood and anxiety disorder, eating disorder and of drug dependence or abuse. There are often more pronounced problems with social skills, less peer acceptance, and lower school achievement (Biedeman et al., 2006; Hinshaw et al., 2006; Mikami et al., 2008; Owens, Hinshaw, Lee & Lahey, 2009; Mikami et al., 2010). A higher risk of psychiatric admissions in adulthood was found in a follow-up study of women compared to men, diagnosed and treated for ADHD in childhood (Dalsgaard et al., 2002).

Other ESSENCE including TD, DCD, and RWD

Tourette's disorder and/or chronic motor/vocal tic disorders (TD) are mostly manifested during childhood and characterized by the presence of impairing multiple motor and/or vocal tics, which have lasted longer than one year according to the DSM-IV (1994). Fluctuations in severity and frequency of the different tics vary over time, and about half of the children affected are tic free after the age of 18 years. Itard (1825) was the first to scientifically describe impairing chronic motor and vocal tics (TD) in a French noblewoman forced to live isolated on account of her impairing tics. The majority of affected children suffer from additional major problems, including as ADHD, OCD, anxiety and ASD (Kadesjö & Gillberg, 2000; Robertson, 2000; Khalifa & von Knorring, 2005). The prevalence rate for TD is estimated at 1-2% of the general population of school age children, with at least a threefold higher rate in boys than girls (Kadesjö & Gillberg, 2000; Khalifa & von Knorring, 2003).

Our group has shown that DCD is present in about half of all individuals with ADHD, although these studies of DCD in ADHD and ASD have usually only included small numbers of girls, and most of our conclusions actually pertain to boys only (Gillberg & Gillberg, 1983; Gillberg, 1989; Landgren, Pettersson, Kjellman & Gillberg, 1996; Kadesjö & Gillberg, 1998, 1999, 2001; Rasmussen & Gillberg, 2000). According to the DSM-IV DCD is defined as motor co-ordination performance markedly inappropriate for age and IQ, causing significant interference with academic achievement or activities in daily living. Overall, there is a general dearth of studies looking at motor control problems associated with ADHD and ASD in girls. However Gaub and Carlson (1997) in their meta-analysis on ADHD reported similar rates of motor problems among girls and boys. Recently, Fliers, Rommelse, Vermeulen, and Attink (2008) replicated these results for adolescents with ADHD.

Reading and writing disorders (RWD) have been shown to be common in clinically referred children with ADHD (predominantly males) (Pennington, Groisser & Welsh, 1993; Kadesjö & Gillberg, 1999). RWD can clinically be divided in reading comprehension and/or word decoding and/or spelling problems. Research has indicated that difficulties in both word decoding and reading comprehension (and spelling) are present at a high rate among children with ADHD (Maughan & Carroll, 2006). Very few studies have looked at RWD in ASD (Minshew, Goldstein, Taylor & Siegel, 1994), and none has reported on reasonably sized group of girls.

Gender issues in child and adolescent psychiatry generally and in ESSENCE in particular

For decades, research on the development of psychopathology in childhood and adolescence has been dominated by a primary focus on boys (Crick & Zahn-Waxler, 2003; Kistner, 2009). The explanations provided to account for these circumstances have been that boys have more “adjustment difficulties” relative to girls, which would make them more likely to elicit the attention of others. Boys’ difficulties have often also had more life threatening consequences for themselves (completed suicide) and others (physical violence) and these problems have been viewed as more problematic than difficulties in girls. We also need to take into account the male dominance in the societies studied (Bourdieu, 1984, 2001; Moi, 1991). This, in itself, at least theoretically, could have contributed to girls being left out from research into child and adolescent psychiatric disorders (and other medical specialities) (Hammarström & Ripper, 1999). Finally virtually all published studies have shown that the prevalence rates of psychiatric disorders, are greater for boys than girls during early and middle childhood (Hartung & Widiger, 1998). However the underlying mechanism, that contribute to the estimated sex differences in prevalences and developmental trajectories of disorders is still not known (Rutter, Caspi & Moffitt, 2003). Although the need for systematic and proactive evaluation of the role of gender in psychological and psychiatric research has been recognized for many years (e.g. Scarr, 1988; Kopp & Gillberg, 1992), developmental psychopathologists have only recently turned serious, systematic attention to this issue (Cicchetti & Sroufe, 2000).

According to existing research, during early childhood (prior to 4 years) girls and boys are equally likely to exhibit adjustment difficulties (Maccoby, Snow & Jacklin, 1984; Keenan & Shaw, 1997). This is in line with the similar child psychiatric clinic referral rates found for both genders during this age-period (Kopp & Gilberg, 2003). However from 5-11 years of age, boys are much over-representative. During adolescence girls attend child psychiatric units more often than boys (Falkestav, Holm & Thernlund, 1997; Kopp & Gillberg, 2003). During adolescence, girls are also more prone than boys to suicide attempts (even though more boys commit suicide), and depression (Ivarsson & Gillberg, 1997; Olsson & von Knorring, 1999).

Most empirical studies indicate that boys are 3-10 times more likely than girls to show adjustment and disruptive behaviours problems such as CD, ODD, ADHD, and physical aggression during the late preschool and elementary school years (McDermott, 1996; Hartung & Widiger, 1998). During early adolescence, adjustment problems tend to be more equally distributed across the genders (McGee, Feehan, Williams & Anderson, 1992; Hartung & Widiger). However, adolescent boys continue to outnumber girls in terms of physical aggression and violence, and they also show more criminal behaviour (Loeber & Stouthamer-Loeber, 1997). Psychotic disorders, in one study from our centre, were equally common among adolescent girls and boys (13-19 years) (Gillberg, Wahlström, Forsman, Hellgren & Gillberg, 1986), although more girls had affective psychosis and boys more often schizofreniform psychosis.

ASD has long been considered to be a rare condition. However, recently, many epidemiological studies have reported as many as 0.5-1.5% of affected children in the general population of school age children with male: female ratios of about 3-4:1 in population cohorts, and about 5-14:1 in clinical settings, with, in general, the highest sex-ratios reported for cognitively relatively high-functioning children with ASD (Wing & Potter, 2002; Fombonne, 2005; Baird et al., 2006; Gillberg, Cederlund, Lamberg & Zeijlon, 2006; Ellefsen, Kampmann, Billstedt, Gillberg & Gillberg, 2007). However two population surveys (Lesinskienė & Puras, 2001; Mattila et al., 2007) have recently found boy: girl ratios for Asperger’s disorder/High Functioning Autism (HFA) of only 1.6- 2:1. Baker (2002) and Sturm et al. (2004) have also recently reported higher rates of clinically referred and assessed girls with ASD without learning disorder (LD). There is, however, a marked uncertainty about the “real” prevalence of ASD in girls.

The most cited prevalence rate for ADHD is about 5% of the general population of school age children (Seahill & Schwab-Stone, 2000). Based on a review of 21 epidemiological studies published before 2005 (Kopp, Hellgren, Petterson, Rehnqvist & Thelander, 2005) we concluded that prevalence rates ranged

from 1.5 to 10.3% of girls in the community, and that boy: girl-ratios varied from 1.1:1 to 3.7:1 in the methodologically sound studies. Age did not influence reported rates in girls, whereas they tended to decrease with age in boys.

Although the gender difference in clinically referred children is usually greater than population ratios with ratios from 16/1-2.4/1 (Gaub & Carlson, 1997; Kopp et al., 2005; Nøvik et al., 2006). However there has been a change during the latest years. From my own study (2003) we changed the ratio from 4% to 40% (including both ADHD and ADHDS) during a 5 years period, caused by more in depth assessment in every girl with suspicion to ADHD. Girls have been reported to be referred when they are older, when school failure is obvious, or when they have an emotional disorder masking the ADHD (Brown, Madan-Swain & Baldwin, 1991; Kato, Nichols, Kerivan & Huffman, 2001; Biederman, Mick, et al., 2002; Quinn, 2008). Although some studies have shown very hyperactive girls coming earlier than boys (Berry et al., 1985).

Is there a gender difference in the phenotypes of ASD and/or ADHD?

The question whether or not girls with ASD have a somewhat different phenotype than boys with ASD, cannot be safely answered on the basis of published research. Possibly the most important gender difference that might influence the presentation of core autistic symptoms has to do with the different social development, and with the different styles in choice of playmates and interests observed in girls and boys in the general population (Maccoby & Jacklin, 1974; Maccoby, 1998; Geary, 2002; Baron-Cohen, 2003). This gender difference in social relationships and in attentional focus - including restricted behaviour - has recently sparked research interest (Kopp & Gillberg, 1992; Baron-Cohen, 1997; Skuse, 2000, 2005, 2006; Baron-Cohen, Knickmeyer & Belmonte, 2005; Knickmeyer, Baron-Cohen, Raggatt & Taylor, 2005). Population surveys on autistic traits at all ages (Baron-Cohen, Wheelwright, Skinner, Martin & Clubley, 2001; Constantino & Todd, 2003; Posserud et al., 2006; Allison et al., 2008; Williams et al., 2008; Skuse et al., 2009) have all confirmed that males have more autistic traits than females. Other studies have confirmed females' greater empathizing ability and males' greater systemizing capacity documented from the first few years up to adulthood (Conellan, Baron-Cohen, Wheelwright, Batki & Ahluwalia, 2000; Baron-Cohen & Wheelwright 2004; Auyeung et al., 2009). These gender differences would reasonably lead to males being more prone to present with the phenotype that we associate with ASD, the symptoms of which are captured in existing autism questionnaires, for example the Autism Spectrum Screening Questionnaire (ASSQ) (Ehlers & Gillberg, 1993)

A female ADHD phenotype with less hyperactive/impulsive behaviours and more inattentive problems (also including shyness and social isolation, and, conversely, hyper-talkativeness), has been proposed in some reports (Gaub & Carlson, 1997; Quinn & Nadeau, 2002, (p. 453); Weiss, Worling & Wasdell, 2003). However there is no empirical data to support a definitive conclusion. On the other hand two meta-analytic studies found females to be less hyperactive and less inattentive than their male counterparts (Gaub & Carlson, 1997; Gershon, 2000). This might partly be explained by the lower scores found in "normal" girls on hyperactive and inattentive items (Achenbach, Howell, McConaughy & Stanger 1995; Westerlund, Ek, Holmberg, Näsvalld & Fernell, 2009). The difference in these levels of hyperactivity and inattention in the general population has led some researchers (McGee & Feehan, 1991; Weiss et al.; Waschbusch & King, 2006) to suggest that diagnostic criteria for ADHD should be adjusted to a different level of cut off for girls, and a recommendation for gender based norms in the questionnaires used for assessment (Arnold, 1996; Collett, Ohan & Myers, 2003). Most studies show similar ADHD core symptoms, similar cognitive and functional impairments at school, and similar comorbid psychopathology in girls and boys (Horn, Wagner & Jalongo, 1989; Sharp et al., 1999; Rucklidge & Tannock, 2001; Biederman & Faraone, 2004; Graetz et al., 2005). However, in clinical settings, girls more often than boys tend to be diagnosed with the inattentive subtype (Biederman, Mick et al., 2002; Rucklidge, 2010). In spite of the similarities found in the clinical presentation of girls and boys with ADHD, considerably fewer girls than boys are referred for assessment and treated adequately (Angold, Erkanli, Egger & Costello, 2000; Bussing, Zima et al., 2003; Bussing et al., 2005; Bauermeister et al., 2007; Ohan & Visser, 2009). This fact is partly explained by boys' more overt acting-out behaviours (including aggressive acts) in public, but also in homesettings, which leads them to be referred for assessments of ADHD (Gaub & Carlson, 1997; Maniadaki, Sonuga-

Barke & Kakouros, 2006). It has also been suggested by Groenewald, Emond, and Sayal (2009) and Ohan and Visser (2009) that parents and teachers believe professional help to be less effective for girls than for boys, and that parents have different explanations for the cause of the symptoms in girls and boys (psychological causes in girls and hereditary factors in boys) (Bussing, Gary, Millis & Garvan, 2003).

Diagnostic criteria for autistic disorder according to the DSM-IV

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

- 1. qualitative impairment in social interaction, as manifested by at least two of the following:**
 - a. marked impairment in the use of multiple nonverbal behaviors such as eye-to eye gaze, facial expression, body postures, and gestures to regulate social interaction
 - b. failure to develop peer relationships appropriate to developmental level
 - c. 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)
 - d. lack of social or emotional reciprocity
 - 2. qualitative impairments in communication as manifested by at least one of the following:**
 - a. delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative models of communication such as gesture or mime)
 - b. in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
 - c. stereotyped and repetitive use of language or idiosyncratic language
 - d. lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level
 - 3. restricted repetitive and stereotyped patterns of behaviour, interests, and activities, as manifested by at least one of the following:**
 - a. encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
 - b. apparently inflexible adherence to specific, non-functional routines or rituals
 - c. stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)
 - d. persistent preoccupation with parts of objects
- B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play.*
- C. The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder.*
-

Diagnostic criteria for Asperger's disorder according to the DSM-IV

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

Diagnostic criteria for Asperger syndrome according to Gillberg and Gillberg (1989/1991)

1. **Social impairment (extreme egocentricity)** (at least two of the following)
 - a) inability to interact with peers
 - b) lack of desire to interact with peers
 - c) lack of appreciation of social cues
 - d) socially and emotionally inappropriate behaviour

 2. **Narrow interest** (at least one of the following)
 - a) exclusion of other activities
 - b) repetitive adherence
 - c) more rote than meaning

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

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

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

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

Diagnostic criteria for attention-deficit/hyperactivity disorder according to the DSM-IV

A. Either (1) or (2):

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

Inattention

- (a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
- (b) often has difficulty sustaining attention in tasks or play activities
- (c) often does not seem to listen when spoken to directly
- (d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behaviour or failure to understand instructions)
- (e) often has difficulty organising tasks and activities (e.g., toys, school assignments, pencils, books, or tools)
- (f) is often easily distracted by extraneous stimuli
- (g) is often forgetful in daily activities

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

Hyperactivity

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

Impulsivity

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

- B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years
- C. Some impairment from the symptoms is present in two or more settings (e.g., at school (or work) and at home).
- D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning
- E. The symptoms do not occur exclusively during the course of PDD, schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g. Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Code based on type:

Attention-deficit/hyperactivity disorder, combined type: if both criteria A1 and A2 are met for the past 6 months

Attention-deficit/hyperactivity disorder, predominantly inattentive type: if criterion A1 is met but not criterion A2 for the past 6 months

Attention-deficit/hyperactivity disorder, predominantly hyperactive-impulsive type: if criterion A2 is met but not A1 for the past 6 months

AIMS

The main aims of the present thesis are to:

- 1) draw attention to the possibility that autism in girls may often be misdiagnosed or missed;
- 2) perform in-depth assessments, using state-of-the-art methodology, and clinically phenotype a large group of girls presenting in various settings as suffering from social and/or attentional deficits;
- 3) estimate the extent to which girls with social and/or attentional deficits are missed or misdiagnosed as regards clinical diagnoses of ASD, ADHD, or TD, and determine the age at which parents first apply for help for such girls;
- 4) analyse “comorbidity” patterns in girls with ASD and/or ADHD;
- 5) validate the functional impairment affecting girls with ASD and/or ADHD by contrasting them with a community sample of girls without any known neuropsychiatric disorder;
- 6) analyse the prevalence, type, and degree of motor control problems suffered by girls with ASD and/or ADHD, examine the clinical usefulness of a brief screening tool for motor control problems, and explore the contribution of certain predictors to such problems;
- 7) analyse the prevalence, type, and degree of reading and writing problems in girls with ASD and/or ADHD; and finally
- 8) develop and examine the clinical usefulness of a new clinical screening tool for autism (ASSQ-REV), particularly with a view to identifying girls with the disorder.

SUBJECTS AND METHODS

Subjects

An overview of all subjects participating in the studies of the present thesis is given in Table 1. The different studies will be referred to using Roman numerals. The target group of study I consisted of six girls with undetermined diagnosis attending the Gothenburg Child Neuropsychiatric Clinic (CNC). The Clinic girls of studies II through V all came from the same group of girls referred to the CNC during 1998-2001. The Community girls referred to in these studies came from one and the same cohort of girls from a Gothenburg suburb. Study V includes a group of Clinic boys matched with the Clinic girls.

Table 1. Number of participants and main diagnoses in the five studies

Group	Case study I <i>n</i> =6 6-10 years	100 Girls study II <i>n</i> =160 3-18 years	Motor study III <i>n</i> =157 3-16 years	Reading study IV <i>n</i> =110 8-17 years	ASSQ study V <i>n</i> =191 6-16 years
<i>Clinic girls</i>	6	100	74	56	71
ASD	6	46	40	20	27
ADHD		46	34	36	37
TD		3			3
Other		5			4
<i>Matched Clinic girls</i>		60	54	49	58
ASD		20	20	18	20
ADHD		34	34	31	32
TD		3			3
Other		3			3
<i>Matched Community girls</i>		60	57	54	58
ADHD		2			
FSIQ<80		1			1
<i>Matched Clinic boys</i>					62
ASD					20
ADHD					35
TD					1
Other					6

The Case study (Study I)

The target group of study I consisted of six girls, 6-10 years of age, with previously undetermined diagnosis. They attended the CNC after having been referred for social impairments.

The 100 Girls study (Study II)

Clinic girls ("All Clinic Girls, ACG")

One hundred Clinic girls, 3-18 years of age, with no prior suspicion of learning disability (LD), were included and examined at the CNC during the years 1998-2001. This group is occasionally referred to as "All Clinic Girls/ACG". About half of the group (*n*=47) were consecutively referred to the CNC for social, attention/academic or tic problems and the remaining 53 were referred directly to the project by different referring physicians (often initiated by e.g. active parents or school health

professionals/physicians aware of the project). The aim of including both types of referrals was to enable examination of a wider severity spectrum of neuropsychiatric disorders in girls. After controlling for IQ, no meaningful differences in terms of demography or overall clinical status were found between the two groups, and we decided to collapse the two for the purpose of the present study. We subgrouped the Clinic girls into three age-bands: 3-6 (“preschool”), 7-12, and 13-18 years comprising 24, 38, and 38 girls, respectively.

Exclusion criteria and attrition

Girls with diagnosed learning disorder (LD) ($FSIQ \leq 70$) already before referral were excluded. However, after full assessment, 12 Clinic girls were found to meet criteria for Learning disorder LD (most of them under age 6 years). These girls were retained because they had not been diagnosed or suspected of LD before entering the study. The two other exclusion criteria were parental inadequate command of the Swedish language, and serious physical disorders (e.g. cerebral palsy or severe epilepsy). We originally targeted 139 clinically referred girls, but 39 were excluded for the following reasons: 14 had LD diagnosed before referral, 2 had parents who were not fluent in Swedish, and 2 girls had severe physical disorders. Seven “no longer had any problems”, and a further 4 had already received an in-depth neuropsychiatric assessment at the time of appointment booking. In addition, 5 girls had mothers who did not want to take part in the study, and 5 failed to respond to contact.

Table 2. Main diagnoses and subtypes in different study groups

Main diagnosis/subtype	ACG	ACG	ACG	ACG	MClinG	MComG	MClinB
	3-18 years n=100	3-6 years n=24	7-12 years n=38	13-18 years n=38	7-16 years n=60	7-16 years n=60	6-16 years n=62
ASD	46	20	14	12	20		20
Autistic disorder	29	14	8	7	10		4
CDD	1	1	0	0	0		0
Asperger’s disorder	6	1	2	3	5		13
PDDNOS	10	4	4	2	5		3
ADHD	46	2	19	25	34	2	35
Combined	29	2	12	15	22	1	21
Inattentive	14	0	4	10	9	1	13
Hyperactive-impulsive	3	0	3	0	3		1
TD	3	0	2	1	3		1
Other	5	2	3	0	3		6

Main diagnoses in Clinic girls

After in-depth assessment at the CNC (see below) ASD, as the main diagnosis, was assigned in 46 of the Clinic girls, ADHD in 46, Tourette syndrome/tic disorder in 3 girls and “Other diagnosis” in 5 girls. Paper II gives a detailed description of all the 100 Clinic girls. For distribution of rates of main diagnoses and subtypes, please refer to Table 2.

ASD

The Clinic girls ASD group comprised 29 cases of autistic disorder, 1 case of childhood disintegrative disorder, 6 of Asperger’s disorder and 10 of PDD NOS/atypical autism.

ADHD

The Clinic girls ADHD group comprised 29 cases with combined subtype, 14 with inattentive subtype, and 3 with hyperactive-impulsive subtype.

TD

Two girls had Tourette's disorder and one girl chronic motor tic disorder as their main diagnoses. (A further 6 Clinic girls had TD as an additional diagnosis).

Other main diagnoses

Five girls had main diagnoses other than ASD, ADHD or TD; one each had mild mental retardation, learning disorder not otherwise specified (NOS), ADHDNOS, sleep disorder, and intermittent explosive disorder. This subgroup of girls with "Other" main diagnoses only appears in Paper V where Clinic girls and Clinic boys are compared.

Preschool girls (under age 7 years at assessment)

Among the Clinic girls of preschool age, 20 out of 24 (83%) had ASD, and 2 (8%) had ADHD. In the other two age-bands the rate of ASD was significantly lower (37% and 32% respectively), and the rate of ADHD significantly higher (50% and 66% respectively).

Matched Clinic Girls (MClinG)

All Clinic girls 7-16 years with a tested FSIQ ≥ 80 ($n=60$) were selected in order to match for age (\pm two months) with the Community girls (see below). MClinG comprised 20 girls with ASD, 34 girls with ADHD, 3 girls with TD and 3 girls with "Other" diagnoses. In papers II and III, comparisons are made between the ASD and ADHD groups of the MClinG and Community girls, and in study IV and V, with modified numbers of girls from the MClinG groups and Community girls.

Community girls (MComG)

Sixty non-clinically referred school girls from the community, 7-16 years of age, were selected consecutively from the local paediatric outpatient register in Mölnlycke, a Gothenburg suburb so as to match the MClinG group (see above). Girls with a known serious medical illness, neuropsychiatric disorder, major academic problems or LD, girls with sibling/s assessed for suspicion of neuropsychiatric disorder, and girls who had parents without adequate Swedish language skills were excluded. In this respect, the girls selected from the paediatric outpatient register, were "ordinary community girls" who had consulted the paediatrician for common childhood disorders. We therefore use the term Community girls for this group of girls. The further in-depth assessment (see below) revealed that two Community girls met full symptom criteria for ADHD and one had FSIQ < 80 , but this had not been established at the time of initial recruitment. Thus, there were 57 girls in the MComG group in study II. In order to recruit the MComG group, 84 families had originally been contacted, but 24 had been excluded due to academic problems ($n=7$), social-interaction problems ($n=3$), and refusal ($n=14$).

The Motor study (Study III)

The participants in the study of motor control problems comprised 54 school age girls (20 ASD girls, 34 ADHD girls) from the MClinG, 20 Clinic girls of preschool age (ClinPG = all the preschool ASD girls from ACG), and 57 Community girls. For the purpose of the motor study we selected from the MClinG (7-16 years) all girls with a main diagnosis of ASD ($n=20$) (autistic disorder (AD) (10), Asperger's disorder (5), PDDNOS (5)) and all with a main diagnosis of ADHD ($n=34$) (combined (22), inattentive (9), hyperactive-impulsive (3)) for comparison with the MComG ($n=57$). In the ASD group, all but one (95%) had ADHD in addition to ASD. In the ADHD group, 29% had some autistic features, while not meeting criteria for ASD.

The Reading study (Study IV)

The participants in the study reported in Paper IV were selected from the larger clinical cohort of 100 girls (ACG) and the MComG of 60 girls (7-16 years), so as to meet the following criteria: (i) chronological age 8 - 17 years, and (ii) full scale IQ above 70 as measured with the Wechsler Intelligence Scale for Children-Third edition (WISC-III; Wechsler 1992). Only Clinic girls with a main diagnosis of ASD and/or ADHD

were included. The total study group comprised 110 girls, including 20 ASD (12 autistic disorder, 4 Asperger's disorder, and 4 PDDNOS) of whom 19 also had ADHD, 36 ADHD (20 combined, 14 inattentive, and 2 hyperactive-impulsive), and 54 Community girls.

The ASSQ study (Study V)

One hundred and ninety one individuals, aged 6-16 years, were included in this study. This cohort consisted of three subgroups: (1) Clinic girls ($n=71$), (2) Clinic boys ($n=62$), and (3) Community girls ($n=58$). The two Clinic groups comprised cases with ASD, ADHD, and clinically referred cases with other neuropsychiatric diagnoses, including TD.

For inclusion in this study a complete ASSQ plus ASSQ-GIRL parent questionnaire (=ASSQ-REV) (see below) had to be completed, and there had to be a full scale IQ score available. Two Clinic girls with missing data from the ASSQ-GIRL were excluded. This led to a reduction of cases in the original Clinic girls' cohort, so that, in the present context, the Clinic girls comprised 71 cases (27 ASD, 37 ADHD, 7 Other, including TD (one each of Mild LD, learning disorder NOS, ADHDNOS, and Intermittent Explosive Disorder, plus three TD). Two of the 60 Community girls were excluded after full assessment, because they met full diagnostic criteria for ADHD. The girl with mild LD was retained for the purpose of this study. The final Community girl group therefore comprised 58 girls.

Clinic boys

Sixty-two boys, 6-16 years of age, referred and evaluated during the same time period and at the same clinic as the Clinic girls. The Clinic boys were all diagnosed and evaluated by one of four experienced neuropsychiatrists/ neuropediatricians and selected retrospectively from the medical records on the register. They were matched for age (± 6 months), intellectual level ($FSIQ \pm 10$ IQ points) and main diagnosis with the 6-16-year olds included in the Clinic girls group of the present study. Inclusion criteria were (i) a fully completed ASSQ-REV and (ii) a full IQ assessment. Exclusion criteria were similar as for the Clinic girls and defined as no LD ($FSIQ < 70$), inadequate parental command of the Swedish language and serious physical disorders (e.g. cerebral palsy and severe epilepsy). In the event, we ended up with a Clinic boy group of 62 cases of whom 20 had ASD, 35 ADHD and 7 Other, including two learning disorder NOS, four ADHDNOS and one TD.

Methods

Clinical neuropsychiatric examination (I-V, Table 3)

All Clinic girls and all Clinic boys received a full neuropsychiatric examination, including assessment of each child and adolescent by interview and examination and interview with the parent(s) regarding the child's early development and behavioural problems. The examination lasted on an average 20 hours for Clinic girls (8 hours for Clinic girls in study (I)), 10 hours for Community girls and 8 hours for Clinic boys. The author (and other specialists at the CNC) examined all the girls. Other doctors and psychologists at the CNC examined the boys. All children were screened using a parent interview schedule covering all child psychiatric and developmental diagnoses of the DSM-III-R (1987) third edition, revised (I), of the DSM-IV (1994) fourth edition (II-V) and of the DSM-IV-TR (2000) text revision (V).

Measures of intellectual functioning

The different developmental and intelligence scales used were chosen so as to take account of the child's chronological and developmental age, language development, and the availability of Swedish translation tests at the time of the studies. The following tests were used: The Griffiths Mental Developmental Scale for preschool children with poor/no language ($n=9$) (Griffiths, 1970) (I, II, III); WPPSI-R for preschoolers with sufficient language ($n=14$) (Wechsler, 1989) (II, III, V); Leiter International Performance Scale (Leiter, 1969) as an addition to other scales in girls with inadequate communication ability (I), WISC-R (Wechsler, 1974) (I), and WISC-III for 7-16-years-olds ($n=69$) (Wechsler, 1992) (II, III, IV, V); and the WAIS-R for 17-18- years-olds ($n=8$) (Wechsler, 1992) (II, III, V). Performance IQ (PIQ) from the WISC-III was used as a measure of nonverbal ability (III, IV), and as one of the possible predictors of motor functioning (III) and reading comprehension (IV). The vocabulary subtest from WISC-III was used as a proxy for oral vocabulary (IV).

Table 3. Instruments used in different studies

Instrument	Study I	Study II	Study III	Study IV	Study V
DSM-III-R	x				
DSM-IV		x	x	x	x
DSM-IV-TR					x
Gillberg & Gillberg Asperger syndrome criteria		x			
Griffiths	x	x	x		
WPPSI-R		x	x		x
WISC-R	x				
WISC-III		x	x	x	x
WAIS-R		x			x
Leiter International Performance Scale	x				
Sally-Anne test (theory of mind)	x				
CARS	x				
Conners-10 items		x			x
CTRS-R:L		x	x	x	
FTF		x	x	x	
ASSQ		x	x	x	x
ASSQ-GIRL					x
ABC	x		x		
DSRS		x			
GAF (DSM-IV)		x	x	x	
Socioeconomic status (SES)		x	x		
Parental educational level		x	x	x	
Severity of Psychosocial Stressors Scale (DSM-III-R)		x			
Economic stress		x			
Early symptoms' scale		x			
ADI-R		x			
CAPA Anxiety-OCD		x			
VABS-DLS		x	x		
ADOS-G		x			
School observation/pre-school observation		x			
Teacher interview		x	x		
General physical examination	x	x			
Minor Physical Anomalies scale (MPA)	x				
Cailler-Asuza Motor Scale		x	x		
Movement-ABC		x	x		
EB- motor test		x	x		
Motor- neurological- perceptual assessment (MNP)		x	x		
Speech development	x	x			
Word decoding ("H4")				x	
Word decoding ("Läs-och skriv"/"LS")				x	
Spelling ("Stavning")				x	
Spelling ("Läs-och skriv"/"LS")				x	
Reading comprehension ("DLS" grade 2-3)				x	
Reading comprehension ("DLS" grade 4-6)				x	
Reading comprehension ("Läs-och skriv"/"LS")				x	

Measure of theory of mind

Sally-Anne test

The Sally-Anne test, a purportedly specific test of theory of mind functions (Baron-Cohen, Leslie & Frith; 1985; Frith, 1989) was included in study I.

Questionnaires

10-item Conners' scale

The 10-item Conners' scale consists of 10 statements regarding the child's behaviour rated on a 4 point Likert scale tapping into attention and activity level with a possible total score of 30. Parents completed the 10-item Conners' scale (Conners, 1973; Goyette, Conners & Ulrich, 1978) (II, V).

CTRS-R:L

The CTRS-R:L (Conners' Teachers' Rating Scale - Revised: Long Form) was developed for assessment of ADHD and comorbid problems and covers 13 different subscales and rated with a 3-level Likert scale (Conners, Sitarenios, Parker & Epstein, 1998). The CTRS-R:L was completed by teachers of all school-age girls (7-18 years). We used the ADHD symptoms subscales: DSM-IV-inattentive (9 items) and DSM-IV-hyperactive-impulsive (9 items), in order to elicit ADHD symptoms (II) and as predictors in study (III) and (IV). The CTRS-R:L total scores (59 items) were used for indication of psychopathology and problem behaviour in study (II).

FTF

The FTF (Five To Fifteen questionnaire) comprises 181 statements, related to behavioural or developmental problems, arranged in domains and subdomains and rated on a 3-level Likert scale. The FTF questionnaire was used for all girls to elicit information about ADHD and comorbidities (Kadesjö et al., 2004). In assessment of ADHD symptoms we used two FTF subdomains: inattention (9 items) and hyperactivity-impulsivity (9 items) and as predictors for reading comprehension problems (IV) respectively motor problems (III). Regarding internalizing and behaviour symptoms we used the FTF domain scores for emotional/behavioural problems (32 items) (II). For peer relationships we selected four items from the domain "social skills" (item 140-143). We used the domain "motor skills" divided in two subdomains, *Gross motor skills* (items 1-7) and *Fine motor skills* (items 8-17) for the parents to report their daughter's motor functioning. The FTF scores from each of these subdomains were compared with the published norm percentiles for each age group (Kadesjö et al.). Cut off for motor dysfunction was set at the 90th centile.

ASSQ, ASSQ-GIRL, and ASSQ-REV

The ASSQ (Autism Spectrum Screening Questionnaire) (Ehlers & Gillberg, 1993; Ehlers, Gillberg & Wing, 1999) was created to screen for symptoms related to "high-functioning autism"/Asperger's disorder. It was completed by parents in girls ≥ 7 years in study II and III, ≥ 8 in study IV and >6 years in study V. The ASSQ comprises 27 items and is rated on a 3-point scale (0-2, maximum possible 54). The cut-off score for probable high-functioning autism spectrum disorder/Asperger's disorder was set by Ehlers et al. (1999) to more than ≥ 19 points. The total ASSQ score was used as a measure of autistic symptomatology in predicting motor functioning problems (III) and reading comprehension problems (IV).

For the purpose better capturing the female phenotype of ASD, 18 new items (ASSQ-GIRL) were chosen after focus group discussions with experienced colleagues, who had raised one or more of the items/symptoms as being often present in girls and adolescents with ASD. The new items cover both symptoms belonging to the autistic "triad" and adaptive functions in daily living skills. The 45-item (27 + 18) combined questionnaire (combining the ASSQ with the ASSQ-GIRL) will be referred to as the ASSQ - Revised Extended Version (ASSQ-REV).

ABC

The Autistic Behaviour Checklist (ABC) was developed to measure severe levels of autistic behaviour problems (Krug, Arick & Almond, 1980). Nordin and Gillberg (1996) on the basis of their studies suggested a lower cut off score for suspected ASD (≥ 45). This instrument was used in the Case study (I)

and in the preschool girls in study III to elicit information about autistic symptoms. The ABC is divided into five domains: perception (maximum score 26), contact (38), behaviour (38), language/speech (31), and other (25). Each item is scored from 4 to 1 with the highest score for symptoms strongly associated with autism (max total scores 158).

DSRS

The DSRS (Birlerson Depression Self-Rating Scale) was developed with a view to eliciting depressive symptoms. Here, it was used in girls ≥ 7 years (Birlerson, 1981). The girls completed the scale after having had each question read out aloud by the first author. DSRS contains 18 statements of the girl's situation the previous week with an intensity rating (*applies most of the time, sometimes or never*). A score of 2, 1 or 0 is awarded for each statement, depending on loading with depressive symptomatology.

Checklists and brief clinician's rating scales

DSM checklists

Diagnostic criteria according to the DSM (1987, 1994) (see Table 3) for childhood disorders were checked for all girls participating in the study. In study V, DSM-IV-TR (2000) also was checked.

Gillberg and Gillberg Asperger syndrome diagnostic criteria

Gillberg and Gillberg diagnostic criteria for Asperger's syndrome (Gillberg, 1991) were checked in Clinic girls with ASD ≥ 6 years (23/29), however, for diagnosis of Asperger's disorder the DSM-IV-criteria were used (see page 14).

Early symptoms

The parents were asked about eleven different symptoms noticed (and time of onset) during the first 3 years of life including regulatory problems (sleep, extensive crying, and feeding problems).

GAF

The DSM-IV Global Assessment of Functioning scale (GAF) (American Psychological Association, 1994) was scored by the author for the current period of time, considering psychological, social, and occupational functioning at the end of the examination of each Clinic and Community girl (II, III) GAF yields scores from 1 to 100, where a score of ≥ 70 indicates degrees of good functioning, or minor transient problems in psychosocial functioning.

Severity of Psychosocial Stressors Scale, Children and Adolescents

The DSM-III-R Severity of Psychosocial Stressors scale (American Psychological Association, 1987) was used for measuring acute and/or long-lasting psychosocial strains for all Clinic and Community girls (II) and was scored after information by parents and girls. The scale runs from 1 (*no stressor*) via 2 (*mild*), 3 (*moderate*), 4 (*difficult*), and 5 (*extreme*) to 6 (*catastrophic*).

Structured and semi-structured interviews

ADI-R

The Autism Diagnostic Interview – Revised (ADI-R) is a standardized investigator-based parent interview for use in the diagnosis of ASD (Lord et al., 1997). ADI-R was administered to parents of all Clinic girls and to 20 parents to the Community girls (on a one in three basis) (II). In accordance with Lord et al. we chose to report total scores and a score of 22 or more is used as a cut off score for presumably ASD.

CAPA, Anxiety and Obsessive-Compulsive Disorders (OCD) modules

The Child and Adolescent Psychiatric Assessment (CAPA) (Angold, Prendergast, Cox, Harrington, Simonoff et al., 1995) is an interviewer-based diagnostic psychiatric interview for girls aged 9 and older and their parents (II). A three-month "primary period" is used for their recalling of symptoms. Anxiety and OCD modules were used when interviewing all the mothers of the girls < 13 years and to all the girls > 12 years.

VABS-DLS

The Vineland Adaptive Behavior Scales - Daily Living Skills domain (VABS-DLS) is a semi-structured caretaker interview instrument that assesses day to day adaptive functioning (Sparrow, Balla & Cicchetti, 1984; Cicchetti, Sparrow, Volkmar, Cohen & Rourke, 1991). The Daily Living Skills' domain contains three subdomains: Personal, Domestic and Community. Age- equivalent standardized scores are reported for the domain, and raw scores for the subdomains. The VABS-DLS was given to all mothers of girls participating in study II and III.

Teacher interview

The educationalist interviewed all the teachers about the girls' behaviour and social problems, educational goal attainment (II) and about whether or not the girl participated in Physical Education (PE) (III) for the relevant grade.

Observational schedules

ADOS-G

The Autism Diagnostic Observation Schedule – Generic (ADOS-G) is a semi structured assessment of social interaction, communication, play and imaginative use of materials for individuals who may have autism or other PDDs (Lord et al., 2000). The ADOS-G was used when observing all Clinic girls and 20 Community girls whose parents had been given the ADI-R in study II.

CARS

The Childhood Autism Rating Scale (CARS) was developed as a diagnostic instrument to distinguish autism from other developmental disabilities in children (Schopler, Reichler, DeVellis & Daly, 1980; Schopler, Reichler & Renner, 1988). The CARS was used for two of the six girls in study I.

Preeschool and School observations

In study II all Clinic and most of the Community girls were observed at pre-school or at school by the study educationalists.

General physical examination

A general physical examination was performed in all cases. In addition to basic measures such as height, weight, and general health rating (not reported in this thesis), it included:

Minor Physical Anomalies (MPA) rating

Examination of Minor Physical Anomalies (MPA) (Waldrop & Halverson, 1971) was performed in study I.

Speech development rating

All Clinic and Community girls were assessed regarding language development and rated as falling into one of four categories by the first author: (1) no language, (2) talks only a few words, (3) more speech but not normal and (4) normal speech (I, II, III).

Motor control examination

The following age/development-appropriate tests for motor performance for diagnostic evaluation were used when examining Clinic and Community girls in study II and III; (1) the *Cailler-Asuza Scale* (Stillman, Sabers, Redfield & Stewart, 1977) for girls between 3- 4 years of age, (2) the *M-ABC* (Movement Assessment Battery for Children) for girls around 4-6 years (Henderson & Sugden, 1992), and (3) the *EB-test* (EB for Eva Beckung, the developer of the test) (Beckung, 2000) for girls aged 7-18 years since the instrument has been developed in our centre, has a wide age range (6-16 years), and because there are Swedish norms available.

The Cailler-Asuza Scale is a developmental motor assessment tool which measures the age of acquisition of motor milestones. The subscales for evaluation of motor development (postural control, locomotion, fine motor development and visomotor control as well as an assessment of the quality of movements (balance, coordination, asymmetries) was also done.

The twelve items of the Movement Assessment Battery for Children (M-ABC) for assessment of fine motor function, bilateral integration and balance in age band 1 were used. Low scores indicate good performance and high scores marked dysfunction (range 0-40).

Almost all Clinic and Community girls six years and over were assessed with the EB-test, a physiotherapy protocol comprising 59 items measuring: gross motor function (27 items), fine motor function (8 items), sensation (10 items), perception (5 items) and neurological tests (9 items). The quality and level of motor and sensory functions were scored on an ordinal four-point scale (0-3, 3 indicating no problems). The cut off for any motor functioning problems was defined as a score of <2.90. A mean score of 0-0.9 points was considered to reflect severe dysfunction, 1.0-1.9 point moderate dysfunction, 2.0-2.8 point mild dysfunction and 2.9-3.0 point no dysfunction.

Motor-Neurological-Perceptual assessment (MNP)

The brief screening test Motor-Neurological-Perceptual assessment (MNP) used in many previous studies from our centre and in clinical practise ("Medical Motor Examination" in Kadesjö & Gillberg, 1999) was performed in all Clinic girls 6 years and above, and in all Community girls by the author (III). The MNP comprises 9 items, each scored as 0= no signs, 1= slight dysfunction and 2= marked dysfunction (total scores range from 0-18) and divided into 3 subclasses, *Gross motor* (4 items: overall clumsiness, hopping 20 times on one foot, standing 20 seconds on one foot, jumping back and forth with alternating legs), *Fine motor* (3 items: cutting out 10 cm diameter paper circle, Bishop maze-tracing (Bishop, 1980), and finger-tapping) and *Neurological* (2 items: diadochokinesis (Gillberg & Gillberg, 1983) and walking on lateral aspects of feet (Fog & Fog, 1963)).

Reading and writing tests

All Clinic and Community school-age girls were given standardized tests of word decoding, reading comprehension and spelling. The assessment took approximately 1.5-2 hours in total. The results are reported in study IV. There was no single broad Swedish literacy test available that span the age range represented in this study. Great care was taken to create a test battery that was as internally homogenous as possible in terms of construct validity, even though this meant that the test stimuli had different "names" depending on age.

Word decoding

The H4-test (Franzén, 1997) a timed tests of single word reading were chosen as measure of word decoding efficiency and used for girls in grades 2 - 6 (8-12 years), while the LS-test (Johansson, 1992) was used for the older girls. The number of correctly read words/time unit was registered and converted to standard scores.

Spelling

The spelling test "Stavning" (Rockberg & Johansson, 1994) were used for girls in grades 2 - 6, while the LS-test was used for older girls. Both tests measure the ability to spell a target word presented in a sentence context.

Reading comprehension

The tests "Diagnostiska läs- och skrivprov" ("Diagnostic reading and writing tests") were used to assess reading comprehension for girls in grades 2 – 6 (DLS grade 2-3: Björkquist & Järpsten, 1975/1976; DLS grade 4-6: Järpsten & Taube, 1997). The LS test (Johansson, 1992) was used for older girls. These tests all consist of passage and text comprehension with comprehension questions or statements in a multiple-choice format.

Laboratory work-up

All Clinic girls with ASD were offered a battery of laboratory work-ups (I, II) (routinely performed on the clinic at that time) and all Clinic girls with ADHD with suspicion of EEG and/or any chromosomal anomalies (symptoms suspected of having convulsive character, symptoms suspected of Fragile X or any other chromosomal anomaly). The results of these tests are not discussed in this thesis.

Socioeconomic status and educational levels

The socioeconomic level was ascertained by using a shortened manual from Statistics Sweden (Statistics Sweden, 1982/1984). The breadwinner's socioeconomic status was divided into four levels (non-manual employees, intermediate, higher civil servants, self-employed) (II, III). The educational levels of all parents were evaluated and divided into four groups: (1) completed comprehensive school only, (2) completed sixth form college, (3) completed vocational training after sixth form college and (4) university degree (II, III, IV). The Clinic girls (II) were living under similar socioeconomic circumstances as Swedish families in the general population. The Community girls were better off than Swedish families with children living in suburbs (Statistics Sweden, 2003).

Economic stress

The economic stress in the family was assessed on a scale from no problems (1) to major problems (4).

Diagnostic process

The DSM-III-R diagnostic criteria were used in study I *and* the DSM-IV diagnostic criteria were used throughout in studies II-V. Exclusion criteria were disregarded. Diagnoses according to DSM-IV were assigned when both symptom *and* impairment criteria for a disorder were met. The main diagnosis was used to define the problems considered most disabling at the time of assessment.

PDDNOS was diagnosed if 4 or 5 criteria for autistic disorder (AD) were met including at least one *criterion* from the social interaction domain. "Autistic traits" was diagnosed if 2-3 criteria were met for AD.

The age-of-onset criterion for ADHD was disregarded because of the uncertain research evidence regarding the importance of an onset before the age of seven (Barkley & Biederman, 1997). The criterion relating to impairing symptoms in two settings (DSM-IV), was considered met if either parents and teachers or by parents and one or more of the clinicians agreed that the ADHD symptoms were causing impairments. ADHDNOS was diagnosed if there were 5 symptoms of at least one of the ADHD subtypes.

Depressive disorder was the term used for all (depressed) mood disorders of clinically impairing quality.

The presence of two or more simultaneous anxiety disorders was used as a significant measure of the experienced added burden and presented as multiple anxiety disorders (Biederman et al., 1999).

Sleep disorder was diagnosed if sleep onset latency exceeded an hour or if there were more than two problematic awakenings every night.

All girls eleven years or older were asked about substance use or abuse (including smoking cigarettes, drinking alcohol and taking drugs). The definition for regular use was set at smoking 1-5 cigarettes daily, drinking alcohol at least once a month, and/or taking drugs sometimes.

In studies II and III developmental coordination disorder (DCD) was diagnosed in accordance with the DSM-IV when specific motor coordination tests demonstrated severe problems relative to norms (see Kopp, Beckung, & Gillberg, 2010).

Reading/Writing Disorder (RWD) in study III was defined as standardized score below 75 on either Word decoding, Reading comprehension and/or Spelling tests, which equals the bottom 5% in the normal distribution (Willcutt & Pennington, 2000), and matches the prevalence rate of the disorder according to the DSM-IV (1994).

On the basis of all available information the first author assigned diagnoses after a thorough discussion with the professionals who had performed the individual assessments in study I-V. In study II, which formed the diagnostic basis of studies II-V, all records and diagnoses were rechecked on two further occasions. Cases presenting diagnostic difficulties even after this process ($n=5$) were discussed with the main scientific supervisor (Christopher Gillberg), before a final decision was made.

Statistical methods used

The SPSS 14.0 was used for all analyses in studies II-V, and SPSS and SAS 9.2 in study V. All significance tests were two-tailed. Due to the many statistical tests carried out the significance level of $\alpha=0.01$ was chosen in most instances. For continuous variables, the Kruskal-Wallis test was used for three-group comparisons, which if significant, was followed up with the Mann-Whitney U-tests for pairwise comparisons. For dichotomous variables chi-square test was used for the three-group comparison, which, if significant, was followed up with Fisher's exact test for pairwise comparisons. For comparisons of ordered categorical variables between two groups Mantel Haenszel-chi-squares tests were used in study V. Comparison across individuals regarding ADHD symptom clusters was analyzed with the Wilcoxon sign rank test in study II. To investigate whether movement impairment was associated with every-day adaptive behaviour as measured by the VABS-DLS in study III, we ran IQ-partialled Pearson's correlations. Convergent validity was measured between the total scores of the ASSQ versions and corresponding scores from the Conners-10-items with Pearson's correlations in study V. For all other correlations, nonparametric Spearman correlation coefficients (r_s) were used.

In study II, approximate effect sizes were calculated for continuous variables according to Rosenthal (1991, p.19). The test statistics were first converted into a z-score by SPSS, and the z-score was then converted into the effect size estimate, r , with the equation $r=z/\sqrt{N}$ (in Field, 2005, p. 532), where N is the number of total observations. Odds ratios (OR) with 95% confidence interval (CI) were calculated to provide an estimate for the relationship between two categorical variables.

In study III, we used four of the continuous variables from the correlation analysis as possible predictors of motor dysfunction in regression analysis. The chosen dependent variable, MNP was approximately normally distributed. In order to select independent predictors of MNP, multiple stepwise linear regression analysis was used. For comparisons across different measures of motor performance percentage of agreements and Cohen's kappa (κ) were calculated for categorical variables. For the test of systematic differences McNemar tests were used in related pairwise motor measurements.

In study IV, we confirmed, according to procedures in Field (2005), that assumptions for regression analysis were met regarding linearity and homoscedasticity between reading comprehension scores and errors of prediction. Distributions were also checked for violations of normality using Kolmogorov-Smirnov tests and histogram inspection. Reading comprehension looked normally distributed and was not significantly different from normality and could therefore reliably be used as dependent variables in regression analysis. The internal consistency of the ASSQ-GIRL was measured using Cronbach's alpha. Bivariate logistic regression was used to calculate odds ratio with 95% CI and ROC area under the curve (AUC). In order to select items for prediction of ASD-diagnosis in different study groups multiple

stepwise logistic regression analyses were used. ROC-curves were produced with a view to assessing and visualizing the discriminating power between ASD and non-ASD cases of the three ASSQ-versions and the selected independent items of the ASSQ-REV for different study groups.

Informed consent and ethics

The mothers of all girls provided informed consent to participate. All girls ≥ 16 years also provided informed consent personally. The Ethics Committee of the University of Gothenburg approved the study of the Community girls and a genetic study to which many of the Clinic girls contributed. The Clinic girls and the Clinic boys were regular clinical patients undergoing in-depth clinical investigations at the CNC. All interviews, questionnaires and other assessment tools were used as part of routine assessment of all patients attending the clinic 1999-2002 (when the Clinical cohorts were established). At the time of the study, no specific ethical approval by and Ethics Committee was required for these patient groups.

RESULTS

Study I

In study I all the 6 girls referred for “unclear” social and/or attention deficits ended up with a diagnosis of autistic disorder (AD) with full symptom criteria, and clinical functional impairment after meticulous assessment. All but one had an IQ>70 IQ and all talked in full sentences. Mean age at diagnosis of autism was 8.2 (SD 1.3) years. However, on average six years earlier, the parents had consulted a professional without being properly “understood” or helped with their daughter’s behaviour and/or deviant development. The mean ABC score was 55 (SD 16).

Study II

Out of the 100 Clinic girls, only 12 had been diagnosed with ASD, ADHD or TD prior to the study, and another 9 girls had been given other child psychiatric diagnoses. Almost half of the Clinic girls (47%) had been referred by a paediatrician, 26% by a child psychiatrist, and 22% by a school health doctor.

Overall rates of main diagnoses among ACG

In the Clinic preschool group 20 out of 24 (83%) had ASD, and 2 out of 24 (8%) had ADHD as their main diagnosis (see Table 2). Among school-age girls and teenage girls the rate of ASD was 37% and 32% respectively, and the rate of ADHD 50% and 66% respectively.

Only three Clinic girls had impaired functioning caused by chronic tics (Tourette’s or chronic motor tic disorder).

Five girls had “Other” main diagnoses (LD, LDNOS, ADHDNOS, sleep disorder, intermittent explosive disorder), and they will only be reported further in study V.

ASD

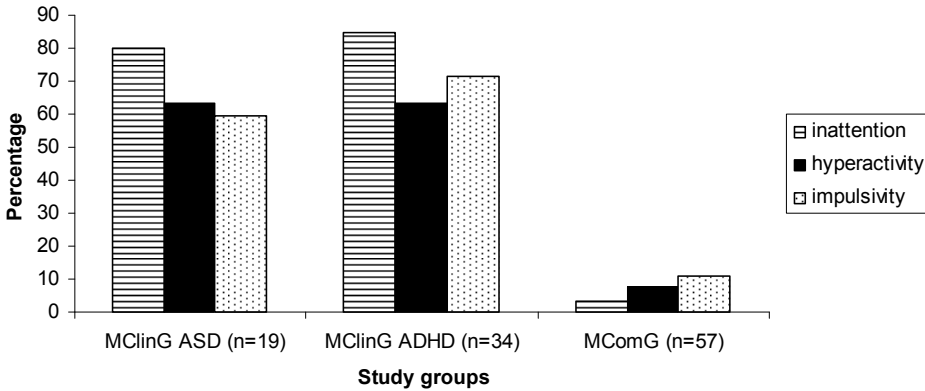
Autistic disorder was the diagnosis assigned in 29 girls (14 of whom were under 7 years of age), Asperger’s disorder in 6, childhood disintegrative disorder in 1, and PDDNOS/atypical autism in 10. Mean age at ASD diagnosis was 8.8 (SD 4.4) years. Comorbid ADHD was diagnosed in 95% of school age girls with ASD. A tendency for fewer symptoms - particularly impulsivity ($p=.06$) and inattention ($p=.12$) - was found in this group than in those with a diagnosis of “main ADHD” (see Figure 1). The only individual symptom that separated the ADHD and ASD groups was that relating to blurting out answers, which was much more frequent in the “main” ADHD group ($p=.027$). As compared with the Community girls, the ASD and ADHD group differed greatly on all three ADHD clusters (inattention, hyperactivity and impulsivity) ($p<.001$).

FSIQ was negatively correlated with number of autistic disorder criteria ($r_s=-0.40$, $p<.01$).

Nine of the 46 girls with ASD, all ≤ 5 years, had no or very little language at the time of evaluation, and 21 of these girls had (superficially) normal speech.

The results from the behaviour and emotional questionnaires were surprisingly similar across the two main diagnostic groups, ASD and ADHD. Significantly higher scores for ASD were only found for autistic symptoms as measured by the ASSQ, ADI-R and ADOS-G. We did not find any meaningful correlation with age in the ASD and the ADHD groups on any of the assessment tools used.

Figure 1. Mean percentage of the three DSM-IV ADHD clusters in the matched study groups



ADHD

In ACG, the mean age at main diagnosis of ADHD was 13.0 (SD 3.4) years. Fifty-four percent of the girls with ADHD were referred during adolescence (≥ 13 years) compared to 26% of the girls with ASD ($p < .02$), and only two girls were younger than 7 years at referral (both with a very high level of hyperactivity). The combined subtype of ADHD was most prevalent (63%), followed by inattentive (30%) and hyperactive-impulsive (6%) subtypes. The most often endorsed domain within the ADHD category was inattention followed by impulsivity and hyperactivity (Figure 1) (inattention compared to hyperactivity $p = .002$, and impulsivity $p = .051$).

In comparison with the Community girls all the DSM-IV symptoms of ADHD were significantly more common in the MClInG with ADHD (Figure 2). Mean values were significantly higher compared to MComG for all 18 items ($p < .001$)

Autistic traits were seen in 28% of all girls with a main diagnosis of ADHD.

TD

TD was diagnosed in 9 Clinic girls (3 with main diagnosis, 3 with ASD and 3 with ADHD). OCD as well as ADHD were present in all except one of these girls. The girls with TD did not differ with regard to FSIQ, VABS-DLS, and GAF from those girls with main ADHD.

Overlap of disorders in Study II

The vast majority of all Clinic girls with a main diagnosis of ASD, ADHD or TD had at least one additional diagnosis (mental retardation, learning disorders, developmental coordination disorder, communication disorders and specific phobia not included) and only six girls (6.3%) had no one. The mean number of additional diagnoses in school-age girls with ASD and ADHD was 3.9 (SD 1.9) and 2.9 (SD 1.6) respectively ($p = .06$).

Figure 2. Individual ADHD symptoms (DSM-IV) in MClInG with ADHD and MComG

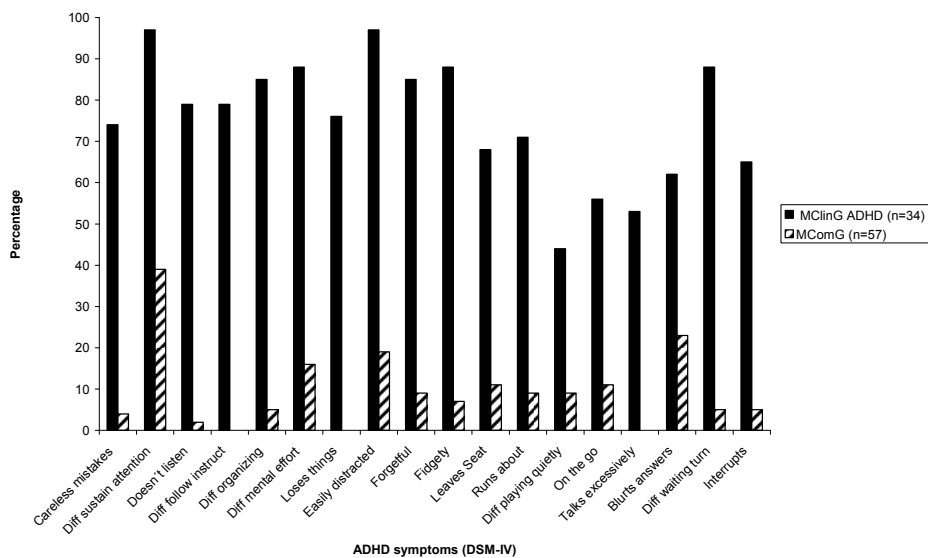


Table 4. The most prevalent additional diagnoses in MClInG and MComG

Additional diagnosis	MClInG ASD n=20 (%)	MClInG ADHD n=34 (%)	MComG n=57 (%)	<i>p</i> ASD vs ADHD	<i>p</i> ASD vs MComG	<i>p</i> ADHD vs MComG
Reading and/or writing disorder ***	8 (40%)	20 (56%)	3 (6%)	.81	.002	<.001
DCD	5 (25%)	10 (29%)	6 (10%)			
ODD at home***	11 (55%)	22 (65%)	0	.67	<.001	<.001
ODD at home and at school***	3 (15%)	13 (38%)	0	.130	.032	<.001
Depressive disorder***	7 (35%)	11 (32%)	2 (3%)	1.0	.002	<.001
Multiple anxiety disorder**	7 (35%)	6 (18%)	3 (5%)	.27	.004	.126
Specific phobia**	8 (40%)	7 (21%)	4 (7%)	.22	.002	.116
OCD***	7 (35%)	11 (32%)	3 (5%)	1.0	.004	.002
Sleep disorder**	8 (40%)	16 (47%)	10 (17%)	.83	.090	.006

Note. ** $p < .01$, *** $p < .001$ on overall calculations

Other comorbid disorders

The comorbidity pattern was similar across the ASD and ADHD groups for depressive disorder, separation anxiety disorder and obsessive-compulsive disorder (OCD), as well as for TD, enuresis and Sleep disorder. However girls with ASD had 2.5 times more multiple anxiety disorders compared to girls with ADHD (Table 4). School-age girls with ADHD showed more self-harm, and previous suicide attempts. Three girls with ADHD had previously had a major depressive episode without reaching the threshold for statistical significance (see Kopp, Berg-Kelly & Gillberg (in press)) for all comorbid disorders).

The girls with ADHD were reported nearly six times more likely (29%) to smoke cigarettes compared to girls with ASD (5%). This difference fell short of statistical significance ($p=.060$). No girl with ASD was drinking alcohol regularly. Only one of the girls with ADHD was addicted to drugs.

Three out of the 34 girls with ADHD (and none of those with ASD) were given a diagnosis of CD. There was some overlap between depressive disorder and multiple anxiety disorders in both the ASD and ADHD groups (20%, $n=5$, and 12%, $n=4$ respectively).

Except for DCD (see below), there was no correlation with age for any comorbid disorder in any of the clinical diagnostic groups.

Early symptoms

The majority of Clinic girls had at least one early symptom, and in all MclinG ($n=60$), the mean number of early symptoms was 2.7 (SD 1.9, possible range 0-11). More early symptoms were noticed in the ASD group (3.4 (SD 2.2)) compared to the ADHD group. In 6/20 girls (30%) girls with ASD and 14/34 (41%) with ADHD did the parents not report any of the early symptoms during the child's first year. The difference as compares with the Community girls was considerable (Table 5).

Table 5. Early symptoms among matched girls

Early symptom	MclinG ASD $n=20$ (%)	MclinG ADHD $n=34$ (%)	MComG $n=57$ (%)	p^1
Interaction problems with parents	12 (60%)	4 (12%)	0	<.001
Sleep disturbances first year	8 (40%)	8 (23%)	10 (17%)	.085
Sleep disturbances first 1- 3 years	10 (50%)	10 (29%)	11 (19%)	.02
Early hyperactivity	5 (25%)	13 (38%)	2 (3%)	<.001
Excessive crying first year	5 (25%)	4 (12%)	6 (10%)	.21
Feeding problems first year	5 (25%)	3 (9%)	2 (3%)	.011
Not satisfied/demands being carried	5 (25%)	3 (9%)	2 (3%)	.094
Temper tantrums (1-3 years)	7 (35%)	12 (35%)	6 (10%)	.007
Often trips and falls	3 (16%)	4 (12%)	0	.015
Difficult to handle	3 (15%)	8 (23%)	0	<.001
Language delay at 3 years	5 (25%)	0	0	.004

Note. ¹on overall calculations

Functional characteristics in ASD and ADHD groups

FSIQ was similar in the ASD and ADHD groups in school-age girls (MClInG) (Table 6). The ASD girls were more impaired in all daily living skills (VABS-DLS). The difference between the two diagnostic groups was most marked in the community subdomain ($p < .008$), while both ASD and ADHD groups differed significantly from the MComG in community and domestic skills ($p < .001$ and $p < .001$ respectively $p = .01$ and $p = .001$). The very low level in community and household competencies (including low in hygiene) - especially in the ASD group - was obvious in the age-inappropriate dependence on others for nearly all daily living activities. In global functioning (GAF) the difference between the two main diagnostic groups was more prominent, with much lower GAF scores in the ASD group (Table 6).

Table 6. Functional characteristics in different study groups

Characteristic	MClInG ASD <i>n</i> =20	MClInG ADHD <i>N</i> =34	MComG <i>n</i> =57	<i>p</i> ASD vs ADHD	<i>p</i> ASD vs MComG	<i>p</i> ADHD vs MComG
Full Scale IQ ***	98.7 (12.5)	97.2 (10.7)	108.5 (11.0)	.71	<.005	<.001
Range	80-120	83-121	89-130			
GAF, current ***	35.0 (6.4)	46.2 (5.4)	84.7 (7.9)	<.001	<.001	<.001
Range	25-50	35-60	67-98			
VABS-DLS total score***	64.8 (23.3)	75.8 (15.6)	98.8 (9.3)	.023	<.001	<.001
Range	24-129	48-103	77-129			

Note. ** $p < .01$, *** $p < .001$ on overall calculations

Peer relationships in ASD and ADHD groups

Relations to peers were difficult for girls both in the ASD and the ADHD group. However problems were more marked for in ASD group. The majority of girls with ASD were “lonely”. The peer problems were present both at school and during leisure times, resulting in parents needing to participate in other activities outside school. Nearly all of the Community girls had a lot of friends and shared many different leisure activities with them.

Table 7. Peer relationships items (FTF) in different study groups

Question (FTF)	MClInG ASD <i>N</i> = 20 (%)	MClInG ADHD <i>n</i> =34 (%)	MComG <i>n</i> =57 (%)	<i>p</i> ¹
Difficulties joining group activities	15 (75%)	20 (59%)	3 (5%)	<.001
Rarely together with same-aged children	14 (70%)	15 (44%)	2 (3%)	<.001
Difficulties participating in group activities	15 (75%)	20 (59%)	3 (5%)	<.001
Difficulties getting friends	15 (75%)	20 (59%)	3 (5%)	<.001

Note. ¹on overall calculations

School situation in ASD and ADHD groups

Both the ASD and ADHD groups showed high levels of school dysfunction as evidenced by their significantly higher percentage of in-school tutoring, placement in special classes (higher for ASD group) and underachievement in math and in Swedish language/literature i.e. not attaining educational goals reported by teachers. Almost every second girl with ASD or ADHD reported having been exposed to bullying (Table 8). In both diagnostic groups the level of truancy was considerable, but girls with ADHD more often had occasional absence, usually came to school but did not participate in lessons, came too late or skipped occasional lessons, while girls with ASD often had longer times of not going to school (from half a week to months or even a whole academic year).

Treatment history in ASD and ADHD groups

All of the girls with ASD and 85% of girls with ADHD in MClInG had been seen by other professionals before the current clinical examination (Table 8). At the age of four, 47% of the all Clinic girls (ASD 40% and ADHD 32% respectively in the MClInG) had consulted a professional for behaviour/learning problems and nearly every second girl with ADHD (48%) had attended a child psychiatric unit prior to our assessment. There was a mean delay of 5.5 and 5.1 years respectively for the ASD and ADHD groups between first seeking help and being given an “appropriate” diagnosis. No girl had received stimulant medication.

Table 8. School situation and treatment history in different study groups

Characteristic	MClInG	MClInG	MComG	<i>p</i>	<i>p</i>	<i>p</i>
	ASD <i>n</i> =20 (%)	ADHD <i>n</i> =34 (%)	<i>n</i> =57 (%)	ASD vs ADHD	ASD vs MComG	ADHD vs MComG
<i>School functioning</i>						
Math underachieving ^{1**}	8 (40%)	17 (50%)	0	.67	<.001	<.001
Swedish language/literature underachieving ^{1***}	6 (30%)	14 (41%)	0	.60	<.001	<.001
Repeated grade	2 (10%)	3 (9%)	0			
Tutoring ***	10 (50%)	12 (35%)	0	.44	<.001	<.001
Special class placement ***	6 (30%)	3 (9%)	0	.106	<.001	.10
Bullying***	12 (60%)	17 (50%)	4 (7%)	.67	<.001	<.001
<i>Treatment history</i>						
Counselling under age 5 ***	8 (40%)	11 (32%)	0	1.0	<.001	<.001
Counselling ever **	20(100%)	29 (85%)	6 (10%)	.18	<.001	<.001
CAP ^{2***}	13 (65%)	17 (50%)	2 (3%)	.44	<.001	<.001

Note. ¹not attained educational goals for relevant grade, ²CAP = Child and Adolescent Psychiatry
 p* < .01, *p* < .001 on overall calculations

Physical disorders

Only a few Clinic girls seemed to be influenced from time to time by their physical disorder during the course of the neuropsychiatric assessment (one girl with generalised epilepsy, one with severe eczema, and one with severe headache after a chicken pox infection) (Table 9).

Matched Clinic and Community cases

MComG had overall significantly fewer psychiatric diagnoses, higher FSIQ and were, overall, functioning very much better than MClInG (Tables 4, 6, 7, 8). The MClInG with ADHD had a 7.5 times increased risk of smoking cigarettes compared to the Community girls (see Kopp, Berg-Kelly & Gillberg (in press)).

Relationship between some background variables and clinical findings

The matched ASD, ADHD and Community groups did not differ significantly regarding mother working outside the home, socioeconomic status, parent education levels, or environmental stress. Both the matched ASD and ADHD groups differed significantly from the MComG with fewer intact families ($p=.008$ respectively $p=.01$) and with more difficult economic circumstances ($p<.002$ respectively $p<.001$). Only 2/57 Community girls lived with a single mother, while 5/20 in the ASD group and 6/34 in the ADHD group ($p=.022$, and $p=.06$, respectively).

Table 9. Physical disorders in the main diagnostic groups and Community girls

Physical disorder	ACG ASD 3-18 years <i>n</i> =46	ACG ADHD 3-18 years <i>n</i> =46	ACG TD 3-18 years <i>n</i> =3	MComG 7-16 years <i>n</i> =60
Valvular pulmonary stenosis	1			
Omphalocele, mitral/tricuspid insufficiency		1		
Generalised epilepsy	2	3		
Absence epilepsy residual state	1			
Velopharynx insufficiency	1			
Kidney disease				1
Uretary reflux		2		1
Severe overweight	3	3		
Short for age	1			
Precocious puberty	1			1
Sensory hearing loss	2			2
Conductive hearing loss	1	3		
Post infectious headache (severe)			1	
Severe allergy				1
Coxa plana	1			
Severe exzema		1		

Study III

DCD

The rate of diagnosed DCD was highest, although not significantly different, in the ADHD group (32%) compared to the ASD group (25%). In the Community group, 12% had DCD (Table 10).

Overall motor control performance

All motor control tests indicated more motor difficulties in the two Clinic groups compared to the Community group (Table 10).

EB-test

Both the ASD and ADHD groups had more motor control dysfunction than the Community group, as indicated by significantly lower mean scores on the EB-test (Table 10). The girls with ADHD showed the lowest scores.

Girls with ASD did particularly poorly on the Sensation subdomain of the EB-test and also showed the lowest mean score on Gross motor ability, and both diagnostic subgroups showed a trend towards dysfunction in the subdomain of Fine motor ability.

Table 10. Overall results of motor findings: mean (SD) or *n* (%)

Motor measurement	MClinG ASD N=20 (%)	MClinG ADHD n=34 (%)	MComG n=57 (%)	<i>p</i> ASD vs ADHD	<i>p</i> ASD vs MComG	<i>p</i> ADHD vs MComG
DCD	5 (25%)	11 (32%)	7 (12%)	.80	.32	.042
EB-test **	2.90 (0.13)	2.90 (0.12)	2.96 (0.57)	.87	.018	.004
Gross motor***	2.93 (0.10)	2.93 (0.12)	2.97 (0.06)	.30	<.001	.010
Fine motor	2.94 (0.11)	2.95 (0.08)	2.99 (0.04)	.80	.023	.021
Neurological test	2.89 (0.20)	2.86 (0.24)	2.93 (0.12)	.36	.86	.122
Perception	2.84 (0.29)	2.85 (0.24)	2.90 (0.20)	.89	.176	.081
Sensation***	2.90 (0.15)	2.93 (0.13)	3.00 (0.03)	.44	<.001	<.001
MNP**	3.70 (2.49)	2.50 (2.50)	1.82 (2.41)	.070	.003	.091
FTF***	0.51 (0.34)	0.50 (0.43)	0.11 (0.18)	.60	<.001	<.001
Not in Physical education (PE)***	10 (53%) ¹	13 (38%)	0	.47	<.001	<.001
Non-right-handedness	7 (35%)	10 (29%)	5 (9%)	.89	.020	.024

Note.¹ One girl had not started school, ***p*<.01, ****p*<.001 on overall calculations

MNP

According to MNP assessment, girls with ASD (45%) had more problems than girls with ADHD (15%) and only this Clinic group differed significantly from the Community group.

FTF reported motor control problems

According to the parent FTF-ratings of motor problems, 65% of the girls with ASD and 59% of those with ADHD were estimated to have considerable gross and/or fine-motor problems. These results dramatically separated the ASD and ADHD groups from the Community group (7%), and the level of parent-reported motor control problems was about twice that documented at professional testing (EB-test and/or MNP). The majority of these Clinic girls (76%) were ≥11 years old, while most of the girls with motor dysfunction according to the original EB-test (64%) and/or MNP (57%) were younger than 11 years.

Physical Education (PE)

About half of the girls with ASD (53%), and two in five (38%) of those with ADHD, did not participate in PE at school, while all the girls in the community group participated in PE. Most of the non-participating Clinic girls were ≥11 years (70% ASD and 92% ADHD).

Comparisons across different motor control measures

In the collapsed matched study group (both Clinic and Community girls) (*n*=111) we found moderate to good agreement (κ =0.40; 0.37-0.60) across the different professional motor measurements and no significant systematic differences. When comparing results on the FTF and the DCD-diagnosis/EB-test and MNP, only fair agreement (κ = 0.20-0.40) was found with many “false positive” FTF cases (Table 11).

Table 11. Motor findings, % agreement, and kappas in MClInG and MComG

Motor measurement	% Agree¹ dysfunction	% Agree "ok"	% Disagree² dysfunction vs "ok"	% Disagree "ok" vs dysfunction	% Agree overall	Cohen's kappa (κ)	p
DCD vs MNP	12 %	73 %	9 %	6 %	85 %	.51	<.001
DCD vs EB	13 %	73 %	8 %	6 %	86 %	.55	<.001
DCD vs FTF	13 %	59 %	8 %	21 %	71 %	.28	.002
EB vs MNP	9 %	72 %	10 %	9 %	81 %	.37	<.001
EB vs FTF	13 %	60 %	6 %	21 %	73 %	.32	<.001
MNP vs FTF	13 %	61 %	5 %	21 %	74 %	.34	<.001

Note. ¹agree=agreement, ²disagree=disagreement

Correlations

The results on the MNP correlated significantly both with those of the EB-test ($r_s=-0.60, p<.001$), and the FTF ($r_s= 0.42, p<.001$) in all matched girls ($n=111$). Younger age was associated with more motor impairments on the MNP and EB-tests but not for the FTF. Higher scores on the MNP correlated significantly with severity of autistic as well as ADHD symptomatology.

Regression analyses

With MNP as the dependent variable in the multiple stepwise linear regression analysis, both age, autistic symptomatology and PIQ were independent predictors, together accounting for 35% of the total variance.

Motor control problems in ClinPG with ASD

The vast majority of preschool girls with ASD (80%) had DCD. In the intellectually average or near average ClinPG ASD group ($n=13$) the rate was 69%, whereas in those with LD ($n=7$) it was 100%. These high rates of DCD contrasted markedly with the DCD frequency among school girls with ASD (25%) ($p=.002$). In the whole ASD subgroup, parents rated motor control problems (FTF) at very similar rates as clinicians.

Study IV

Reading comprehension, word decoding and spelling performance

Girls with ASD did not differ statistically, when comparing means (SD), from girls with ADHD or from Community girls as regards reading comprehension, word decoding or spelling. Girls with ASD performed, on average, within the normal range on the three literacy measures, while girls with ADHD performed about one standard deviation below the population mean on all three tests. Girls with ADHD also differed significantly on the three tests from the Community girls (Table 12).

Reading and writing disorders

In the ASD group and in the ADHD group 40% (8/20) and 56% (20/36) respectively, had at least one index of reading/writing disorder according to the test results on reading comprehension, word decoding and/or spelling (n.s). The corresponding rate among the Community girls was 6% (3/54) ($p<.001$). In more than half of the cases in the Clinic groups two or three impairments in the domains of reading comprehension, word decoding and/or spelling were present.

Table 12. Reading and spelling results in the matched study groups

Measures	ASD	ADHD	MComG	<i>p</i>	<i>p</i>	<i>p</i>
	<i>n</i> = 20 mean (SD)	<i>n</i> = 36 mean (SD)	<i>n</i> = 54 mean (SD)	ASD vs ADHD	ASD vs MComG	ADHD vs MComG
Word decoding**	94.5 (24.1)	85.6 (23.3)	98.6 (15.4)	.20	.36	< .001
Reading comprehension***	93.2 (16.8)	87.9 (17.6)	101.1 (11.9)	.25	.16	< .001
Spelling***	89.8 (20.4)	82.2 (19.8)	99.2 (11.0)	.16	.09	< .001

Note. ** $p < .01$, *** $p < .001$ on overall calculations

Correlations

ASSQ scores correlated significantly with reading comprehension problems ($r_s = -0.32$, $p < .001$), but not with word decoding or spelling. Significant negative correlations were observed between ADHD symptomatology and word decoding, reading comprehension and spelling ($r_s = -0.33$, $r_s = -0.42$, $r_s = -0.38$, $p < .001$).

Predictors

In testing whether autistic and/or ADHD symptomatology might be linked to reading comprehension problems, these factors were entered into stepwise regression analyses, with oral vocabulary as step 1, word decoding as step 2, nonverbal ability (PIQ) as step 3. The ordering of autistic symptomatology and ADHD symptomatology was altered in the 4th and 5th step, after oral vocabulary, word decoding and nonverbal ability. Step 1-3 all accounted for unique variance in reading comprehension. Both autistic and ADHD symptomatology accounted for significant, although small proportions, of the variance as regards reading comprehension. However when the ADHD factor was entered as the 4th step (and the autistic factor as 5th) this symptomatology accounted for 7.1% of the variance without autistic features contributing to the variance.

Study V

Mean scores

Girls with ASD did not differ significantly from boys with ASD on the mean scores of the ASSQ, ASSQ-GIRL, or the ASSQ-REV (Table 13). The ASD groups of girls and boys had significantly higher means on the three ASSQ-versions compared to girls and boys with ADHD. No mean score differences were found between girls and boys with ADHD. The Community girls differed significantly ($p < .001$) from the ASD girl group as well as from the ADHD girl group on all ASSQ-versions.

Correlations

Significant correlations were found between total scores of the ASSQ and the ASSQ-GIRL in all study groups without any significant effect for age. Male gender was significantly correlated with higher mean scores on both ASSQ ($r_s = -0.30$) and ASSQ-GIRL ($r_s = -0.25$).

Response analyses

ASD

The distributions of the response categories no (0), somewhat (1) and definitive (2) of the ASSQ-REV items in the different study groups are listed in Table 14. The distribution of individual ASSQ-REV items across girls and boys with ASD showed non-significant differences on a majority of the items.

Table 13. Means (SD) of the ASSQ-versions and Conners-10 item questionnaire

Questionnaire	Girls ASD n=27	Girls ADHD n=37	<i>p</i> Girls ASD vs ADHD	Boys ASD n=20	Boys ADHD n= 35	Girls MCom n=58	<i>p</i> Boys ASD vs ADHD	<i>p</i> Girls vs boys ASD	<i>p</i> Girls vs boys ADHD	<i>p</i> Girls ASD vs girls MCom	<i>p</i> Girls ADHD vs girls MCom
ASSQ	24.3	13 .0	<.001	24.6	14.4	2.6	<.001	.88	.63	<.001	<.001
(SD)	(9.1)	(6.0)		(8.7)	(9.7)	(3.0)					
ASSQ-GIRL	14.4	9.2	<.001	13.9	9.1	1.7	.010	.74	.66	<.001	<.001
(SD)	(5.3)	(4.7)		(6.7)	(6.4)	(1.9)					
ASSQ- REV	38.7	22.3	<.001	38.5	23.5	4.3	.001	.79	.97	<.001	<.001
(SD)	(13.4)	(8.9)		(14.5)	(15.3)	(4.6)					
Conners-10	15.2	16.8	.21	13.0 ¹	15.0 ²	1.9 ³	.43	.40	.40	<.001	<.001
(SD)	(6.8)	(6.5)		(9.0)	(8.7)	(2.0)					

Note. ¹n=15, ²n=34, ³n=57, MCom=MComG

Only the item 17 “lacks best friend” was significant ($p < .005$) with higher scores in the ASD boy group. Four further items showed statistical trends ($p < .05$) with more rated symptoms among girls than boys, item 8 “has a different voice/speech”, item 22 “difficulties in completing daily activities because of compulsory repetitions”, item 33 “avoids demands”, and item 40 “interacts mostly with younger children”. When only taking into account the response category “definitive”, item 33 “avoids demands” was the one that reached statistical significance ($p = .008$) with a much higher endorsed symptom rate in girls.

“Male-oriented” Asperger syndrome items

In the original ASSQ-study, 16 of the 27 items were considered most specific for Asperger syndrome (Ehlers & Gillberg, 1993), six of these 16 in the present study were endorsed only in boys (“is old-fashioned”, “is regarded as an eccentric professor”, lives in own world with restricted idiosyncratic intellectual interests”, “accumulates facts on certain subjects”, “lacks common sense”, and “is poor at games”), and one item was endorsed only in girls “different voice or speech”.

ADHD

Boys with ADHD were twice more likely than girls with ADHD to be ASSQ high scorers ($ASSQ \geq 19$). However only three individual items significantly differentiated boys from girls (“accumulates facts on certain subjects” and “literal understanding”) and girls with ADHD more often than the boys with the same diagnosis had the item “avoids demands” endorsed (Table 14).

ASD and ADHD

Girls and boys with ASD scored higher than girls and boys with ADHD on the majority of ASSQ-REV items (Table 14). Girls with ASD and girls with ADHD differed more often than boys with ASD and ADHD on the ASSQ-REV items (significant difference on 13 and 7 items respectively). On two of the “social interaction items” (“can be with other children but only on own terms” and “lack best friends”) the difference between girls with ASD and ADHD was less marked than for boys with these diagnoses. Boys with ADHD scored higher than boys with ASD on item 41 “engages in dangerous activities”, while girls with ASD were more prone to dangerous activities compared to girls with ADHD.

Table 14. ASSQ and ASSQ-GIRL: % somewhat and definitive responses (definitive in brackets)

Item	Girls ASD n=27 (%)	Boys ASD n=20 (%)	p	Girls ADHD n=37 (%)	Boys ADHD n=35 (%)	p	MCom n=58 (%)	p Girls ASD vs ADHD	p Boys ASD vs ADHD	p Girls ASD vs MCom	p Girls ADHD vs MCom	
<i>ASSQ</i>												
1. Is old-fashioned or precocious*	52 (18)	75 (25)	.24	27 (3)	29 (6)	.83	29 (3)	.021	.001	.017	.85	
2. Is regarded as an "eccentric professor" by other children*	33 (15)	50 (25)	.27	3 (0)	23 (0)	.012	12 (2)	<.001	.005	.010	.125	
3. Lives somewhat in a world of his/her own with restricted idiosyncratic intellectual interests*	85 (26)	90 (45)	.26	30 (3)	43 (14)	.144	5 (2)	<.001	<.001	<.001	.005	
4. Accumulates facts*	56 (18)	65 (35)	.36	8 (3)	44 (23)	<.001	0 (0)	<.001	.189	<.001	.056	
5. Has a literal understanding of ambiguous and meta-phorical language*	44 (33)	55 (20)	1.0	14 (3)	43 (17)	.006	0 (0)	.001	.59	<.001	.007	
6. Has a deviant style of communication with an old-fashioned or "robotlike" language*	56 (41)	65 (35)	1.0	13 (5)	15 (6)	1.0	3 (2)	<.001	<.001	<.001	.117	
7. Invents idiosyncratic words and expressions	37 (15)	20 (15)	.56	8 (0)	32 (3)	.014	9 (2)	.002	1.0	.002	.77	
8. Has a different voice or speech*	78 (48)	50 (20)	.035	27 (16)	34 (3)	.73	7 (0)	<.001	.09	<.001	.001	
9. Expresses sounds involuntarily; clear threats, smacks or screams	41 (37)	50 (25)	1.0	32 (22)	46 (20)	.57	3 (3)	.32	.73	<.001	<.001	
10. Is surprisingly good at some things and surprisingly poor at others*	78 (52)	85 (65)	.46	59 (22)	70 (26)	.44	7 (0)	.021	.020	<.001	<.001	
11. Uses language freely but fails to make adjustments to fit social contexts or the needs of different listeners*	70 (56)	90 (45)	.72	73 (46)	63 (29)	.205	17 (2)	.77	.052	<.001	<.001	
12. Lacks empathy*	78 (33)	70 (20)	.42	49 (16)	40 (20)	.88	9 (0)	.023	.21	<.001	<.001	
13. Makes naïve and embarrassing remarks*	48 (33)	60 (25)	1.0	51 (30)	51 (31)	1.0	10 (2)	1.0	1.0	<.001	<.001	

14. Has a deviant style of gaze	74 (48)	60 (30)	.23	30 (8)	31 (6)	1.0	3 (2)	<.001	.013	<.001	.001
15. Wishes to be sociable but fails to make relationships with peers*	81 (48)	70 (50)	.72	57 (13)	54 (20)	.87	9 (3)	.003	.067	<.001	<.001
16. Can be with other children but only on his/her terms	70 (37)	85 (35)	.70	73 (19)	51 (11)	.090	15 (0)	.50	.007	<.001	<.001
17. Lacks best friends	48 (30)	85 (70)	.005	62 (32)	66 (26)	.88	28 (5)	.47	.006	.009	.001
18. Lacks common sense*	41 (11)	65 (10)	.28	40 (5)	51 (9)	.35	0 (0)	.84	.51	<.001	<.001
19. Is poor at games; no idea of cooperating in a team, own goals*	89 (63)	95 (80)	.26	51 (19)	51 (20)	1.0	7 (5)	<.001	<.001	<.001	<.001
20. Has clumsy, ill coordinated, ungainly, awkward movements or gestures*	55 (33)	60 (20)	.73	54 (30)	34 (9)	.036	21 (5)	.88	.077	<.001	<.001
21. Has involuntary face or body movements	48 (41)	40 (15)	.25	30 (27)	26 (17)	.58	3 (3)	.180	.59	<.001	<.001
22. Has difficulties completing simple daily activities because of compulsory repetition of certain actions or thoughts	45 (30)	20 (5)	.043	16 (5)	26 (11)	.34	2 (0)	.006	.53	<.001	.010
23. Has special routines; insists on no change*	71 (41)	75 (40)	1.0	27 (8)	48 (17)	.096	3 (2)	<.001	.037	<.001	.003
24. Shows idiosyncratic attachment to objects	63 (30)	50 (40)	1.0	24 (5)	23 (3)	.83	10 (2)	.001	.003	<.001	.113
25. Is bullied by other children	45 (15)	45 (10)	1.0	51 (24)	43 (17)	.46	3 (2)	.43	.85	<.001	<.001
26. Has markedly unusual facial expression	30 (7)	30 (5)	1.0	11 (0)	14 (3)	.56	0 (0)	.038	.27	<.001	.021
27. Has markedly unusual posture	41 (11)	30 (15)	.84	13 (5)	17 (3)	1.0	0 (0)	.040	.163	<.001	.007
<i>ASSQ-GIRL</i>											
28. Copies you (can be in a very discrete way)	37 (26)	40 (15)	.86	11 (5)	20 (9)	.41	9 (2)	.012	.22	<.001	.62
29. Episodes of eating problems	70 (48)	75 (35)	.86	49 (27)	31 (6)	.044	22 (3)	.064	<.001	<.001	<.001
30. No time perception	78 (56)	60 (45)	.32	70 (38)	60 (20)	.145	14 (3)	.29	.31	<.001	<.001
31. Too much sympathy	41 (5)	55 (20)	.44	30 (8)	34 (14)	.61	9 (0)	.36	.27	<.001	.004
32. Extremely interested in pop/ rock bands, soap operas or natural disasters	22 (15)	45 (20)	.26	16 (5)	37 (9)	.119	2 (0)	.43	.43	.002	.010
33. Avoids demands	85 (63)	75 (20)	.020	78 (51)	48 (11)	<.001	7 (3)	.42	.110	<.001	<.001
34. Very determined	89 (48)	85 (60)	.84	43 (13)	57 (31)	.109	21 (5)	<.001	.023	<.001	.030

35. Difficulties with choice; always avoids choosing	59 (52)	85 (45)	.50	54 (24)	48 (17)	.55	14 (3)	.160	.005	<.001	<.001
36. Difficulties with self-care	78 (33)	45 (25)	.105	46 (19)	46 (14)	.88	9 (2)	.034	.72	<.001	<.001
37. Carefree or overmeticulous as regards physical appearance/dress	63 (33)	60 (35)	1.0	32 (5)	51 (14)	.082	9 (2)	.003	.22	<.001	.008
38. Naïve	30 (7)	30 (25)	.44	35 (8)	34 (11)	1.0	7 (0)	.84	.72	.004	<.001
39. Comes too close to others	33 (26)	35 (15)	.73	27 (13)	34 (6)	1.0	7 (2)	.43	.67	.001	.006
40. Interacts mostly with younger children	59 (41)	35 (10)	.039	54 (19)	37 (11)	.204	5 (0)	.23	1.0	<.001	<.001
41. Engages in dangerous activities	22 (18)	5 (5)	.151	24 (11)	51 (17)	.054	5 (0)	.86	.005	.004	.003
42. Exaggeratedly fanciful	26 (15)	50 (15)	.33	32 (13)	34 (9)	.87	0 (0)	.86	.31	<.001	<.001
43. Talks without content	30 (18)	50 (20)	.36	22 (8)	26 (11)	.72	0 (0)	.37	.132	<.001	<.001
44. Writes long stories (can be in stark contrast to level of talk)	18 (11)	35 (10)	.52	11 (0)	9 (6)	.78	2 (0)	.21	.090	.006	.073
45. Acts or lives different parts (TV stars, videos, animals)	41 (33)	40 (25)	.75	13 (3)	26 (11)	.158	2 (0)	.002	.20	<.001	.027

Note. * indicates ASSQ-items most specific for Asperger's syndrome according to Ehlers and Gillberg (1993)

Community girls

Community girls differed significantly from girls with ASD on all except two items (“old-fashioned” and “eccentric professor”). Fewer than 10% of Community girls scored definitely on any of the 45 ASSQ-REV items. Community girls also differed significantly from girls with ADHD on the majority of items (Table 14).

Convergent validity of the ASSQ-GIRL

Convergent validity (Pearson) between parent ASSQ-GIRL and the full ASSQ scale was good ($r=0.85$, $n=191$, $p<.001$). ASSQ-GIRL scores and Conners-10 scores were less strongly correlated ($r=0.66$, $n=184$, $p<.001$).

Known-groups validity of the ASSQ-GIRL

The mean total scores of the ASSQ-GIRL differentiated between the ASD and ADHD groups of both girls and boys, but this was not the case with the Conners-10 (Table 13).

Internal consistency/content validity of the ASSQ-GIRL

The internal consistency (Cronbach's α) of the ASSQ-GIRL items in all study groups were all high in total group, all girl group, Clinic girl group, Clinic boy group (0.85, 0.85, 0.73, 0.81) and somewhat lower in Community group (0.48) showing that the content of the instrument has a high internal consistency.

ASD versus non-ASD cases

Discriminant validity was demonstrated by determining the ability to distinguish ASD from non-ASD participants on all ASSQ-REV items by logistic regression and ROC analyses. Some items showed acceptable to excellent discriminating ability (area under the curve $AUC > 0.70$). The five most important items ($p<.01$) for each study group are presented in Table 15. Only one item (“lives in own world”) distinguished well ($AUC \geq 0.80$) across all five groups. The item “different voice/or speech” distinguished in all three girl groups and the items “robotlike language”, “eating problems” and “can be with other children but only on own terms” only in the boy group. The items “avoids demands”, “poor at games” and “lives in own world” were found to best distinguish ASD from non-ASD in the collapsed group of ASD girls and Community girls.

Prediction of ASD

ROC analyses were performed in order to best predict an ASD-diagnosis versus non-ASD with logistic stepwise regression analyses. The sum scores of ASSQ, ASSQ-GIRL and ASSQ-REV, and the most significant ASSQ, and ASSQ-GIRL items for each study group were selected (Figure 3a-e). All three ASSQ-versions revealed significant effects in all study groups with $AUC \geq 0.79$, except in the Clinic boy group ($AUC = 0.73$). The ASSQ captured more ASD-diagnoses than ASSQ-GIRL or ASSQ-REV in all study groups except in the collapsed group of ASD girls and Community girls. However three items (“lives in own world”, “deviant gaze” and “poor at games”) in the total group and one single item (“poor at games”) in the Clinic boy group showed higher predicting ability than the sum score of ASSQ. High predictive power was also shown for the ASSQ-GIRL items “very determined”, and “self-care problems” in the Clinic girls and “no time perception”, “avoids demands” and “talks without contents” in the ASD girl and Community group.

Table 15. Logistic regression analyses distinguishing ASD from non-ASD diagnosis on the five most important ASSQ-REV items in different study groups

ASSQ-REV item	Total group <i>n</i> =191 AUC ¹	All girls <i>n</i> =129 AUC	Clinic girls <i>n</i> =71 AUC	Clinic boys <i>n</i> =62 AUC	ASD girls and Community girls <i>n</i> =85 AUC
3. Lives in own world	0.85	0.87	0.82	0.80	0.90
6. Has a “robotlike” language				0.76	
8. Different voice/speech		0.83	0.77		0.87
10. Uneven abilities	0.77				0.87
14. Deviant style of gaze	0.77	0.82	0.78		
16. Other children on own terms				0.71	
19. Poor at games	0.84	0.84		0.84	0.91
23. Insists on no change			0.75		
29. Eating problems				0.76	
33. Avoids demands					0.90
34. Very determined	0.79	0.83	0.77		

Note. ¹AUC= Area under the curve, all *p* < .001

Figure 3 a-e. ROC curves for different ASSQ versions in different study groups

3 a. Total group (n=191)

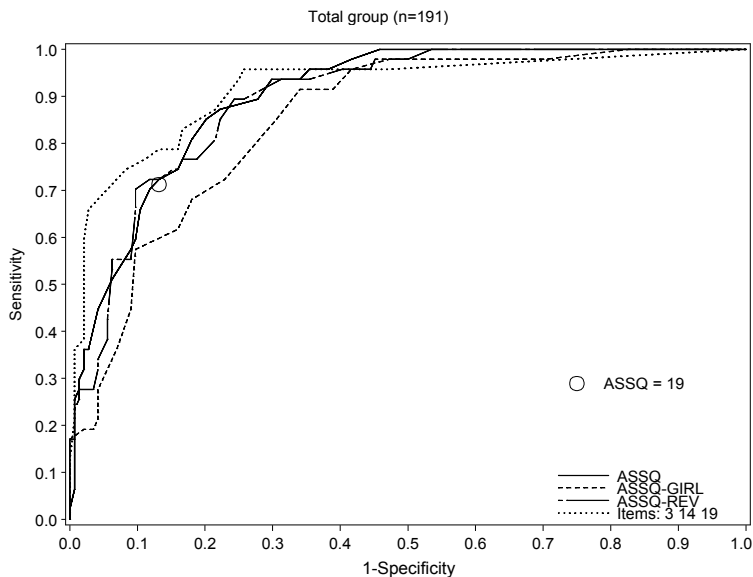


Figure 3b. All girls ($n=129$)

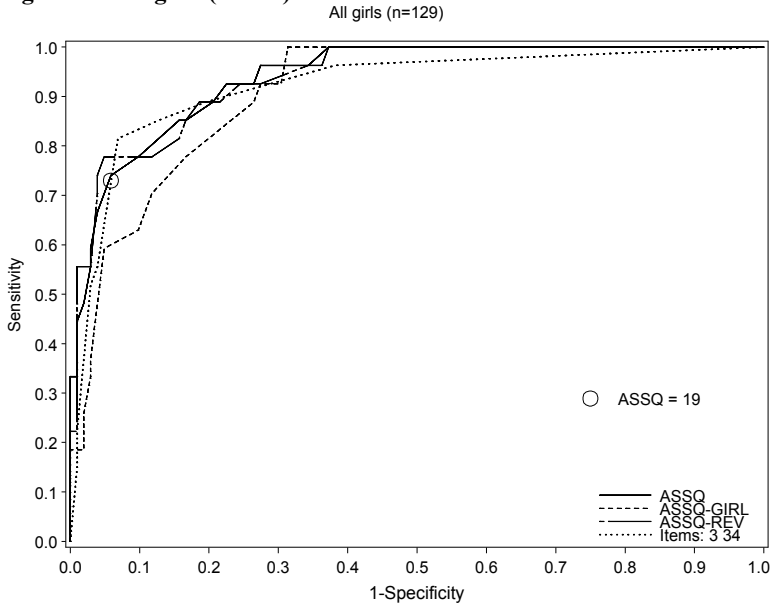


Figure 3 c. Clinic girls ($n=71$)

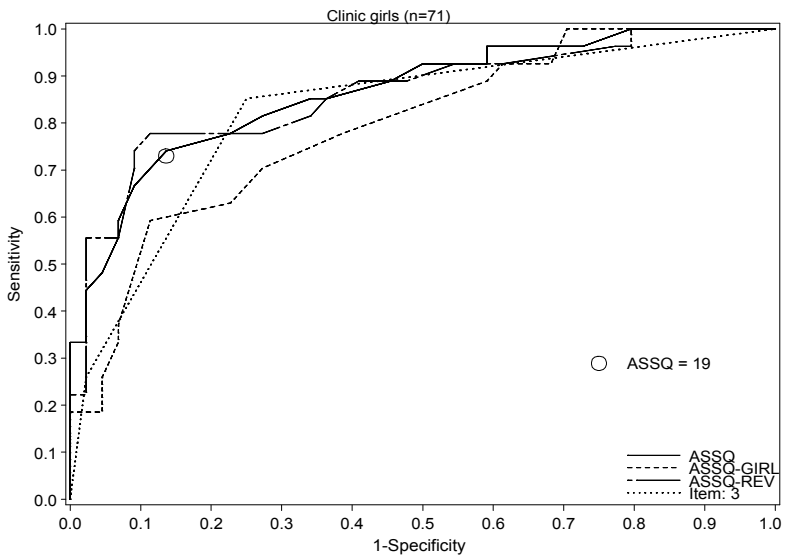
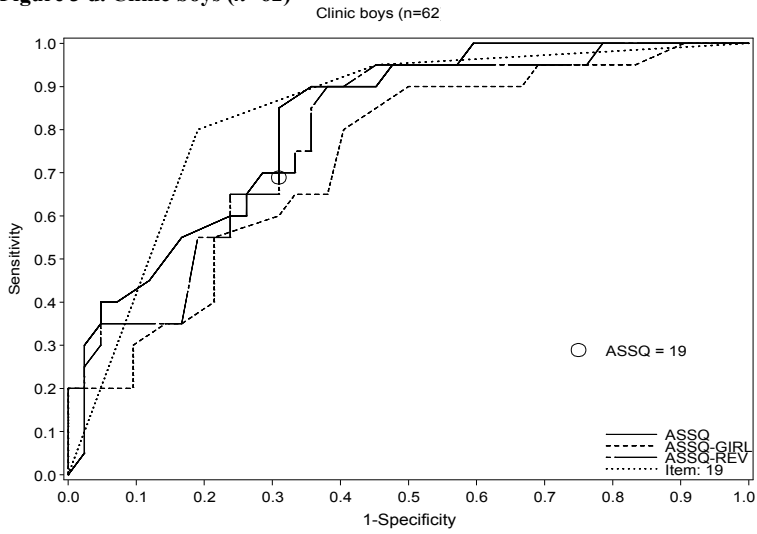
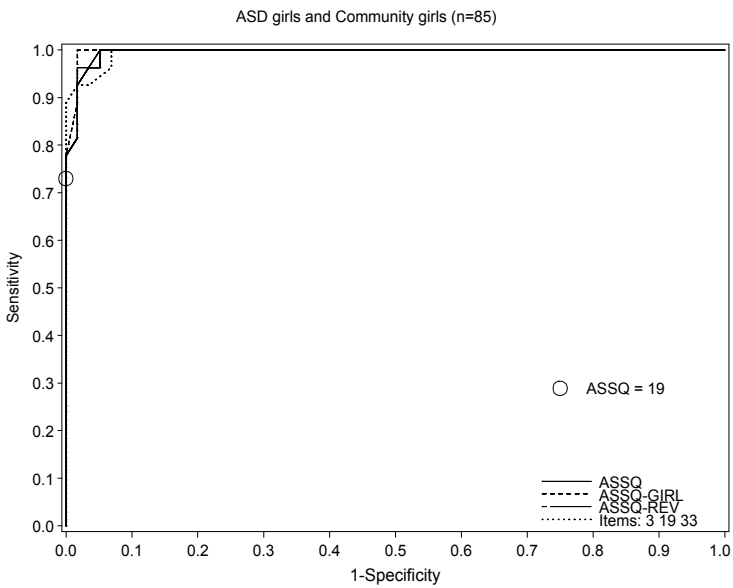


Figure 3 d. Clinic boys (n=62)



Figur 3 e. ASD girls and Community girls (n=85)



DISCUSSION

General findings

The results of this thesis, which is based on one of the most comprehensive and time consuming studies of girls with neuropsychiatric disorders ever performed, demonstrate that girls up to 18 years of age, referred for neuropsychiatric assessment because of social and/or attention/academic deficits, usually (in more than ninety per cent of the cases) meet symptom criteria for ASD or ADHD or both. The one hundred clinically referred girls of the major study were moderately or severely impaired by their ASD/ADHD symptoms at the time of the study to the extent that clinical diagnoses of ASD and/or ADHD were clearly warranted. Their ASD and ADHD, almost invariably, had not been recognised, much less diagnosed, before the in-depth assessment in connection with the thesis study. This is not to say that the girls had not been flagged up as problem cases before they were referred for the assessment. Instead, in the majority of cases, they had been recognised as having a developmental, motor, language or behaviour/emotional problem (including regulatory problems) years before a “correct” diagnosis was finally established. Parents had worried about their child’s development usually from the preschool years, even in cases where diagnoses of ASD/ADHD were not established until well into the teenage years. In the Community group of sixty girls, only two met diagnostic criteria for ADHD, and these two girls were mildly (rather than severely) affected by their symptoms. There was no case of ASD in the Community group.

The study results further show that clinically referred girls with social/attention deficits not only meet full diagnostic criteria for ASD/ADHD, but that when they do, they usually have co-existing symptoms of both disorders. In addition, they very often have mild-moderate motor control problems, amounting to impairing developmental coordination disorder in a large minority of all cases. They also very often have impairing, previously unrecognised reading and/or writing problems, as well as a range of other impairing psychiatric problems and disorders, including oppositional defiant disorder, anxiety, OCD and depressive conditions, and problems with sleep onset latency. Finally, they also have frequently occurring problems with peer relationships, bullying and with attaining educational goals at school. The global functioning and adaptive levels in daily living skills was low in both main diagnostic groups, although lower in the ASD group. Taken together the findings show that the phenotype of ASD and ADHD in girls is at least as severe as that in clinic boys with similar diagnoses.

There were also clear indications that, even though the ASSQ-REV (ASSQ+ASSQ-GIRL) questionnaire did not increase precision in targeting girls with ASD, some of the individual items from this instrument clearly separated girls with ASD from boys with ASD (and from Community girls without psychiatric problems). These items from the ASSQ-GIRL might usefully be added to existing screening instruments for ASD and other neuropsychiatric disorders so that more girls with “hidden” neurodevelopmental impairments might be recognised at early school age at the very latest.

Before more generalisable conclusions can be drawn, including about implications for future clinical and research developments, there is a need to discuss the representativeness of the various study groups included, the appropriateness of the sample size, the psychometric properties and validity of the instruments used, the diagnostic criteria adhered to, and the fact that rigorous blindness to group status could not be achieved.

General discussion about methodology

Representativeness of the study groups included

All five studies in the thesis included smaller and larger samples of clinically referred girls - and in study V also a reasonably sized group of clinically referred boys. All studies, except the original case study that sparked the development of the major project, also included a relatively large sample of girls from the community.

The Child Neuropsychiatric Clinic (CNC) to which the Clinic girls were all referred (and where the Clinic boys were also worked up) is a national/regional clinic for ASD and other neuropsychiatric disorders in Gothenburg, as well as an internationally recognised frontline centre for neuropsychiatric research in Sweden. Doctors in child well baby clinics, child and adolescent psychiatry, child neurology, community pediatrics, and school health services in the city of Gothenburg and the region of Västra Götaland were the main sources of referral. Consistent with the experience of other neuropsychiatric centres in the western world, the majority of patients referred to this neuropsychiatric clinic are boys, and functioning at a variety of intellectual levels (ranging from SMR to superior IQ). The most common diagnoses delivered at the CNC at the time of the present main study (about eight years ago) were ASD, ADHD, and in 15-20% other neuropsychiatric or developmental disorders, including MR, DCD, TD, and OCD.

In order to ensure a wider severity spectrum of neuropsychiatric disorders in girls we included two types of referrals, one of which (about half of the group) consisted of girls consecutively referred to the clinic, and the other half was referred directly to the project. In the youngest group many girls were referred by paediatricians, while among the older group of girls (referred directly to the project) the referral sources were more evenly distributed (paediatricians 30%, child psychiatrists 35%, and school health doctors 30%). Thus, the directly referred group of girls were older, had higher IQ, more main ADHD diagnoses, and better global functioning. However, they did have similar socioeconomic status and family situation as the younger children. When adjusting for IQ (comparing the directly referred girls with all other girls with IQ>70), only the total number of DSM-IV ADHD criteria and the inattention criteria significantly separated the two referral groups. The groups were therefore combined in this study.

With a view to enabling recruitment of a sufficient number of clinic attending girls without too much of adverse psychosocial factors and symptoms, we opted for accepting girls into the project only if they had an estimated/assumed IQ of 70 or above, and if their parents – and they, themselves, had a good command of the Swedish language and no severe physical disorder. To further validate our results we recruited a comparison group of sixty girls without any known neuropsychiatric disorder. These Community girls were drawn from a community child health register and were matched on a group-wise basis to the Clinic girls who were 7-16 years old at the time and who had an estimated IQ of 80 or above. The greater proportion of reported findings from the major study refers to comparisons between these matched Clinic girls with a main diagnosis of ASD or ADHD on the one hand and the Community girls without any disorder on the other. Study V (of the ASSQ-REV questionnaire) also included a matched Clinic group of boys examined around the same time and in the same clinic as the Clinic girls.

There were good indications that the matched Clinic girls and Clinic boys, functioning in the near average or average intellectual range, were comparable to other clinically referred cases with ASD and/or ADHD. However, the larger group of Clinic girls, which included a large minority of girls of preschool age, was not necessarily representative of girls with ASD and/or ADHD *in the general population*. The Community girls lived in a more advantaged socioeconomic situation in terms of parental education, single parent household and economic stress than did the Clinic girls. This could have slightly inflated observed differences between Clinic and Community girls. Nevertheless the Clinic girls came from socio-economically “normal” and, generally, non-dysfunctional families and no girl or parent with inadequate command of the Swedish language took part in the study. In other words, the Clinic girls included in this study were - in some respects – a little better off than the majority of clinic girls attending our clinic. In these socioeconomic aspects, then, the Clinic girls were not *very* unlike the Community sample.

All in all, the girls with ASD and/or ADHD diagnoses in this study, are believed to be fairly representative of non-mentally retarded clinically referred girls with these types of problems. Nevertheless, it does not seem unlikely that some under-inclusion of very severe cases may have occurred. The Community girls came from a *relatively* affluent background, probably balancing out the effect of having possibly lost a number of very severely affected individuals with ASD/ADHD in the recruitment procedure. Thus, when weighing the circumstances, it is concluded that results and significant differences across the Clinic and Community groups are likely to be generalisable to clinically referred girls with social and/or attention deficits not only in Sweden, but in much of the rest of the western world.

Sample sizes and scope of assessments

The sample size in study I was very small. However, at the time when the study was published, even very small numbers were acceptable in publications trying to draw attention to neglected clinical phenomena. Also, the consistency of the findings in that study was what triggered the planning of the remaining studies in the thesis.

By and large, the number of cases and “controls” included in the four remaining papers must be considered sufficient for the purposes intended. The extremely detailed assessment of neuropsychiatric status and developmental history has probably never before been given to such a large group of girls ($n=100$) with social and/or attention deficits (25-30 hours of assessments for every girl included). It is doubtful whether there was ever any more in-depth study of psychiatric morbidity in a reasonably large group of girls ($n=60$) from the community (15-20 hours of assessment of each girl).

The boys in the study ($n=60$) were not examined in exactly the same way as the girls, and the extent of probing into all possible areas of developmental aberrations and psychopathology may have been slightly more restricted than in both groups of girls. Nevertheless, all the 60 boys included did receive an in-depth multi-disciplinary assessment that lasted, on average, 8 hours.

It is perhaps worth highlighting here that all the girls in the study were seen and examined for several hours by myself. The boys were examined by other doctors, psychologists, and other paramedical workers.

Instruments used

First of all, again, I examined all the girls personally psychiatrically in structured and semi-structured ways. I have estimated that I have spent at the very least 1800 hours examining all the girls (Clinic and Community) participating in the study. Also, it might be worth mentioning the standard clinical psychiatric interview, child observation, and diagnostic decisions practiced at the CNC all have good-excellent reliability in previously published studies (Steffenburg et al., 1989).

All the structured and semi-structured instruments (except one, see below) used in the study - in addition to the general clinical examinations - have been well tested in systematic studies, and all have been shown to have good-excellent inter- and intra-rater reliability.

Diagnostic criteria used

I made diagnoses in accordance with the DSM-IV (1994) throughout studies II-V. For study I, I used the DSM-III-R (1987). In the majority of girls with ASD I also checked the criteria for Asperger syndrome first published by the Gillbergs (Gillberg & Gillberg, 1989) and elaborated in a later publication (Gillberg, 1991). However, these were used only for assessment purposes and I did not make Asperger’s disorder diagnoses based on these criteria. For “atypical autism/PDDNOS” I constructed an algorithm on the basis of DSM-IV autistic disorder criteria (the social criterion and a total of 4 or more of the 6 autistic disorder criteria met, but not criteria for autistic disorder or Asperger’s disorder), seeing as there is no operationalised algorithm for diagnosing this condition under the ICD-10 or the DSM-IV.

The DSM is much the most used and accepted diagnostic manual of mental disorders that currently exists and this fact alone was reason enough for me to be using it for diagnosing disorders in my studies.

The DSM-V proposed criteria for ASD and ADHD have just been published, but it has not yet been possible for me to go back to my cases and re-assess them using the new criteria. However, given the detail that has gone into describing the phenotype of the individuals include in my study, it will not be difficult to diagnose them in accordance with the proposed DSM-V and then compare the degree of overlap with results obtained by using the DSM-IV.

Blindness of examiners

Due to the clinical nature of the study, it was not possible to perform the assessments referred to here on a basis of blindness on the part of the clinicians. This is a problem when it comes to comparing the results across index and community cases: there was an expectation that the girls referred would be affected by clinically diagnosable behavioural problems and a rather different expectation during the assessment of the Community girls. However, a lot of structured instruments were used, including those that were not immediately recognisable as measures of psychopathology (such as VABS-DLS, motor and reading/writing tests), and there were still very significant differences between Clinic and Community girls on these. In summary, I am convinced that we would have found similarly sized differences between Community girls and Clinic girls even if we had been able to keep the clinical examiners blind to original group status.

General discussion about limitations and strengths

One of the shortcomings of this study was that the cases were recruited from a sample of girls referred to a specialist clinic, meaning that it is not possible to know how generalizable the findings of the study are to the general population of girls with social and/or attention deficits. However, to some extent we did our best to balance this by recruiting not only a referred clinically needy sample, but also one that could, to some extent, be seen as an advertisement sample. We did this with a view to attracting, if at all possible, a more borderline group of individuals so as to enable study of a wider severity spectrum of neuropsychiatric disorders in girls.

Another clear limitation was the fact that, the general group status of the children was already known to the researchers, when they examined the children. This, in itself might have contributed towards inflating differences across groups. However, as has already been discussed in the foregoing, maintaining blindness in a clinic routine setting is not possible. Also, the Clinic girls were referred for developmental problems and impairing symptoms, meaning that the clinical aims (in addition to the research aims) were also to offer help specifically to these affected girls, and to their parents. For obvious reasons, it would therefore be unethical to remain unaware of the general status (Clinic or Community) of the girls. Notwithstanding this drawback, I believe that the very nature of the in-depth study, the fact that some of the instruments were not focused on the main outcome issues, and that differences vis-à-vis the Community group were usually very marked contribute to making it seem impossible that all the positive findings could have been produced by “wishful thinking” and bias on the part of the examiners.

There was no reliability study performed for diagnostic or MNP assessments or ratings of GAF scores. However, the fact that the same child psychiatrist – performed all parent interviews, MNP examinations, and interviewed and made clinical assessment of all girls in the study lends support to the notion that measurement error must have been reduced to a minimum.

A major strength of the study was that all girls were examined by a stable and well trained multiprofessional team (neuropsychiatrist, neuropsychologists, educationalists, physiotherapists, and social worker). Every girl was observed and examined by five different professionals well trained and highly experienced in neuropsychiatry generally, and autism and ADHD in particular. Further, all reading and writing tests were performed by the same educationalist.

A unique strength of the study was that the clinical assessments were extensive and meticulous, and similar/identical in all girls. The use of well researched interviews, questionnaires and standardised tests plus standard diagnostic criteria for diagnosis added further value.

The study group as a whole was fairly large even though some of the diagnostic subgroups - and age groups - were small enough, precluding generalised conclusions regarding these. It may be worth mentioning here that the relatively small sample of girls and boys with ASD is no smaller than that of the few published comparative gender studies of school-age girls and boys with ASD.

Given the large number of analyses conducted, there is a risk that some of the reportedly significant

findings may instead be spurious. However, all of the “positive” findings were weighed clinically and reported in the context of clinical reasonableness.

Discussion of results obtained in each of the five sub-studies

The Case study (Study I)

The case study of six Clinic girls highlighted the uncertainty of the diagnostic process – and the ambiguity of commonly used instruments - in the field of ASD in girls with near average IQ. All these girls met criteria for autism and had a rather typical phenotype. None of them had received a clinical ASD diagnosis before entering the present study.

ABC

Five of the six of Clinic girls scored below the recommended ABC-score of 67 for autism (Krug et al. 1980), which would indicate that most of these girls did not have “typical” autism. However, Nordin and Gillberg (1996) have showed a higher specificity (1.0) and sensitivity (0.93) with a cut-off score of 45 on the ABC in their screening study of ASD in children with physical and mental disabilities.

Early consultations

All the girls had been seen by experts in the field long before a diagnosis of autism was made, indicating the impairing nature of their problems.

Symptom level

None of the six girls exhibited autistic aloofness. Nevertheless, the type of social impairments shown by these girls tended towards “clinging” to other people, imitating their speech without a deeper understanding, and treating people as objects. Some of the girls were fairly active and gave an odd impression, a type of behaviour often found in autism and outlined by Wing (1989). All the girls had a tendency towards repetitive questioning and were very talkative. The fascination with particular objects or parts of objects, a behaviour pattern often highly characteristic of boys with ASD, was not typical of the girls described here. The six girls tended to be very handicapped (even though no graded functioning scale was used).

Theoretical and clinical implications

Girls with symptoms of autism, may not have quite the same behavioural phenotype as boys. The whole autism behavioural phenotype may – unwittingly - have become copied from typical male cases. Girls may have more language and better social observational and imitation skills (Maccoby & Jacklin, 1974; Halpern, 1992, pp. 64-67; Geary, 1998, pp. 261-275), which would tend to obscure the core deficit to a considerable extent. The less exceptional visuospatial skills encountered in these girls, skills that are very often encountered in boys with autism, would also make them less obvious candidates for a diagnosis of typical autism. Another factor contributing to girls being unrecognized may to some extent be their less violent behavioural style with higher frustration threshold and a tendency to less likely get into quarrels and fights (Gove, 1979). The bottom line would be that girls with severe social communication/interaction deficits would not be suspected of suffering from ASD and hence, of course, not even considered for a diagnosis of this type. The girls, more likely, previously received unspecific diagnoses of “learning disorder”, perceptual problems”, family relationship problems, adjustment disorder, or were given no diagnosis at all.

The 100 Girls study (Study II)

The 100 girls study is probably the biggest truly in-depth study ever published on girls up to 18 years of age looking at almost every possible neuropsychiatric-neurodevelopmental problem. The vast majority – more than ninety per cent - of the clinic girls referred for social and/or attention deficits met criteria for a main clinical diagnosis of ASD or ADHD, and only a small minority met criteria for TD. Very few – eight per cent - of these girls had been given “adequate” diagnoses of this kind before the study occurred.

ASD

Almost half of the 100 Clinic girls were diagnosed with ASD and almost all of them were “high-functioning” (FSIQ >65 in accordance with DeMyer (1981). Girls with ASD were also referred at a younger age than those with other diagnoses, usually from 3 years to middle school age. The youngest girls tended to be the most disabled in the sample. Since ADHD is considered to be about five to ten times more common than ASD, we did not expect to find similar rates of ASD and ADHD diagnoses in our referred sample. The existing predominant idea at the time of the start of the project was that girls with near average or average IQ rarely met ASD criteria. However, recently, at least two studies have reported a more even gender ratio (Baker, 2002; Sturm et al., 2004). The high rate of ASD may, to some extent, have been caused by the status of the specialist clinic (being perceived by some of the referrers as an autism specialist centre) but also by the gradual introduction of a broader diagnostic concept of ASD during the course of the study, and better ascertainment as well as growing public awareness about female ASD, which, in turn, at least to some extent, might have been caused by published autobiographies written by females with ASD in recent years (Grandin & Scariano, 1986; Williams, 1993; Grandin, 1995; Gerland, 1996; Schäfer, 1996; Brattberg, 1999).

The majority of the Clinic girls with ASD, were diagnosed with autistic disorder (about half < 7 years) and only a minority with Asperger’s disorder or PDDNOS. This was partly due to our use of the ADI-R, where the majority of parents reported awareness of severe problems in any of the domains of social interaction/communication or symbolic or imitative play as early as before the age of three, and our strict use of the DSM-IV manual (an autistic disorder diagnosis was always given priority if the criteria for this disorder was met). In accordance with the Gillberg and Gillberg criteria for Asperger syndrome, 69% of the girls with ASD had some kind of narrow interest. This finding was somewhat surprising given that the general view about girls and ASD up until now has been that girls rarely show special interests. Usually the girls were intensely fixated on some kind of “social” interest, either relating to animals (horses, dogs, “My little pony”, birds, rodents), foreign cultures (Japan, Egypt), fairy-tales figures (Pipi Longstockings), famous people, comic strip personalities (Donald Duck, Manga), or they were extremely interested in painting, pottery, beauty products, and clothes. These interests are in contrast to the interest patterns usually seen in boys, who more often concentrate on tabulating facts, watching cars, trains and planes, focusing on construction work, meteorology, history, geography, flags, washing machines, television, CD-records, computers, dynamite, and dinosaurs (Gillberg, 1989; Gillberg, 1991).

ADHD

In the subgroup with ADHD (also almost half of the whole group of Clinic girls), the combined subtype was the most common in all age groups, followed by the inattentive subtype - consistent with a few previous female ADHD studies (e.g. Biederman et al., 1999; Graetz et al., 2005). The relative proportions correspond with what has been found in studies of boys with ADHD (Biederman, Mick et al., 2002). However, research on predominately older girls has found relatively more of the inattentive subtype (Rucklidge & Tannock, 2001). In our study, all but one of the girls with the predominately inattentive type was older than 11 years. It is notable that results from ADHD cluster analysis studies have revealed impulsivity symptoms as the second (second to inattention) most prominent cluster among school-age girls with ADHD. These results support the early stance of Virginia Douglas (1972) that problems with sustained attention and control of impulsive responding are the most important symptoms in ADHD. Only a minority of girls with ADHD (4/46) had no impulsivity symptoms at all. This minority would probably correspond to an inattentive-hypoactive subtype of ADHD. The findings highlight the issue of whether or not there really exists a reasonably common separate sluggish/hypoactive type of ADHD. Obviously, at least in our clinical setting this subgroup is rare, and our findings correspond with the report by Harrington and Waldman (2010).

All the Clinic girls with ADHD had some impairing symptoms in at least two settings. However, this was not always reported from school and home, but from home and in the clinical settings, where the long observation and examination time (on several different occasions) proved to be a helpful diagnostic tool. This finding is to be seriously considered, when diagnosing girls with a parental reported functioning impairment, however not confirmed by teachers.

TD

Even if chronic motor and/or vocal tics diagnosed as the most impairing symptoms were uncommon in our Clinic sample, almost ten per cent of the Clinic girls had a (main diagnosis or “second line”) diagnosis of TD, causing distress to the girl or the environment. Similar to the predominately male study by Kadesjö and Gillberg (2000), problems subsumed under other diagnostic terms (ASD, ADHD) were more impairing in most of these girls. A similar comorbidity/overlap pattern has also been reported in the population-based study by Khalifa and von Knorring (2005). The high rate of transient or chronic tics without major impairment (61%) in all Clinic girls was much higher than in population studies (Khalifa & von Knorring, 2003) suggesting that mild tics are associated with a host of other neuropsychiatric disorders, disorders that are so impairing that the tics go almost unnoticed in many cases.

Overlap of disorders

The high rate of additional disorders has been reported in ADHD studies during recent years (Biederman et al., 1999; Kadesjö & Gillberg, 2001; Hinshaw, 2002). Only a few studies on ASD have reported separate “comorbid” diagnoses, even though behavioural and emotional problems are well-known to be common in ASD cases (DSM-IV). The high rate of co-existing emotional disorders in ADHD has given rise to the question whether such psychiatric symptoms might have been present already during early childhood. Our study indicates that young girls with ADHD show emotional disorders even though more severe cases of depressive and self-destructive behaviour become more prevalent among the older girls.

We did not expect to find such a high rate (80%) of coexisting ADHD in the ASD group. We were also surprised by the striking resemblance in the ADHD phenotype (especially as regards inattentive and hyperactive symptoms), irrespective of whether the main diagnosis was ASD or ADHD. However, recently, both Frazier et al. (2001) and Lee and Ousley (2006) have suggested that the majority of clinically referred boys, with ASD have ADHD symptoms (83% and 78% respectively). Frazier et al. also found a striking homogeneity in ADHD symptoms, irrespective of ASD status. These results highlight the issue of whether or not ADHD-like symptoms are consequences of ASD, or whether symptom clusters are wholly or partially independent of each other.

The reported comorbidity patterns in the ASD and ADHD groups were surprisingly similar with a high number of additional diagnoses, even though, on average, the ASD group was generally somewhat more impaired by these additional problems.

ODD

The most common additional diagnosis – disregarding the ASD/ADHD overlap - for both ASD and ADHD was ODD. We did not expect to find that both girls with ASD and ADHD behaved in a disturbing violent manner at home. This was in contrast to the teachers’ reports, especially for girls with ASD, and girls with ADHD inattentive subtype. However it has been reported by Hinshaw (2002) and Graetz et al. (2005) that girls with ADHD are more often defiant towards mothers than towards teachers. Also Sula Wolff (1995) always maintained that her “schizoid” girls - of whom many had ASD - often showed oppositional and conduct disorders. Similar findings were recently reported by Mattila et al. (in press) with 33% (4/12) of girls with HFA/Asperger’s disorder having ODD. The less extrovert and less violent behaviour at school compared to home settings are worth attention. The difference in overtly aggressive and domineering behaviour between girls and boys (Maccoby, 1998, pp.34-37) is one of the important factors in this context. Some researchers have suggested that young girls and adolescent girls show aggression in school also, but in a more verbal and indirect way than boys and often directed towards other females (Björkqvist, 1994; Abikoff et al., 2002). Carlson and co-workers have shown that girls with ADHD and ODD feel unhappier and are more socially impaired than boys with similar diagnoses (Carlson, Tamm & Gaub, 1997). Biederman has shown that ODD in childhood led to worse outcome (including a higher risk for major depression) in adolescence for girls with ADHD (Biederman et al., 2008). Dalsgaard et al. (2002) in their follow-up studies of clinic attenders with ADHD found a higher risk of psychiatric admissions in adulthood in those girls who also had ODD/CD. Taking all these risks into

consideration there appears to be a clear need to detect girls with ADHD at a young age, so that they can get access to adequate early treatment.

Other comorbid disorders

Leyfer et al. (2006) have found high rates of psychiatric disorders, especially specific phobia (44%), and OCD (37%), in referred children with ASD (mainly boys). These findings parallel those from our study on girls with ASD (40% and 35%, respectively). Compared to girls with ADHD, girls with ASD were two to three times more likely to have multiple anxiety disorders. The fearfulness often described in cases of autism has, however, only rarely been diagnosed as a separate comorbid disorder, with an obvious risk of missing opportunities for adequate treatment. However, Kuusikko et al. (2008) recently reported social anxiety symptoms in more than 50% of children and adolescents (a minority were girls) with high-functioning autism/Asperger's disorder and with more social anxiety symptoms with age, contrary to findings in typically developing children.

Patterns of additional diagnoses in girls with ADHD, similar to those of our study, have been reported by Biederman et al. (1999). Forty per cent of school-age girls with ASD and 47% of girls with ADHD also suffered from sleep disorder. Similar high rates have been reported in high functioning boys with ASD as well as in girls with ADHD (Biederman et al., 1999; Allik, Larsson & Smedje, 2006; Hvolby, Jørgensen & Bilenberg, 2009). Prolonged sleep onset latency was also reported by some of the adolescent girls with ADHD as one of their most distressing symptoms. This indicates that there is a need for closer examination of sleep difficulties in young girls with social and attention deficits, and an incentive to develop better treatments for this type of problems.

We replicated results reported by Biederman's group, showing girls with ADHD smoking cigarettes much more often than Community girls (Biederman et al., 1999). Biederman's 5-year follow-up study on female ADHD (2006) indicated an elevated risk to develop a substance use disorder in young adulthood. These findings in our study are but one of the many reasons why there is a need to follow-up the girls into young adulthood and beyond. Other researchers have confirmed the frequent use and risk of cigarette smoking in girls and women with ADHD (Pinkhardt et al., 2009).

Matched Clinic and Community girls

The difference between the Community girls and the matched Clinic girls with ASD and ADHD were considerable in all respects, with Clinic girls being much more impaired, having many more disorders, lower FSIQ, more school dysfunctions, disabilities in daily living skills and in peer relationships. The huge discrepancy found between girls with a main diagnosis of ASD and/or ADHD and girls from the Community without any neuropsychiatric diagnosis provides strong support for the notion that it is essential to develop services that have the skills to diagnose ASD and ADHD early for adequate treatment in girls. There is good evidence that both ASD and ADHD can and should be treated as early as possible and that interventions have good effects (MTA Cooperative Group, 1999a, 1999b; Sharp et al., 1999; Howlin, Gordon, Pasco, Wade & Charman, 2005; Golubchik, Sever & Weizman, 2009; Huizink, van Lier & Crijnen, 2009; Eldevik, Jahr, Eikeseth, Hastings, & Hughes, 2010).

Pre-school girls

Some of the most difficult girls from the point of view of differential diagnosis were found in the pre-school group. This was particularly true in the case of girls who had normal or nearly normal early language, who were very shy, and/or very hyperactive. Multiple informants, long examination time, and trained educationalists for preschool observations appeared to be extremely helpful in the diagnostic process. Only two girls with a main diagnosis of ADHD were diagnosed in this age group. This corresponds well with reports from other ADHD researchers (Barkley & Biederman, 1997; Nadeau, Littman & Quinn, 1999) who have found late referral ages for girls with ADHD in contrast to boys. The majority of preschool girls with ASD had some language abnormalities, even in the intellectually able group, in contrast to the school-age girls with ASD, among whom only a very few had obvious language problems.

Early symptoms

The very high rates of parent-noticed early symptoms in this Clinic group, highlights the need to increase awareness, generally and specifically among child health staff, that early “symptoms” may be markers of ESSENCE. Parents need to be taken “seriously” whenever they raise the issue of a worrying problem, such as in respect of longstanding severe sleep problems, excessive crying, frequent and severe temper tantrums or hyperactivity, in the girl before school age.

Relationship between some background variables and clinical findings

Single parent household, more economic stress and lower socioeconomic situations are known to be adverse factors for children’s mental health and somatic complaints (Rutter, Tizard, Yule, Graham & Whitmore, 1976; Biederman, Faraone, & Monuteaux, 2002). Some of the Clinic girls had experienced severe stressors, such as physical or sexual abuse, divorces or parental substance abuse but the majority of these girls were living under minor stress. We did not find any significant correlation between higher indices of stress and clinical findings (number of autistic symptoms, number of additional diagnoses, GAF score or FSIQ), although there was a moderate correlation, albeit non-significant, for environmental stress and number of ADHD symptoms in the matched Clinic group ($r_s = 0.28, p = .030, n = 60$). In the ADHD group a similar trend was also found for economic stress and more ADHD criteria.

It appears, then, that the clinical findings are better explained by the neuropsychiatric disorder itself, the co-existing disorders, and the school situation. However, adverse social factors would contribute to a heavier burden for the girls as well as the parents. In this context it is important to consider the high rate of experienced bullying in the Clinic group, which may have been one possible factor contributing to the high rate of non-attendance at school for girls with ASD and ADHD.

Age trends

The lower referral age in the ASD group of girls compared to the ADHD group (about a 4 year difference) may be explained by the occurrence of qualitative impairments in several key areas of development, most notably in the social-communication domain, an area of dysfunction that is almost universally accepted as necessitating early referral. The majority of Clinic girls with ADHD were 11 years or older. The late referral age for girls with ADHD, in contrast to boys, has been highlighted by Berry et al. (1985), Kato et al. (2001) and Rucklidge and Tannock (2001). Other studies have reported similar referral ages for girls and boys with ADHD (Nøvik et al., 2006). When similar referral age is reported, some researchers find that girls with ADHD have more severe problems than referred boys with ADHD (Gaub & Carlsson, 1997), while others do not find any differences in impairments or symptoms across the genders (Horn et al., 1989; Biederman, Mick, et al., 2002; Yang et al., 2004). Boys’ more disruptive acting out behaviour (usually demonstrated both outwith and in the home), has mostly been stated as the reason for their earlier referral. Girls’ symptoms are reported as inattention or learning problems, and therefore more difficult to detect (Kashani, Chapel, Ellis & Shekim, 1979; Gaub & Carlson, 1997). Irrespective of the causes of barriers to detection in girls with ADHD, a referral and diagnosis age of 13 years is too high to be accepted as adequate considering the negative consequences of this disorder.

IQ trends

Similar to many previous studies the matched school-age girls with ADHD had IQs in the normal range (Biederman et al., 1999; Hinshaw 2002). In our study, having low normal or normal IQ was originally a prerequisite for entry into the study. However both the ADHD and ASD groups had significantly lower IQ than the girls in the Community sample. In spite of functioning in the “normal” IQ range, the lower IQ - taken together with the executive function deficits found in girls with ADHD (and in the majority of girls with ASD) - influences the learning situation in a negative fashion. This was also supported by the finding of high rates of reported underachievement in both Swedish language/literature, and mathematics (40-50%).

Peer relationships

That girls with ASD were loners was not surprising to us. Nevertheless the high rate of peer problems, also reported in the ADHD group was more than we had expected. However, peer problems were among

the most reported and noticed problems by teachers in both girls with ASD and ADHD (not attention problems or underachievement). Both Biederman's and Hinshaw's groups have found peer rejection to be very common in girls (and boys) with ADHD (Greene et al., 2001; Hinshaw, 2002), and girls with and without ODD received even higher peer dislike scores than boys with similar diagnoses (Carlson et al., 1997). Zalecki and Hinshaw (2004), and Abikoff et al. (2002) reported the ADHD combined subtype was associated with more verbal aggressivity towards peers, and the inattentive subtype with being more alone.

Impairments in adaptive behaviours (GAF, VABS- DLS)

Both girls with ASD and girls with ADHD had severe impairment in adaptive functioning. The very low GAF-scores indicate the considerable burden of impairments - and the need for early detection. Girls with ASD had lower GAF scores than those with ADHD, and both groups had much lower scores than girls from the Community sample. Mattila et al. (in press) found significantly lower functional levels using CGAS (Schorre & Vandvik, 2004) in a combined sample of community- and clinic- based girls ($n=12$) than boys ($n=38$) with HFA/Asperger's disorder. This might be due to the greater severity of problems in the referred female cases. However the number of girls in that study was far too low for any generalised conclusion to be drawn. Higher GAF scores have been reported in girls with ADHD who have been on medication (Biederman et al., 1999). The high rate of co-existing OCD (35%) in our ADHD group might have contributed to the low GAF, similar finding were reported by Sukhodolsky et al. (2005). The disability in daily living skills separated the ASD group from the ADHD group (VABS-DLS). However, even for the ADHD group the ability level was considerably lower than expected on the basis of population norms.

The girls in our sample had never been properly psychoeducationally or pharmacologically treated for ADHD up to the time of the study. It is possible that if these girls had been treated – psychoeducationally and/or pharmacologically - from an earlier age (as their histories indicated they should have been) their GAF and VABS-DLS scores might have been higher.

Treatment history and barrier to detection

The degree of earlier consultations in the Clinic group of girls (ASD 100%, ADHD 85%) for behaviour or deviant development problems - prior to our study and without getting an appropriate diagnosis - was higher than we had expected. Nearly every second school-age girl with ADHD and about two thirds of those with ASD had attended a child psychiatric clinic before our study took place. Parents had reported major concerns already before age 3 years in two thirds of the cases, and an equal proportion had noted symptoms (with or without major concerns attached) before age one year. The fact that “correct” diagnoses of ASD and ADHD were not established until almost 9 and 13 years respectively draws attention to the need for increased “ESSENCE”-awareness among staff in child health clinics, speech therapy centres, community pediatrics and child and adolescent mental health services. These girls should not have had to wait so long for adequate assessment and intervention. Although detection in the preschool years or early school age at the very latest is preferable, knowledge and awareness about ASD and ADHD in girls among staff working in school health and adolescent medicine is required so as to prevent further diagnostic delay in adolescence or even into adulthood.

Various barriers to detection may have contributed to the misdiagnosing. In a recent review of the literature on girls with ADHD, Staller and Faraone (2006) pointed out that identification of girls with ADHD is hampered by parental and teacher bias and confusion. Bussing, Zima, et al. (2003) have reported boys with similar severity of ADHD symptoms as girls, being 5 times more likely to be referred for examination. In their study the difference was caused by opinions and perceptions on the part of the mothers of the original cause of the problem. Kato et al. (2001) reported higher verbal IQ being a risk for girls with ADHD to be identified later. The diagnostic manual (DSM-IV) in itself, with more male oriented behaviour items, may also contribute to the under-identification of girls (Ohan & Johnston, 2005; Waschbusch & King, 2006). However, our results showed that professional clinicians also contributed to the misdiagnosing of girls with ADHD as well as of ASD. From experience it is also clear that published research reports have contributed to the confusion among clinicians; the enormous number of publications

that focus on boys with ASD and ADHD and the tiny number of publications on girls, suggest that girls must only very rarely have ASD or ADHD.

The Motor study (Study III)

The overall rate of DCD and motor control problems

Lower rates of DCD were found in school girls with ASD (25%) and with ADHD (32%) than reported in previous predominately male studies by Gillberg (1998), Kadesjö and Gillberg (2001), Pitcher, Piek and Hay (2003), Hilton et al. (2007), Ming, Brimacombe and Wagner (2007), and Green et al. (2009). Girls may actually generally have better motor skills than boys – as has been reported by Larson and colleagues (2007) – and this could contribute towards explaining our low rates here. More marked motor impairments have been found in younger children with a main diagnosis of ASD or ADHD (Gillberg & Gillberg, 1983; Ming et al.). Another possible explanation for our (relatively) lower reported DCD rates might be our strict inclusion criterion of $IQ \geq 80$, since motor impairments are known to be less common among normally intelligent children than among those with intellectual disability $FSIQ < 70$ (Lam & Henderson, 1987).

When looking separately at the preschool girls with ASD, a different picture emerges: those girls with ASD, who also had LD, and about two thirds of those with average or near average IQ, had DCD. These results correspond well with those reported by Green et al. (2009) on predominately 9-10 years old boys with ASD and a wide IQ range.

The use of different motor tests for different age- groups, along with the effects of young age, and severity of autistic symptoms, might have contributed to the age differences in DCD prevalence rates.

Motor problems by diagnostic subgroup

There were no marked differences, between the ASD and ADHD groups in terms of type of motor problems, and we could not confirm the finding of more motor impairments in ASD than in ADHD as reported by Dewey, Cantell and Crawford (2007), and Pan, Tsai and Chu (in press).

MNP

A large and significant correlation ($r_s = -0.60$) was found between the MNP and the EB-test. However, the percentage of agreement as well as patterns of systematic differences varied across different diagnostic subgroups. Our findings confirmed moderate to good agreement in the collapsed group of girls, but not in the Community sample, suggesting that the MNP only would be a good very brief alternative in clinical settings as a screening test for motor coordination impairments.

Parent questionnaire (FTF)

Parents reported nearly twice as high rates of motor skills impairments in school-girls with ASD (65%) and ADHD (59%) compared to the rates established using professional tests. The majority (76%) of impaired girls on the FTF were ≥ 11 years of age, while the majority of girls with impairment according to professional tests were 10 years or younger. This effect might partly be due to the fact that the professional tests measure a range of very specific motor skills, while the FTF addresses the functional manifestations of motor coordination in daily living activities.

Severity of autistic symptoms and motor coordination problems

According to the stepwise multiple regression analysis, there was a connection between motor coordination problems and autistic symptoms in the group of Clinic girls. This agrees well with findings obtained in reports on predominately male participants, both in clinic and population groups (Kadesjö & Gillberg, 1999; Piek & Dyck, 2004; Hilton et al., 2007).

Daily living skills and motor impairments in school girls

There was a significant relationship between motor impairments and lower abilities in daily living skills (VABS-DLS). The results further illustrate the burden that families of girls with neuropsychiatric disorders have to deal with on a daily basis.

PE

The low rate of participation in PE among girls with ASD (53%) and ADHD (38%) has not been reported previously (for girls). Hans Adler (1981) has shown that the rate of participation in PE in ADHD and similar conditions is very low in boys. In clinical practice PE is often the first school subject to be dropped for clinically referred girls with ASD and or ADHD, possibly caused by problems associated directly with the main diagnosis, by motor impairments, bullying, or combinations of these. There is a need to adjust PE to girls (and boys) with neuropsychiatric impairments, so as to contribute to the early implementation physical activity routines and a generally better health condition in these children.

The Reading study (Study IV)

RWD

In the ADHD group 56% and in the ASD group 40% had at least one reading or writing disorder. Reading comprehension disorder was found in 22% of girls with ADHD, and this prevalence rate was lower than that reported (40%) from a mixed gender study of ADHD by Kadesjö and Gillberg (2001). This difference in rates is partly explained by different definitions of reading disorders (under 5th centile in our study, 10th centile in other studies). In Biederman, Mick, et al.'s (2002) comparative ADHD study of girls and boys, 5% of the girls and 24% of the boys had a reading disorder when using a discrepancy-achievement criterion based on IQ, whereas 11-15% of girls were found in Hinshaw's "girl" study (2002) using a basic reading achievement test (WIAT) (Wechsler, 1992). If boys with ADHD more often than girls have comorbid RWD, then this fact could contribute to the higher referral rate found in boys.

ADHD and autistic symptoms and literacy skills

In the correlation analyses we found that ADHD and autistic symptoms were negatively linked with all literacy measures. Low level of autistic symptoms was correlated with good reading comprehension. In two separate regression analyses both ADHD and autistic symptoms explained significant, albeit rather small, proportions of the variance in reading comprehension, suggesting that both neuropsychiatric disorders might somehow be directly related to reading comprehension difficulties.

The ASSQ study (Study V)

The ASSQ study reported on the development of the ASSQ-REV, which is a new set of screening questionnaire items (ASSQ-GIRL) plus the original ASSQ, for parents selected with a view to better capturing the female phenotype of ASD in school age girls. The results of the study supported the use of some of the new ASSQ-GIRL items for screening and clinical purposes in addition to other measurements in the diagnostic process of ASD, but the full set of the ASSQ-REV items did not contribute to better detection of girls with ASD than did use of the "old" ASSQ on its own.

The ASSQ, ASSQ-GIRL, and ASSQ-REV sum scores

The finding of similar total scores from the parent-rated questionnaires ASSQ, ASSQ-GIRL, and ASSQ-REV, in Clinic referred girls and boys with ASD is consistent with previous studies on the ASSQ (Ehlers et al., 1999; Mattila et al., 2009). However, it is noteworthy that the original ASSQ items were based on the descriptions of Hans Asperger's male cases (1944), and might therefore, almost by definition, be more effective at detecting social communication difficulties and interest patterns in boys than in girls.

The majority of the ASSQ-REV items were endorsed more often for boys than for girls with ASD, but girls were more often rated "definitely applies". There are different possible reasons for this finding. Firstly, milder cases of boys with ASD might be referred to clinics, in contrast to girls with ASD who would be referred only when more severe and obvious problems are present. This has been shown to be the case for girls with ADHD (James & Taylor, 1990; Gaub & Carlson, 1997). Secondly, the overall higher rates of autistic traits found in "normal" boys compared to girls might mask discrepancies between more and less symptomatic boys with ASD (Baron-Cohen, Wheelwright et al., 2001; Constantino & Todd, 2003; Baron-Cohen, Hoekstra et al., 2006; Posserud et al., 2006; Williams et al., 2008; Skuse et al., 2009) in contrast to girls with ASD who differ more markedly from "normal" girls (and would therefore, more often be scored "definitely abnormal").

Response analyses

At the ASSQ-REV individual item level the most striking gender differences were in terms of “lacks best friends” (more boys with ASD), and “interacts mostly with younger children”, “avoids demands”, “has a different voice/speech”, and “difficulties completing simple daily activities” (more girls with ASD).

“Lacks best friends” at a glance, would appear to be a more severe qualitative impairment of social-interaction than would “interacts mostly with younger children”. However, before accepting such a conclusion one needs to consider the data regarding social interaction in gender-typical play and choice of playmates described by Maccoby (1998, pp. 32-58), and Geary (1998, pp. 221-247). “Normal” boys’ preference to play in same-age male groups may unconditionally prevent a boy with ASD from joining in. In contrast, “normal” girls usually play with one or two other girls, and this could provide a girl with ASD scope to choose younger or older girls (Maccoby, 1998). “Normal” girls have been suggested to be more sensitive and caring towards others than boys are, and this might possibly lead to a situation in which girls with atypical development may be invited into a girl group in spite of social interaction problems (Hoffman, 1977; Gilligan, 1982).

There is a clear risk that parents and professionals may overlook the lack of social reciprocity in girls, and see them as more social (and not autistic) than they actually are. This was suggested by Wing already in 1981, and by our group in the early 1990s. The studies by McLennan et al. (1993) and Holtmann et al. (2008) have confirmed that high-functioning adolescent girls with ASD actually show *more* difficulty in establishing peer relationships than boys.

The ASSQ-GIRL item “avoids demands” was scored significantly higher in girls than boys with ASD (and ADHD). This item relates to the concept of “pathological demand avoidance” (PDA) now often considered a subgroup of ASD (Newson, Le Mare’chal & David, 2003). The avoidance in PDA is connected with social anxiety and obsessive demand resistance, and, in contrast to classic ASD, to better pretend play. Different reasons for the gender difference regarding “demand avoidance” include (i) parents having a less demanding attitude towards boys than girls leading girls to “forced” avoidance, (ii) girls with diagnosed ASD and/or ADHD also meeting criteria for a diagnosis of PDA, (iii) higher “comorbid” rates of social anxiety in girls than boys, (iv) girls being more likely to avoid demands passively in contrast to boys who may be more likely to refuse or defy actively (and this would lead to boys being perceived as “defiant”, whereas girls would be seen as “avoidant” (Björkqvist, 1994). Irrespective of the cause, this gender-difference in resisting demands seems to be a distinct signal in girls with an underlying disability.

“Male-oriented” Asperger syndrome items

In the original ASSQ-study, 16 of the 27 items were considered most specific for Asperger syndrome (Ehlers & Gillberg, 1993), and six of these 16 items in our study were endorsed much more often in boys (“is old-fashioned”, “is regarded as an eccentric professor”, lives in own world with restricted idiosyncratic intellectual interests”, “accumulates facts on certain subjects”, “lacks common sense”, and “is poor at games”), while one item was endorsed much more often in girls “different voice or speech”. The endorsed “male” symptoms, typical of the generally held notion of the core features of Asperger’s disorder, highlight the issue of whether or not the current delineation of Asperger syndrome is, in fact, only the male presentation of the disorder.

ADHD

When comparing girls and boys with ADHD, higher rates of endorsed ASSQ-REV items were found in boys than in girls. It is of interest – and clearly in need of replication in other studies - that girls with ADHD had the same high rates of certain interaction problems (“can be with other children on own terms” and “lack best friends”) as girls with ASD. This has previously been reported in ADHD studies by Carlson et al. (1997), Rucklidge and Tannock (2001), Quinn and Wigal (2004), and Zalecki and Hinshaw (2004). These gender-differences probably contribute to some confounding in clinical diagnostic practice so that, unless systematically targeted and explored in detail, the ASD in girls will be overlooked and misdiagnosed as ADHD “only”.

Convergent validity of the ASSQ-GIRL

ASSQ-GIRL demonstrated good convergent validity in correlation analysis with the previously well-validated ASSQ (Ehlers et al., 1999; Posserud, Lundervold & Gillberg, 2009). ASSQ-GIRL appears to have complementary rather than equivalent psychometric properties in contrast to the Conners-10 item scale (Streiner, 1993).

Known- groups validity and internal consistency

The known-groups validity for the ASSQ-GIRL was good, and a high ASSQ-GIRL (and ASSQ) score significantly differentiated girls (and boys) with ASD from other children, clinical and non-clinical. The Conners-10, on the other hand, did not distinguish between ASD and ADHD. The reliability measured with Cronbach's α , showed good internal consistency ($\alpha=0.85$).

ASD versus non-ASD cases

A set of very interesting ASSQ-REV items were identified, showing a striking gender-difference in the Clinic groups when using logistic regression analyses for examination of every item's ability to distinguish between ASD and non-ASD cases. Only the item, "lives in own world", distinguished well between ASD and non-ASD in all study groups (including Clinic girl group and Clinic boy group). Five important items differentiated Clinic girls from Clinic boys, ("robotlike language", "other children on own terms", and "eating problems" in boys and "different voice" and "insists on no change" in girls), and ("avoids demands") separated the collapsed group of girls with ASD and Community girls from boys. All these findings indicate that different ASSQ-REV items are differently loaded depending on gender, clinic and community status.

Prediction of ASD

In contrast with our hypothesis, the original ASSQ was the best predictor (of the three ASSQ-versions) for an ASD diagnosis for both girls and boys in calculations using stepwise logistic regression. The sum score of the ASSQ-REV did not capture more cases of girls with ASD than did the ASSQ. However the ASSQ-GIRL distinguished between ASD and non-ASD better in female groups than in the male group. Some items appeared to be especially powerful in terms of "female ASD orientation", viz. "very determined" and "self-care problems" (in Clinic girls), "no time perception", "avoids demands", and "talks without content" (in ASD girls and Community girls' group) (not specifically reported in table).

We confirmed Posserud's finding (2008) that some items were extremely "ASD-loaded" and even better predictors than the whole ASSQ, both in the total group ("deviant gaze", "poor at games" and "lives in own world") and in the Clinic boy group ("poor at games").

These findings suggest that some items are more predictive in boys, and might be termed "male-oriented", while other items are more predictive in girls ("female-oriented"). The findings illustrate the importance of studying gender differences in symptoms presented at the item level rather than just at the collapsed score level, in research as well as in diagnostic work-up, of girls and boys with ASD.

CLINICAL CONCLUSIONS

There can be no doubt that, at least a few years ago, when the present studies were performed, girls with ASD and/or ADHD receive these clinical diagnoses much later than would have been adequate/ necessary. Girls who present with social communication and/or attention deficits at a young age, be it at the well baby clinic, a speech and language clinic, at the GP's, a community pediatric service, or in child and adolescent mental health services, need to be comprehensively assessed from the outset with a view to diagnosing a condition (or several conditions) within the ESSENCE group of disorders. Whenever social and/or attention deficits cause impairment and concern in young girls, there is a very high risk that the underlying problem may be ASD, ADHD, or even a combination of the two. Unless girls with such early onset problems are seen by a multidisciplinary team with *a much more pronounced focus on girls* and with expertise in the field and a clear understanding that ASD/ADHD is to be expected rather than ruled out with a view to reassuring the parents, the risk is great that one or both of these conditions will be missed or misdiagnosed. There is also a considerable risk that co-existing disorders and problems may also be missed, misdiagnosed or diagnosed instead of the "underlying" neuropsychiatric disorder. Many of the girls with ASD/ADHD had various types of anxiety disorder and there is a possibility that, unless ASD and ADHD are *always* specifically looked for in girls presenting with impairing anxiety, only the anxiety disorder will be recognized. Girls with ASD/ADHD are moderately or severely functionally impaired by the symptoms associated with the disorder(s), and there are usually one, two or several co-existing impairing psychiatric disorders. The high rate of peer problems found is important to take into consideration when discussing need for earlier detection, particularly as regards the ADHD group. The elevated risk of cigarette smoking among girls with ADHD highlights the urgent need for early treatment in order to prevent further negative health consequences for adolescent girls, women, their fetuses, babies, and children. The risk is also considerable that motor control problems and reading and writing disorders cause additional functional impairments, including exclusion from PE, academic failure, bullying, and truancy. All these findings underscore the severity of ASD and ADHD, and strongly support the importance of early recognition of these disorders in girls. This means that all girls coming for evaluation for social and/or attention impairments need to be screened and possibly meticulously worked up with a view to excluding or diagnosing DCD, RWD, and intervening for problems associated with such disorders whenever relevant. The ASSQ is clearly a useful screening tool for ASD in clinical practice (as has been shown in many other studies, including in the general population), but it would probably work even better in the detection of girls with ASD if some of the individual items from the new ASSQ-GIRL were added to the existing version.

A keen interest and awareness together with raised knowledge levels among health professionals about possible barriers to the detection of girls with ASD and ADHD are clearly needed in attempts to close the gender gap that exists across population sex-ratios and clinic sex-ratios in this field of medicine.

IMPLICATIONS FOR RESEARCH

All future studies in the field of ASD, ADHD and other disorders/conditions subsumed under the ESSENCE acronym, whether focusing on young children, adolescents, or adults, need to take a much clearer gender perspective into account. Results of various examinations performed on “children”, “teenagers”, “adults” or “groups of people”, need to separately present results for girls and boys, women and men. All new studies in the field must either power their samples to include sufficient numbers of females and males for meaningful conclusions to be drawn, or explicitly state why this has not been achieved or planned. Researchers in the field will need to be aware that the clinical presentation of ASD and ADHD in females may be slightly (or sometimes even very) different from that expected on the basis of notions of the gestalts of these conditions that have usually been modelled around males. Many future studies of these disorders — including at individual item/symptom levels — will only be clinically meaningful if the full range of problems associated with ESSENCE are acknowledged and screened and/or diagnostically assessed. This applies, of course, in both genders. This implies that studies launched with a plan to examine, for instance, “autism” must include instruments that will tap into the so called comorbidities, not just autism-specific methodology. Large populations of infants, girls and boys, preferably a large antenatally identified birth cohort, need to be followed prospectively with in-depth assessments from the beginning of life of social and/or attention deficits and all the possibly associated problems at several time-points during childhood and into adult life, so that risk factors and early markers (including regulatory problems) for ESSENCE can be identified in a scientifically valid way. Such birth cohort studies have never been performed, and they are urgently needed, in order that we might begin the hard work of reducing the number of girls (and boys, but girls much more) with lifelong disabling (unless early diagnosed and early intervened for) disorders, currently missed or misdiagnosed well into the school years in the majority of cases. Looked after girls, girls with social problems, girls who are acting out and living socially dangerous lives need to be considered for diagnoses of ASD, ADHD or other ESSENCE in all future research studies. More specifically, the girls included in the present thesis should be followed up when they have reached early adult life (as many of them have already). The ASSQ with items as suggested in this thesis needs to be tested in new clinical and population studies. The last, but not the least important, implication for future research is that ASD and ADHD should be considered whenever *any* female is evaluated for *any* kind of emotional, behavioural or developmental problem. There has to be a screen included for such problems in *all* clinical psychiatric research.

SWEDISH SUMMARY (SAMMANFATTNING PÅ SVENSKA)

På 1980-talet började jag, som barnpsykiater, fundera över om flickor med kamratproblem och sociala samspelssvårigheter kanske ofta hade autism utan att få korrekt diagnos. Tillsammans med min handledare genomförde jag en mindre fallstudie av 6 flickor som bekräftade mina misstankar. Jag planerade sedan min fortsatta forskning med detta som utgångspunkt. Vid denna tid fanns ännu mycket begränsad forskning om flickor med tidigt debuterande psykiska problem. Framför allt saknades information om flickor med autism och ADHD. Min huvudstudie inriktades därför mot dessa grupper.

Avhandlingsarbetet kom att handla först och främst om 100 flickor som före vuxen ålder kommit till undersökning hos läkare (barnläkare, skolläkare, barnpsykiatriker) med anledning av svårigheter med social interaktion och/eller koncentrationsförmåga i eller utanför skolan. Flickornas föräldrar hade i allmänhet oroat sig för deras beteende eller utveckling redan under de första levnadsåren. De hade också tidigt sökt hjälp, dock utan att få adekvat diagnos på flickornas problem. När flickorna till sist remitterades till Barnneuropsykiatriska kliniken visade det sig, efter mycket detaljerad psykiatrisk och psykologisk undersökning (omfattande sammanlagt flera dagars bedömning i och utanför kliniken), att nästan hälften av dem hade autism eller andra autismspektrumstörningar (med eller utan ADHD) och att lika många hade ADHD (med eller utan autistiska drag) som huvuddiagnos. Bara ungefär en av tio av dessa flickor hade fått mostvarande diagnos i samband med att föräldrarna primärt konsulterade någon med anledning av den oro de upplevt på grund av de sociala problemen och koncentrationssvårigheterna. Istället hade flickornas svårigheter diagnostiserats som ångest, depression, familjerelationsproblem eller ospecifika anpassningsproblem. Ofta hade ingen diagnos alls ställts, trots att det var uppenbart att flickorna var svårt funktionshindrade i många olika miljöer (i skolan, bland kamrater, på fritiden, i familjen, på läkarmottagningar, vid psykologundersökning). Jämfört med de 60 flickor utan allvarliga kända problem, som jag också undersökte, var de 100 flickorna exceptionellt funktionshindrade inom alla områden som jag studerade (psykiatriskt, psykologiskt, motoriskt, akademiskt och vad gäller kamratkontakter).

Flickorna med autism och ADHD i min studie hade så gott som alltid ytterligare psykiatriska och utvecklingsneurologiska diagnoser. Ångest, depression, trotsyndrom, sociala beteendestörningar, motoriska koordinationsrubbnings och läs- och skrivsvårigheter var regel i båda grupperna, även om autismgruppen var ännu mera negativt belastad än gruppen med ADHD.

Resultaten är särskilt oroande mot bakgrund av att dessa flickor, i genomsnitt *inte* var tungt belastade av sociala missförhållanden och att de, i nästan samtliga fall, hade begåvning inom den så kallade normalvariationen.

Vi har också genomfört en delstudie syftande till att utveckla ett bättre instrument för att tidigt identifiera dessa flickor som är i stort behov av tidiga insatser för att undvika psykologisk och medicinsk "felutveckling". Vi utgick då från ASSQ (Autism Spectrum Screening Questionnaire), ett screeninginstrument för autismspektrumstörningar som tagits fram genom forskning vid vår institution och som nu är det mest välundersökta av alla screeninginstrument avseende autism i världen. Vi lade till ett antal frågor som vi kliniskt bedömde skulle vara värdefulla för att fånga upp flickor med autism. Vi jämförde "våra" flickor i huvudstudien med pojkar med motsvarande klinisk diagnos (och flickorna utan kända problem). Ett litet antal "flick-specifika" symptom framkom, men, på det hela taget var "original-ASSQ" lika bra eller bättre än summan av de nya frågorna. Delstudien var värdefull framför allt för att den ytterligare validerade ASSQ, men också för att den tydde på att tre eller fyra "flick-frågor" bör läggas till originalversionen för att, om möjligt upptäcka autism hos flickor tidigare än vad som idag är fallet.

Sammantaget tyder resultaten från mina studier på att flickor med autism och ADHD ofta antingen helt missas eller feldiagnostiseras inom barnsjukvården (inklusive inom barn- och ungdomspsykiatri). Resultaten antyder också att det finns risk för att deras betydande "samsjuklighet" bagatelliseras. Detta är

mycket allvarligt eftersom det numera finns effektiva behandlingsmetoder både vid autism och ADHD (och väldokumenterade interventioner vid/för de svårigheter som så ofta förekommer i tillägg till "grunddiagnosen"). Behovet av utbildning om flickor med psykiska problem, sociala interaktionssvårigheter och/eller koncentrationssvårigheter inom alla samhällets offentliga verksamheter är mycket stort.

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APPENDIX

ASSQ-GIRL, 18 new screening items believed to tap into the autism phenotype of girls

ASSQ-GIRL item	No	Somewhat	Yes
28. Copies you (can be in a very discrete way)	[]	[]	[]
29. Episodes of eating problems	[]	[]	[]
30. No time perception*	[]	[]	[]
31. Too much sympathy	[]	[]	[]
32. Extremely interested in pop/ rock bands, soap operas or natural disasters	[]	[]	[]
33. Avoids demands*	[]	[]	[]
34. Very determined*	[]	[]	[]
35. Difficulties with choice; always avoids choosing	[]	[]	[]
36. Difficulties with selfcare*	[]	[]	[]
37. Carefree or overmeticulous as regards physical appearance/dress	[]	[]	[]
38. Naïve	[]	[]	[]
39. Comes too close to others	[]	[]	[]
40. Interacts mostly with younger children*	[]	[]	[]
41. Engages in dangerous activities	[]	[]	[]
42. Exaggeratedly fanciful	[]	[]	[]
43. Talks without content*	[]	[]	[]
44. Writes long stories (can be in stark contrast to level of talk)	[]	[]	[]
45. Acts or lives different parts (TV stars, videos, animals)	[]	[]	[]

Note. *indicates items which were considered most specific in girls with ASD (see study V)

ORIGINAL PAPERS I-V