ESSENCE: Child and Adult Studies of Verbal and Nonverbal Skills in ASD and ADHD

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ABSTRACT

Aim: Longitudinal analysis of verbal and nonverbal deficits and skills and their contribution to clinical presentation in children and adults with ESSENCE/Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations. **Methods:** Forty school children with autism spectrum disorder (ASD) or attention-deficit/hyperactivity disorder (ADHD) or both were contrasted with 21 similarly aged children from the community who had screened positive for language disorder (LD) at 30 months. Also, 69 young adult males with ASD (Asperger syndrome) were followed longitudinally - neuropsychologically, psychiatrically and according to self/parent report - for an average of almost 10 years. **Results:** Clinic children with ASD and/or ADHD and community children with early LD had very similar verbal/nonverbal test and developmental profiles. Retelling of a story was linked both to verbal and nonverbal factors in the collapsed group with ADHD/ASD/LD. Nonverbal learning problems, persisting from childhood to adult age, in ASD, were associated with reduced tested and perceived executive functioning (EF). Good and superior verbal skills predicted better EF even in the presence of less good nonverbal skills. **Conclusion:** Young school age children seen in clinics with ASD/ADHD have almost identical verbal and nonverbal test profiles and problems as those screening positive for LD already at 2.5 years. Narrative skills at young school age were linked both to verbal and nonverbal test results. Boys with ASD (Asperger syndrome) become men with ASD, and their functioning in adulthood is linked to verbal skills and nonverbal deficits in childhood. – These longitudinal studies demonstrate the importance of full neuropsychological and psychiatric assessments in ESSENCE. These conditions are often lifelong. Many of them should be recognisable or at least broadly categorisable as ESSENCE already at 2.5 years. Follow-up assessment, both in school and in young adult age, is clearly important. Realistic prognosis and individual intervention plans based on such assessments are needed in ESSENCE.

Keywords: ESSENCE, neuropsychology, autism spectrum disorder, Asperger syndrome, ADHD, nonverbal learning disability, children, adults

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SAMMANFATTNING PÅ SVENSKA

Neuropsykiatriska diagnoser ställs och är definierade på basen av specifika kombinationer av olika svårigheter enligt DSM-IV (1994) eller ICD-10 (1993). Senare tids forskning talar för att olika diagnoser (autism, Aspergers syndrom/AS, Attention-Deficit/Hyperactivity Disorder/ADHD) i själva verket utgör delmängder av avvikelser inom mer övergripande utvecklingsneurologiska eller kognitiva funktionsdimensioner (såsom social interaktion, kommunikation, beteende, allmän kognition, uppmärksamhet).

Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE) är ett samlingsnamn för att beskriva olika typer av utvecklingsavvikelser som föranleder föräldrar att tidigt söka hjälp för sitt barn. Barnen kan ha svårigheter inom olika utvecklingsområden; språk, kommunikation, kognition, motorik och beteende. Problem som uppmärksammas före 5 års ålder och som har varat längre än 6 månader, är ofta symptom på neuropsykiatriska svårigheter (t.ex. autism, AS och ADHD) som diagnostiseras först vid utredningar flera år senare. Symptom på ESSENCE i barndomen varslar ofta om livslånga svårigheter.

Syftet med avhandlingen var att undersöka hur verbal och ickeverbal förmåga påverkar neuropsykologisk och adaptiv funktion inom grupper av barn och vuxna med ESSENCE (autism, AS och ADHD och språkstörning).

I de två första artiklarna studerades skolbarn med neuropsykiatriska tillstånd (autismspektrumstörning/ASD, ADHD och språkstörning); i de två sista artiklarna studerades unga män med AS longitudinellt.

Fyrtio skolbarn som remitterats till barnneuropsykiatrisk klinik och diagnostiserats med ASD eller ADHD jämfördes med en populationsbaserad grupp med 21 barn som identifierats som språkförsenade vid språkscreening på BVC vid 2.5 års ålder. Resultaten visade att den kognitiva profilen var nära nog identisk i båda grupperna. ”Klinikbarnen” hade också haft tidig kontakt med logoped. Detta talar för att tidig multidisciplinär utredning skulle kunna ge möjlighet till tidig upptäckt av ESSENCE problematik under tidiga barnaår.

De 40 klinikbarnen och de 21 barnen med tidigare diagnostiserad språkstörning behandlades i studie II som en grupp och undersöktes i fråga om huruvida muntlig berättarförmåga är en unik verbal förmåga eller om den också är påverkad av förmågan att uppfatta ett visuellt händelseförlopp.

Muntlig berättarförmåga visade sig inte bara vara kopplad till språk/verbal funktion utan också till visuell sekvenseringsförmåga. Detta skulle kunna innebära att barn med dessa svårigheter behöver träna ”ramen” för återberättande både verbalt och visuellt och att bildserier kan vara en hjälp att förstå ett sammanhang bättre.

I de två sista arbetena studerades 69 unga män med AS longitudinellt. Gruppen testades vid två tillfällen med ca 10 års mellanrum. Ickeverbala inlärningssvårigheter (NLD för Nonverbal Learning Disability) definierades som ickeverbal IQ signifikant lägre än verbal IQ. Gruppen med AS delades in i tre undergrupper, i) ”livstids” NLD, dvs. NLD både i barndomen och i vuxen ålder, (ii) ”barndoms” NLD, dvs. NLD enbart vid första tillfället, eller (iii) ingen NLD någonsin. Resultatet visade att de som hade livstids NLD hade sämre prognos såväl testmässigt som när det gällde egenrapporterade upplevda problem med organisations- och planeringsförmåga.

De 69 unga männen undersöktes också med avseende på social kommunikation och interaktion genom intervju med föräldrar. Resultaten visade att hög verbal förmåga inte påverkade social kommunikation och interaktion, men däremot organisations- och planeringsförmåga, dvs. exekutiva funktioner positivt. Det fanns en trend att hög verbal IQ hade större positiv betydelse än hög performance IQ. Det framkom också att relativt hög ålder vid AS-diagnos predicerade större problem tio år senare.

Sammanfattningsvis talar resultaten för att det är angeläget att i så låg ålder som möjligt, och därefter vid flera uppföljningstillfällen, studera/testa den kognitiva profilen vid ESSENCE, och att med resultaten av sådan testning som bas lägga grunden för realistisk prognos och kontinuerlig anpassning av den pedagogiska/psykologiska miljön. Det går att upptäcka ESSENCE eller symptom på ESSENCE redan i förskoleåldern. Uppföljningen av barn – pojkar *och* flickor - med ESSENCE - genom skolåren och in i vuxenåldern – måste komma att stå i fokus i svensk hälsovård under det närmaste decenniet.

LIST OF PAPERS

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

I. Hagberg, B., Miniscalco, C., Gillberg, C. Clinic attenders with autism or attention-deficit/hyperactivity disorder: cognitive profile at school age and its relationship to preschool indicators of language delay. Research in Developmental Disabilities, 2010; 31:1-8.

II. Åsberg, Johnels, J., Hagberg, B., Gillberg, C., Miniscalco, C. Narrative retelling in children with neurodevelopmental disorders: Is there a role for non-verbal temporal-sequencing skills? Scandinavian Journal of Psychology, 2013; 20: 121-133.

III. Hagberg, B.S., Nydén, A., Cederlund, M., Gillberg, C. Asperger syndrome and "non-verbal learning problems" in a longitudinal perspective: neuropsychological and social adaptive outcome in early adult life. Psychiatry Research, 2013; Epub ahead of print.

IV. Hagberg, B.S., Nydén, A., Gillberg, C. Non-verbal learning problems in Asperger syndrome: reported autism, attention/activity and executive dysfunctions. Submitted.

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ABBREVIATIONS

ADHD	Attention-Deficit/Hyperactivity Disorder
APA	American Psychiatric Association
AS	Asperger Syndrome
ASD	Autism Spectrum Disorder
BIQ	Borderline IQ
BST	Bus Story Test
CNC	Child Neuropsychiatry Clinic
DCD	Developmental Coordination Disorder
DEX	Dysexecutive Syndrome Questionnaire
DISCO	Diagnostic Interview for Social and COmmunication disorder
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
ESSENCE	Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations
EF	Executive Function
FD	Freedom from Distractibilty
FSIQ	Full Scale IQ
GAF	Global Assessment of Functioning
ICD-10	International Classification of Diseases. Tenth Revision
IDD	Intellectual Developmental Disorder
LD	Language Disorder/Delay
NLD	Nonverbal Learning Disability
PIQ	Performance IQ
PS	Processing Speed

ROCF	Rey-Osterrieth Complex Figure test
SLP	Speech and Language Pathologist
SNAP-IV	Swanson, Nolan And Pelham questionnaire. Fourth Edition
TOL	Tower of London
TROG	Test for the Reception Of Grammar
VABS	Vineland Adaptive Behavior Scales
VIQ	Verbal IQ
WISC-III	Wechsler Intelligence Scale for Children. Third Edition
WAIS-III	Wechsler Adult Intelligence Scale. Third Edition

1 INTRODUCTION

Neurodevelopmental disorders are early onset conditions that are usually (but not always) symptomatic in early life, and that involve some degree of specific or general cognitive, perceptual, developmental, and/or behavioural, impairment. There is significant overlap across differently labelled categorical disorders. Neurodevelopmental disorder diagnoses are based on specific combinations of different difficulties according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, 1994; DSM-5, 2013) and the International Statistical Classification of Diseases and Related Health Problems - Tenth Revision (ICD-10, 1993). Recent research suggests that different neurodevelopmental disorders such as Asperger syndrome (AS), autism, and Attention-Deficit/Hyperactivity Disorder (ADHD), may not be anything other than subsets of symptom clusters from broader abnormalities/variations of developmental, neurological or cognitive dimensions such as social interaction, communication, attention, and general behaviour.

1.1 Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE)

ESSENCE is an acronym that covers a number of differently labelled disorders such as ADHD, with or without Oppositional Defiant Disorder (ODD), tic disorders (including Tourette syndrome), Developmental Coordination Disorder (DCD), Language Disorder/Delay (LD), Intellectual Developmental Disorder (IDD), and Autism Spectrum Disorder (ASD) (Gillberg, 2010). The specific impairing symptoms, exhibited before the age of 3-5 years, are in the areas of (a) general development, (b) communication and language, (c) social inter-relatedness, (d) motor coordination, (e) attention, (f) activity, (g) behaviour, (h) mood, and/or (i) sleep. Children who are referred to clinics because of concern about such symptoms usually have more than one major problem. The symptoms are part of overlapping ("comorbid") disorders, e.g. ASD, ADHD, and LD. Long-term follow-up studies of children with ESSENCE show that these conditions persist into adulthood (Rasmussen and Gillberg, 2000; Billstedt et al, 2005). At least 5% of the child population have ESSENCE into adulthood. Most adults with ESSENCE also meet criteria for additional psychiatric disorders such as depression, anxiety, substance use, or personality disorders (Nylander et al, 2009; Lugnegård et al, 2011, 2012).

Individuals with ESSENCE have their psychiatric diagnoses made on the basis of behavioural symptoms. Underlying or associated with the behavioural symptoms are often cognitive and perceptual problems that can be specifically targeted in verbal and nonverbal tests, such as those measuring “intelligence”; executive functions (EF), central coherence, theory of mind, language, narrative ability, and memory.

1.2 Cognition

Cognition refers to “thinking” and “knowledge acquisition”. The term is nowadays often used to cover a whole set of mental processes, including verbal and nonverbal factors such as language, learning, memory, reasoning, problem solving, and attention. Cognition is related to but not identical with intelligence. The Intelligence Quotient (IQ) is a construct developed with a view to measuring a hypothesised general cognitive ability.

In 1905, Alfred Binet, developed the first IQ-test. It was the forerunner of the Stanford-Binet test that is used to this day in cognitive assessment of children. Originally, these tests were developed with a view to discriminating “normal” from “retarded” children.

David Wechsler, later (in the mid-1930s), developed a test battery that comprised subtests from Binet and from tests developed by World War I psychologists. Wechsler´s major contribution in this field was to introduce a standard battery of nonverbal tests and put this “performance scale” on an equal footing with the more “respected” verbal scale (Kaufman and Lichtenberger, 2002). Wechsler viewed intelligence as a global entity, and the scale was intended to provide measures of global ability. The Wechsler tests are now the most widely used tests of general intelligence and include versions for preschool children (Wechsler Preschool and Primary Scale of Intelligence/WPPSI), school age children (Wechsler Intelligence Scale for Children/WISC), and adults (Wechsler Adult Intelligence Scale/WAIS). The scales cover Verbal IQ (VIQ) and nonverbal Performance IQ (PIQ) as well as Full Scale IQ (FSIQ). FSIQ is often a good predictor of school achievement (Wechsler, 1992). In the field of ESSENCE, those with ASD and ADHD with an overall IQ above 70 have considerably better outcomes than those with IQ below this level (Starr et al, 2003; Howlin et al, 2004; Cederlund et al, 2008).

The cognitive profile derived from an IQ test is often analysed in both clinical and research settings. An “even” cognitive profile is believed to

reflect well-integrated features and the ability to automate i.e. to use ones abilities in routine situations. An “uneven” cognitive profile, on the other hand, can negatively influence learning ability and social functioning. An uneven profile is often reported both in ASD and ADHD. Individuals with AS often have better verbal than nonverbal skills (Klin et al, 1995; Gunter et al, 2002; Ghaziuddin and Mountain-Kimchi, 2004), whereas individuals with a diagnosis of “classic” autism tend to have higher PIQ than VIQ (Dahlgren Sandberg et al, 1993; Shah and Frith, 1993), although, this pattern may not always apply (Ambery et al, 2006). A significantly higher PIQ than VIQ has also been found in studies of adolescent groups with antisocial behaviours (Isen, 2010). This, in turn, has been suggested to be a consequence of antisocial behaviour in late childhood and early adolescence affecting the ability to profit from schooling.

Indices of VIQ-PIQ discrepancies are not the only way of assessing intellectual strengths and weaknesses. In the WISC-III the Kaufman four-factor solution was introduced. These factors are *Verbal Comprehension* (with subtests Information, Comprehension, Similarities, Vocabulary), *Perceptual Organisation* (subtests Picture Completion, Picture Arrangement, Object Assembly, Block Design), *Freedom from Distractibility* (subtests Arithmetic and Digit Span) *and Processing Speed* (subtests Coding, Symbol Search) (Kaufman, 1994). In the current versions of the Wechsler scales (WISC-IV, WAIS-III, and WAIS-IV) *Freedom from Distractibility* is replaced with *Working Memory* (subtests Digit Span, Digit-Letter Sequencing).

1.3 Executive Functions

The concept of Executive Function (EF) - the major function of the frontal lobes and of the prefrontal areas specifically - has occupied researchers for many years. Luria (1966) described EF as a “set of capacities underlying the ability to maintain an appropriate problem-solving strategy for attainment of a future goal”.

EF can be described as an umbrella term subsuming several cognitive processes, including inhibition, working memory, cognitive flexibility/shifting, and planning (Pennington and Ozonoff, 1996; Hill, 2004; Corbett et al, 2009).

Inhibition refers to the ability to suppress a dominant prepotent response, but it also entails interference control, directed forgetting, emotional control, and motor control (Nigg, 2000). There is a rapid development of inhibition

between ages 3-5. The child learns how to "stop and think" before acting. After age 5, the child enters into more social settings and schooling which require increased self control. The improvement of inhibition continues up to adolescence (Best et al, 2009). Tests that are used to assess inhibition are often referred to as "Go-No Go" tasks.

Working memory (WM) involves the ability to maintain and manipulate information over brief periods of time. WM is crucial for all cognitive tasks and it is where information is temporarily stored while solving cognitive problems (Kaufman and Lichtenberger, 2002). Attention and concentration play fundamental roles in WM in order to be able to perform adequately (Lezak et al, 2012). There is a linear increase in performance from age 4-15 years for a battery of WM tasks targeting different modalities e.g. auditory and visual tasks of varying complexity (Gathercole et al, 2004).

Shifting is the ability to shift between more complex task sets. This ability also improves with age, typically until early adolescence.

Planning is the ability to formulate actions in advance and to approach a task in an organised, strategic, and efficient manner (Anderson, 2001). Tasks that evaluate planning ability require the child to prepare multiple steps of action in advance and to evaluate these steps and change course if necessary. The test Tower of London is one of the most frequently used tests for the evaluation of this ability. The ability to create more complex plans develops in late childhood or adolescence (Best et al, 2009).

The abilities just referred to are needed for *new and complex* situations in everyday life. They are different from "automatisation", which refers to an effective way of handling *routine* situations.

Reported EF deficits in ASD include problems with planning, cognitive flexibility, and WM (Corbett et al, 2009). Individuals with ASD appear to be inflexible and rigid, they do not learn from mistakes, and are often preoccupied with narrow interests (Happé and Frith, 2006). Deficits in EF are sometimes described as underlying both theory of mind problems and weak central coherence (Ozonoff, 1997; Hill, 2004), see below.

Individuals with ADHD are often greatly impaired by deficits in their inhibitory control (Happé and Frith, 2006; Sinzig et al, 2008a). Set shifting and response inhibition are also reported to be impaired (Barkley, 1997; Happé and Frith, 2006). Social interaction deficits in individuals with ADHD

are believed to be related to poor execution of social skills rather than to a basic deficit in the skill itself (Nijmeijer et al, 2008).

1.4 Central Coherence and Theory of Mind

Individuals with ASD have limitations regarding the ability to understand the context, to make wholes of parts, and to "see the bigger picture". This ability is called central coherence. In ASD there is usually a detailed peripheral focused processing style and "weak" central coherence (Frith, 1996). Individuals with AS have difficulty putting together different types of information from events in order to understand the context, to see consequences, and to be able to predict what will happen (Shah and Frith, 1993; Happé, 1994a). Happé and Frith (2006) reported weak central coherence in a group of individuals with ASD compared with controls on testing with the Block Design and Embedded Figures tests. These tests measure not only visuospatial function but also the ability to extract information from context (Happé and Frith, 2006).

ASD is typically associated with dysfunction in social interaction which can be interpreted in the context of mentalising or "theory of mind" problems. Having a theory of mind refers to the ability to infer what others are thinking (believing, desiring) in order to explain and predict their behaviour (Frith, 1989; Baron-Cohen, 1995). People with ASD have limited mentalising abilities/theory of mind, which may mean that it can be hard for them to understand why other people behave and react the way they do. Limited theory of mind skills also lead to difficulties communicating wishes, feelings, and thoughts to other people (Frith, 2012).

1.5 LD and Narrative Ability

In Sweden, children with LD are often identified by language screening programs run at Child Health Centres/Well Baby Clinics at 2.5 and 4 years (Westerlund and Sundelin, 2000; Miniscalco Mattson et al, 2001). At 2.5 years of age the child´s ability to communicate and to produce and understand single and multiword utterances is assessed. At 4 years, the focus in assessment is on the expressive speech and language (phonology and grammar). Risk factors for persisting language problems depend on the cognitive development, the level of language severity, and presence of other developmental disorders (Conti-Ramsden et al, 2006; Snowling et al, 2006). Language delay and language impairments are common in ADHD and ASD. The prevalence of LD in Sweden is about 6% (Miniscalco et al, 2003), and

from international studies the range is from 1-15% depending on which definition of LD is used (Law et al, 2000).

Narrative retelling has been shown to be an important longitudinal predictor of communicative (Bishop and Edmundson, 1987) and academic skill development (Fazio et al, 1996). Narrative skills include and require linguistic, cognitive, and social ability (Botting, 2002; Norbury and Bishop, 2003). Assessing the narrative production and comprehension provides a way of examining pragmatic functioning. Narrative retelling or other tasks of oral narrative production present a great challenge for children with ESSENCE (e.g. LD, ADHD, and ASD) (Botting, 2002; Norbury and Bishop, 2003; Miniscalco et al, 2006).

One aspect of narrative telling is storytelling. Lezak and other researchers have recommended storytelling as an examination method in brain impaired patients. “Storytelling elicits the flow of verbal behaviour, brings out the quality of the patient´s abilities to organize and maintain ideas, and may reveal characteristic attitudes and behavioural propensities” (Lezak et al., 2012).

1.6 Adaptive Behaviour

Adaptive behaviour refers to skills which are necessary in order to function in everyday life and to live an independent life. Adaptive skills include communication (how an individual understands instructions and how the individual speaks in full sentences and makes himself understood) daily living skills (e.g. dressing and eating independently), social adaptive behaviour (independence at home and in the community), being able to interact with peers and grown-ups (adapting to rules in society and at home), and motor skills (both gross motor skills and fine motor skills). The Vineland Adaptive Behavior Scales (VABS) is an instrument that is often used to evaluate adaptive functioning (Sparrow et al, 1984).

In order to plan for adequate intervention and education, assessment of the level of adaptive behaviour skills is important as a complement to tested IQ. In the general population, IQ and adaptive composite scores are highly correlated (Liss et al., 2001). It has also been reported that overall adaptive functioning is lower than cognitive level in higher functioning individuals with ASD (Lopata et al, 2013). Individuals with ASD have been characterised by impairments in everyday tasks such as hygiene, eating and dressing (Gillberg, 2002). It has further been suggested that individuals with ASD have a distinct profile on the VABS with highest scores on Daily Living

skills, lowest on Socialization, and intermediate on Communication (Kraijer, 2000; Bölte and Poustka, 2002; Sparrow et al, 2005). – Recently, a Swedish study, using the Adaptive Behavior Assessment System (ABAS), an instrument yielding information similar to that obtained using the VABS, demonstrated that children with ADHD had very low levels of adaptive functioning, on par with or lower than those shown by children with IDD (Lindblad et al, 2013).

1.7 ADHD

There are nine criteria for inattention and nine separate criteria for hyperactivity/impulsivity in the DSM-IV diagnostic algorithm for ADHD (Table A). Six or more criteria for inattention *and* six or more criteria for hyperactivity/impulsivity are required for the diagnosis of ADHD combined type. For the diagnosis of ADHD predominantly inattentive type, 6 or more out of 9 criteria for inattention, but fewer than six criteria for hyperactivity/impulsivity, have to be met. Six or more criteria for hyperactivity/impulsivity but fewer than six criteria for inattention are required for the diagnosis ADHD predominantly hyperactivity/impulsivity type. For a diagnosis of any type of ADHD to be made at all there must be clinical impairment and onset of symptoms in early childhood.

Motor control problems, behaviour problems, ODD, language problems, and autistic features are often seen in ADHD already during the preschool years (Kadesjö and Gillberg, 2001; Kadesjö et al, 2003; Tetnowski, 2004; Miniscalco et al, 2006).

The ADHD prevalence in the general population is around 5-8% (Fombonne, 2005). There are more boys (3-4:1) affected by (or diagnosed with) ADHD than there are girls (Scahill and Schaw-Stone, 2000; Kopp et al, 2010).

Table A. ADHD: DSM-IV diagnostic criteria (1994)

Inattention **Six or more**	**Hyperactivity**	**Impulsivity** **Six or more**
often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities	often fidgets with hands or feet or squirms in seat	often blurts out answers before questions have been completed
often has difficulty sustaining attention in tasks or play activities	often leaves seat in classroom or in other situations in which remaining seated is expected	often has difficulty awaiting turn
often does not seem to listen when spoken to directly	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)	often interrupts or intrudes on others (e.g., butts into conversations or games)
often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace	often has difficulty playing or engaging in leisure activities quietly	
often has difficulty organizing tasks and activities	is often "on the go" or often acts as if "driven by a motor"	
often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)	often talks excessively	
often loses things necessary for tasks or activities (e.g. toys, school assignments, pencils, books, or tools)		
is often easily distracted by extraneous stimuli		
is often forgetful in daily activities		

- Either six (or more) of the symptoms of **inattention** and/or six (or more) of **hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level.

- Some inattentive symptoms or hyperactive-impulsive that caused impairment were present before age 7 years.

- Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).

- There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.

- The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, 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).

1.8 Autism, ASD, and AS

1.8.1 Autism in the DSM-IV, Pervasive Developmental Disorders, ASD

Children with autistic disorder ("autism"), according to the DSM-IV, have impairments in three different domains: a) reciprocal social interaction, b) communication and language, and c) behaviour and interests. According to this manual the features of autistic disorder ("classic autism") must be clinically present before the age of 3 years. Children with this variant of "classic autism" are often referred initially for examination of delayed language development (Dahlgren and Gillberg, 1989). According to the DSM-5 (APA 2013) there are only two symptom domains in autism ("autism spectrum disorder"): (1) social-communication problems, and (2) repetitive behaviours.

Autistic disorder under the DSM-IV (Table B) is one of the variants of "pervasive developmental disorders" (PDDs) or ASDs. ASDs also include AS and PDD Not Otherwise Specified (PDDNOS), sometimes referred to as atypical autism.

Children with ASDs often lack communicative competence and they have pervasive pragmatic deficits. They are also often referred to special clinics for delayed language development at around 2.5 years of age (Dahlgren and Gillberg, 1989; Miniscalco et al, 2006). They may also have motor control problems, perceptual abnormalities, repetitive movements, behaviour problems, hyper- or hypoactivity, sleep, or feeding problems early on (Gillberg et al, 2006; Gillberg, 2010; Coleman and Gillberg, 2012).

The prevalence of DSM-IV PDD/ASD is about 0.6-1.2%. Boys are much more often affected than girls (Baird et al, 2006; Ellefsen et al, 2007; Nygren et al, 2012).

Table B. Autistic disorder: DSM-IV diagnostic criteria (1994)

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) Marked 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 modes of communication such as gesture or mime)

(b) in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others

(c) stereotyped and repetitive use of language or idiosyncratic language

(d) lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level

(3) Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:

(a) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus

(b) apparently inflexible adherence to specific, nonfunctional 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.

1.8.2 AS

AS is currently diagnosed under different sets of diagnostic criteria. The DSM-IV (Table C) and ICD-10 criteria for AS have been recognised as imperfect, given that they require normal early development in the first three years of life, a criterion that is almost never met by individuals who otherwise meet the symptom criteria for the disorder. The criteria most commonly used in practice are those published by Gillberg (1991) (Table D), based on the symptom area list published by Gillberg and Gillberg (1989), which, in turn, was based on Hans Asperger´s original case descriptions of "his" disorder. There is also a set of criteria published by Szatmari et al (1989).

Table C. Asperger´s disorder: DSM-IV diagnostic criteria (1994)

Qualitative impairment in social interaction, as manifested by at least two of the following:

(1) marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body posture, and gestures to regulate social interaction

(2) failure to develop peer relationships appropriate to developmental level

(3) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, ringing, or pointing out objects of interest to other people)

(4) lack of social or emotional reciprocity

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, nonfunctional routines or rituals

(3) stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)

(4) persistent preoccupation with parts of objects

The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning

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)

There is no clinically significant delay in cognitive development or in the development of age-appropriate self-help skills, adaptive behavior (other than in social interaction), and curiosity about the environment in childhood

Criteria are not met for another specific Pervasive Developmental Disorder or Schizophrenia

Table D. Asperger syndrome: Gillberg diagnostic criteria (1989, 1991)

All six criteria must be met for confirmation of diagnosis:

1. Severe impairment in reciprocal social interaction (at least two of the following)

-inability to interact with peers
-lack of desire to interact with peers
-lack of appreciation of social cues
-socially and emotionally inappropriate behaviour

2. All-absorbing narrow interest (at least one of the following)

-exclusion of other activities
-repetitive adherence
-more rote than meaning

3. Imposition of routines and interests (at least one of the following)

-on self, in aspects of life
-on others

4. Speech and language problems (at least three of the following)

-delayed development
-superficially perfect expressive language
-formal, pedantic language
-odd prosody, peculiar voice characteristics
-impairment of comprehension including misinterpretations of literal/implied meanings

5. Non-verbal communication problems (at least one of the following)

-limited use of gestures
-clumsy/gauche body language
-limited facial expression
-inappropriate expression
-peculiar, stiff gaze

6. Motor clumsiness

-poor performance on neurodevelopmental examination

1.8.3 DSM-5

In May 2013, the American Psychiatric Association published a new version of the DSM. In the DSM-5 (APA 2013), AS has been removed as an independently coded disorder and is instead incorporated under the ASD umbrella category. The DSM-5, unlike the DSM-IV does not distinguish between social interaction and communication. Two, rather than three main areas are referred to: Criterion A) impairment in reciprocal social communication and social interaction, and Criterion B) restricted, repetitive patterns of behaviour, interests, and activities. The symptoms are present from early childhood (Criterion C) and limit or impair everyday functioning (Criterion D).

Added to the overall ASD diagnosis in the DSM-5 are severity measures. This probably will make the clinical picture clearer since more individual factors can be specified. Severity is specified for three levels: 1) requiring support; 2) requiring substantial support; 3) requiring very substantial support.

Some studies have already shown reduced rates of ASD diagnoses under the draft version of the DSM-5, and the draft criteria were less sensitive in respect of identification of some individuals with ASDs, particularly those with AS and so called “high-functioning” autism (Mattila et al, 2011; McPartland et al, 2012; Wilson et al, 2013), i.e. those with autistic disorder but no IDD.

1.9 Nonverbal Learning Disability

Nonverbal Learning Disability (NLD) is a neuropsychological construct (unlike the operationalised categorical constructs of the DSM) characterised, among other features, by a significantly lower PIQ than VIQ on testing. Other problems in NLD include deficits as regards novel problem solving, visual spatial learning and visual memory, tactile perception, psychomotor skills, and mathematics (Rourke, 1989). Rote verbal memory, language form, amount of verbal associations, and verbal/language output are often well developed. These problems and assets lead to increased difficulties in formal learning (e.g., arithmetic and science) and in terms of psychosocial functioning (Rourke et al, 2002). NLD characteristics are seen before 6 years of age, with delays in reaching almost all developmental milestones.

Similarities between the clinical presentations of AS and NLD include problems with social communication and reciprocity, nonverbal

communication, pragmatic language, and visual-spatial skills (Gunter et al, 2002; Rourke et al, 2002). Planning and mental flexibility are often problematic both in AS and NLD (Ozonoff and Jensen, 1999).

Klin has suggested an overlap between AS and NLD based on data that individuals with AS often have significantly higher VIQ than PIQ (which, as outlined in the foregoing is one of the characteristics of NLD) (Klin et al, 1995). However, at least two studies found no indication of VIQ significantly higher than PIQ in AS (Ambery et al, 2006, Ryburn et al, 2009).

It has been suggested that the NLD syndrome affects the right hemisphere more than the left because it is made up of relatively more white matter and has longer communication links than the left hemisphere (Goldberg and Costa, 1981; Rourke, 1995). Similar claims have been made for right hemisphere dysfunction in AS (Stroganova et al, 2007; Gold and Faust, 2010).

2 AIM

The overall aim of this thesis is to longitudinally examine how verbal/language and nonverbal skills affect neuropsychological and adaptive functioning within groups of children and young adults with ESSENCE (ASD and ADHD). More specifically, the aims were to analyse;

- whether or not clinic cases of children with ESSENCE (ASD, ADHD, or both), had been identified by the language screening surveillance programmes performed at child well baby clinics at different ages during the preschool period;

- whether or not this group of psychiatric clinic referred school age children with ESSENCE differed verbally or nonverbally from non-referred community children with preschool LD;

- whether or not, in the collapsed group of children with ESSENCE (ASD, ADHD and early identified LD) oral narrative retelling skills might be associated not just with verbal/language functioning but also with nonverbal narrative temporal sequencing;

- the longitudinal impact of NLD on the neuropsychological (particularly EF) and social adaptive outcomes in a group of males diagnosed within one of the ESSENCE categories (AS), followed from childhood into adolescence and young adult life;

- the longitudinal impact of NLD on experiential (parent- and self-reported) problems in different ESSENCE domains; and

- the influence of age at diagnosis, VIQ, and PIQ on outcome in terms of EF in young men with AS.

3 METHODS

An overview of all subjects participating in the studies of the present thesis is given in Table E.

Table E. Study Groups: Characteristics of groups examined in studies I, II, III, and IV

Study	I	II	III	IV
Object of study	**Verbal and nonverbal problems in primary school children with ESSENCE and their relation to early language delay**	**Narrative ability in ESSENCE: relation to verbal and nonverbal problems**	**Longitudinal impact of NLD in young men with AS: neuropsychological and social adaptive profiles**	**Longitudinal impact of NLD in young men with AS: parent- and self-reported outcomes**
Target group	**61**	**61**	**100**	**100**
Attrition	**0**	**6**	**31**	**32**
Group examined	**61(40+21)**	**55**	**69**	**68**
Age range: years	**6.4-9.9, 7.4-9.1**	**6.0-9.1**	**16.0-36.5**	**16.0-36.5**
Male:Female	**36:4, 17:4**	**47:8**	**69:0**	**68:0**
Mental development level	**FSIQ>70 Mean=88.7**	**FSIQ>70 Mean=92.7**	**FSIQ>70 Mean=103.5**	**FSIQ>70 Mean=103.6**
Diagnostic criteria	**DSM-IV/ICD-10/ Gillberg´s AS criteria**	**DSM-IV/ICD-10/ Gillberg´s AS criteria**	**DSM-IV/ICD-10/ Gillberg´s AS criteria**	**DSM-IV/ICD-10/ Gillberg´s AS criteria**
Measurements	**Neuropsychiatric examination, Wechsler scales**	**Neuropsychiatric examination, Wechsler scales, BST, TROG**	**Neuropsychiatric examination, Wechsler scales, Gottschaldt Hidden Figures, Claeson-Dahl, ROCF, VABS, GAF**	**Neuropsychiatric examination, Wechsler scales, DISCO-10, SNAP-IV, DEX self-report questionnaire**

3.1 Subjects and Procedure

In study I, 40 primary school age children referred to a specialist clinic (Child Neuropsychiatry Clinic, CNC, Gothenburg) for ESSENCE (and diagnosed with ADHD, ASD or the combination of the two without clinical suspicion of IDD), were assessed cognitively (verbal and nonverbally) and as regards language development and language function at a mean age of 7.3 years. They were contrasted with a group of 21 children from the community who had been flagged at 2.5 years and documented to have LD in a general health care screening programme, and who had been followed up psychiatrically and neuropsychologically and in respect of language at a mean age of 7.9 years.

In study II, 55 of the 61 children from Study I were included. To be included in the study, a full scale IQ (FSIQ) in excess of 70 according to testing with the WISC-III (Wechsler, 1999) was required. Thirty-six participants were patients at the CNC, and the remaining 19 participants were from the community sample with LD. Five children tested below IQ 70 and were therefore excluded. Three of these children came from the clinical sample and two from the community sample. One child was excluded from further study because of a diagnosis of cerebellar ataxia. In the collapsed group, 21 children had ASD (12 children overlapping with ADHD), 25 had ADHD (13 overlapping with DCD), and 9 had language impairment (2 overlapping with borderline IQ (BIQ) and 1 with dyslexia).

In study III and study IV, 69 and 68 males respectively (all with tested childhood IQ≥70), with AS were tested with the WAIS-III. Sixty-eight of the 69 men from study III had a DISCO-interview completed (which was a requirement for inclusion in study IV). All 69/68 males with AS included were recruited from a group of 100 consecutive clinic cases of males, diagnosed by Gillberg and Gillberg criteria (Gillberg, 1991) as suffering from AS (Cederlund and Gillberg, 2004) at the CNC, in the years 1985-1999, and had been approached for follow-up at the CNC in 2003-2005. In addition to meeting Gillberg´s criteria, all the 69 males also met ICD-10 and DSM-IV symptom criteria for AS (but not usually the criterion requiring normal development in the first three years of life). The mean age at AS diagnosis was 12.4 years (SD 4.4, range 6.4-24.5) and at the time of follow-up 22.2 years (SD 4.7, range 16.0-36.5). All 69/68 individuals had been tested with a Wechsler scale both at time 1 (the time of original AS diagnosis) and time 2 (follow-up in young adult age).

The participants in study III and IV were divided into three groups depending on whether or not the individual had a VIQ>PIQ difference of 15 or more IQ scores; (1) *persistent* NLD (P-NLD) - VIQ>PIQ at time 1 and time 2 (n=15), (2) *childhood* NLD (CO-NLD) - VIQ>PIQ at time 1 but not at time 2 (n=18), (3) *no* NLD *ever* (NO-NLD) - never had VIQ>PIQ (n=36).

3.2 Instruments

Instruments used in the different studies are briefly reviewed in Table E.

3.2.1 Diagnostic Criteria Used

The DSM-IV (American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th edition, 1994) criteria were checked for ASD and ADHD in study I and II. The Gillberg criteria for AS (1989, 1991) were used in study III and IV (as were the symptom criteria for AS in the DSM-IV/ICD-10). The Diagnostic Interview for Social and COmmunication disorders (DISCO-10) was used for all young men with AS in study IV, see further below. The DISCO diagnostic algorithm systems are ICD-10 (WHO, 1993), DSM-III-R (APA, 1987), and DSM-IV criteria (APA, 1994). Algorithms based on Kanner's 'Early Infantile Autism' (Kanner and Eisenberg, 1956), Gillberg and Gillberg's definition of AS (1989), Wing and Gould's ASD (1979), and 'Social Impairment' (1979) are also operationally defined.

3.2.2 Motor Examination

A brief motor examination, including the items described by Kadesjö and Gillberg (1999) was used in Study I and Study II.

3.2.3 The Wechsler Scales

The Wechsler scales for children (WISC-R and WISC-III) (Wechsler, 1974; Wechsler, 1999) and for adults (WAIS-R and WAIS-III) (Wechsler, 1981; Wechsler, 2003) are well-established IQ-tests, including FSIQ, VIQ, and PIQ, and four factors according to Kaufman: Verbal Comprehension (VC), Perceptual Organisation (PO), Freedom from Distractibility (FD), and Processing Speed (PS). The Wechsler scales were used in all studies. The results are presented as standard scores (mean=100, SD=15).

3.2.4 Test for Reception Of Grammar

The Test for Reception Of Grammar (TROG) is used to examine the child´s verbal comprehension and understanding of syntactic structures of increasing

difficulty (Bishop, 1989). It involves matching a total of 80 orally presented sentences to the correct picture out of a choice of four. The TROG has age norms for Swedish children (Holmberg and Lundälv, 1998). The test was used in study II and the results are presented in standard scores (mean=100, SD=15).

3.2.5 The Bus Story Test

The Swedish version of the Bus Story Test (BST) (Renfrew, 1997; Svensson and Tuominen-Eriksson, 2000) was used in study II. The child is told a story by a test administrator using 12 cartoon pictures, with three pictures per page. While looking at the pictures the child is asked to retell the story. The respondent's narration was videotaped using a SONY Handicam DCR-TRV50E and an external microphone. Ortographical transcription was done according to the Swedish manual (Svensson and Tuominen-Eriksson, 2000). BST includes subscores presenting three different aspects of narrative ability. The length and complexity of the sentences in the child's narrative retell are represented by the subscores *Sentence Length* and *Subordinate Clauses* subscores respectively. The subscore *Information* is a measure of the child's ability to retell critical story elements in a distinct way. The five longest sentences were selected in each sample, and the mean value was calculated as the *Sentence Length* score. The number of *Subordinate Clauses* score was calculated, providing a measure of expressive grammatical complexity. The BST results are expressed in raw scores for *Sentence Length* and *Subordinate Clauses* and *Information* is expressed in standard scores.

3.2.6 Tower of London Test

In study III, the Tower of London test (TOL) (Shallice, 1982; Culbertson and Zillmer, 2001), was used specifically to detect deficits in planning and strategy. It is included in a recommended set of tests for comprehensive assessment of EF (Goldberg and Bougakov, 2005). It consists of two boards with pegs and several beads with different colours. In the TOL the coloured beads must be moved one-by-one from an initial state to match a goal state. Instructions are given to plan the whole sequence of moves ahead to determine the order of moves necessary to rearrange the three coloured balls. The results are presented in standard scores (mean=100, SD=15).

3.2.7 Gottschaldt's Hidden Figures Test

Originally the Gottschaldt´s Hidden Figures test was used in studies of abilities of patients with brain damage. The test requires the subject to analyse the figure-ground relationship in order to distinguish the figure from the interfering surroundings. The test is a series of redundant meaningless

geometrical patterns shown to the participant who is asked to pencil out a simple geometrical figure which is embedded. The Gottschaldt's Hidden Figures Test (Gottschaldt, 1928; Thurstone, 2001) was used in study III and IV to measure figure-ground discrimination abilities (an aspect of central coherence). The results are presented as stanine (range 1-9, mean=5, SD=2).

3.2.8 Claeson-Dahl Test of Memory

Verbal auditory learning and memory were measured in study III by using the Claeson-Dahl test (Claeson et al, 1998). The test consists of 10 non-related bisyllabic words, which are read aloud and may be repeated up to 10 times. There is free recall immediately after each reading, after an interval of 15 seconds, and also after 30 minutes. The results are presented as T-scores (mean=50, SD=10).

3.2.9 Rey-Osterrieth Complex Figure Test

Originally the Rey-Osterrieth Complex Figure test (ROCF) was devised by Andre Rey (1941) for investigation of both perceptual organisation and visual memory in brain impaired subjects (Lezak et al, 2012). Osterrieth standardised Rey´s procedure and developed the test in 1944 (Lezak et al, 2012).

In Study III, the ROCF (Osterrieth, 1944; Meyers and Meyers, 1995) was used to assess visual memory. The proband was asked to reproduce a complicated line drawing, first by copying and then from memory. How the proband copies the figure will bear significant relation to figure recall. If the proband approaches the copying task conceptually, dealing first with the overall picture and thereafter with the details, one by one, he/she will recall the figure much better than the proband who copies the details one by one (Lezak et al, 2012). Individuals with ASD tend to copy details one by one and do not approach the figure as a whole. The results are presented as stanine (range 1-9, mean=5, SD=2).

3.2.10 Vineland Adaptive Behavior Scales

The Vineland Adaptive Behavior Scales (VABS) is a well established and often used parent and teacher interview measuring adaptive skills of children and adults. It is also used in several studies regarding ASD and social adaptive skills (Lopata et al, 2013).

Parents of all participants in study III were given the VABS (Sparrow et al, 1984). The VABS was used here as a semi-structured interview with a parent/caregiver. The interview evaluates adaptive functioning in four

domains, three of which were assessed here: (1) communication (receptive, expressive, and written), (2) daily living skills (personal, domestic, community), and (3) socialization (interpersonal relationships, play and leisure time, coping skills). The fourth domain, motor skills (fine, gross) for which norms are only available for children under 6 years of age, was not assessed in this study. The results are presented as standard scores (mean=100, SD=15).

3.2.11 The Global Assessment of Functioning Scale

The Global Assessment of Functioning scale (GAF) (APA, 1994) was used to measure current psychosocial functioning. It yields scores of 0-100, and a score of ≥70 indicates "good functioning" or "only a mildly abnormal psychosocial situation".

3.2.12 Swanson, Nolan and Pelham Questionnaire, Fourth Version

Parents of men with AS in Study IV were given the Swanson, Nolan, and Pelham Questionnaire, Fourth Version (SNAP-IV) (Swanson et al, 1983). The SNAP-IV rating scale is a revision of the Swanson, Nolan and Pelham Questionnaire (SNAP), (Swanson et al, 1983). There are items (all individual items scored 0-3) from the DSM-IV (1994) criteria for ADHD and ODD. Nine items measure inattention (ADHD-In), and 9 measure hyperactivity-impulsivity (ADHD-H/Im). The 18 items together measure ADHD combined (ADHD-C). Cut-off score for possible ADHD caseness was ADHD-In=1.78, ADHD-H/Im=1.44, and ADHD-C=1.67. Scores were calculated by summing the scores on the items in each category and dividing by the number of items in that category.

3.2.13 The Dysexecutive Syndrome Questionnaire

The participants in study IV were given the Dysexecutive Syndrome Questionnaire (DEX) (Wilson et al, 1999). It is a 20-item, sensitive and ecologically valid self-report questionnaire designed to assess everyday signs of EF problems (Burgess et al, 1998). The DEX includes four subscales: Cognition, Emotion, Motivation, and Behaviour. Each subscale and subdivision factor is scored 0-4, higher score indicating more daily life problems. In addition, a five factor subdivision system was used: Inhibition, Intentionality, Executive Memory, Positive Affect, and Negative Affect (Burgess et al, 1998).

Examples of questions from the four different subscales: Cognition: *I find it hard to concentrate and I get easily distracted*. Motivation: *I find it hard to think ahead and plan for the future*. Behaviour: *I'm often very restless and cannot sit still*. Emotion: *I find it hard to show my feelings*.

3.2.14 DISCO-10

The DISCO-10 is a 2-4 hour semi-structured interview intended for interview with a person (often a parent), who knew the individual well when she/he was young. The DISCO is designed for use from early childhood into adult life (Wing et al, 2002). The purpose of the interview is to help the clinician in the diagnostic assessment of persons with ASD and other developmental disorders affecting social interaction and communication (Wing et al, 2002). Different algorithms are available for diagnostic decisions. This interview was used in study IV with the individuals' parents.

3.3 Statistical Methods Used

Study I: Differences between groups were analysed using Kruskal-Wallis and Dunn's Multiple Comparison Test or the Mann-Whitney test.

Study II: Independent t-tests and ANOVA were used in group comparison. Correlation and linear regression analysis were used to examine associations between predictors and narrative measures. Finally, principal component analysis was used to examine how the variables of interest clustered together.

Study III and IV: For comparisons between groups, an overall Kruskal-Wallis test was first used for continuous variables. For pairwise comparison between two groups, Mann-Whitney U-test was used for continuous variables, and Fischer's exact test for dichotomous variables. For analysis of changes over time within groups, Wilcoxon Signed Rank test was used. For correlation analysis, Spearman correlation coefficient was used. In study IV; in order to select independent predictors (age at diagnosis, VIQ, PIQ, VIQ-PIQ difference) for DEX total (score above median), a stepwise multiple logistic regression analysis was performed. Adjusted odds ratio with 95% confidence intervals and adjusted p-value are presented. All significance tests were two-sided and conducted at the 5%-level of significance.

3.4 Ethics

The studies were approved by the Regional Ethics Review Board in Gothenburg. Parents provided written informed consent, as did all the adult men with AS participating in Study III and Study IV.

4 RESULTS

Overall, no specific statistical analyses relating to gender were conducted due to the small number of girls in study I and II. In study III and IV only men participated.

4.1 The Child ESSENCE/Language Study

The Child ESSENCE/Language Study included 40 children referred to the CNC and 21 children who had been screened at 2.5 years of age and then diagnosed by a speech and language pathologist (SLP) as having LD. In the collapsed group 53 of the 61 children had an ESSENCE diagnosis at age 7 years with different overlapping of ASD, ADHD, BIQ, and DCD.

4.1.1 History of Early Contact with SLP in Clinical ESSENCE Group

The majority of the children (60%) with "clinical ESSENCE" (ASD and/or ADHD diagnosis) at early school age had been in contact with SLP services during preschool years (Table 1). Children with ASD and ASD/ADHD had had significantly (p=0.0175) more SLP contact (71%) during the preschool period compared with those who had ADHD (22%) only. A minority of the group with ASD (29%) had had no previous SLP contact. There was also a trend that children with ASD had been in contact with a SLP earlier than those with ADHD. Overall, the clinical ESSENCE group that had had a previous SLP contact tended to have a lower FSIQ (83.3) than those who did not (FSIQ 93.1) (n.s.).

Table 1. SLP contact in 40 clinic children with ASD and/or ADHD

SLP contact at age (years)	ASD (n=10) male/female	ASD/ADHD (n=21) male/female	ADHD (n=9) male/female	Total (n=40) male/female
2.5	**5/0**	**6/1**	**1/0**	**12/1**
4.0	**1/0**	**4/2**	**0/0**	**5/2**
5.5	**1/0**	**2/0**	**1/0**	**4/0**
No contact	**3/0**	**5/1**	**7/0**	**15/1**

4.1.2 Verbal and Nonverbal Characteristics in the Clinical ESSENCE Group

The mean FSIQ in the clinical ESSENCE group was somewhat lower than population norms (ASD mean=89.5, ADHD mean=89.5, ASD/ADHD mean=88.0) (Table 2). The overall cognitive profile did not separate the groups with ASD, ADHD and ASD/ADHD from each other. However, the children with ASD had a slightly higher score on the nonverbal PO factor (WISC-III), compared with ASD/ADHD and ADHD. The groups with ASD and ASD/ADHD had lower results on FD (WISC-III) than the group with ADHD.

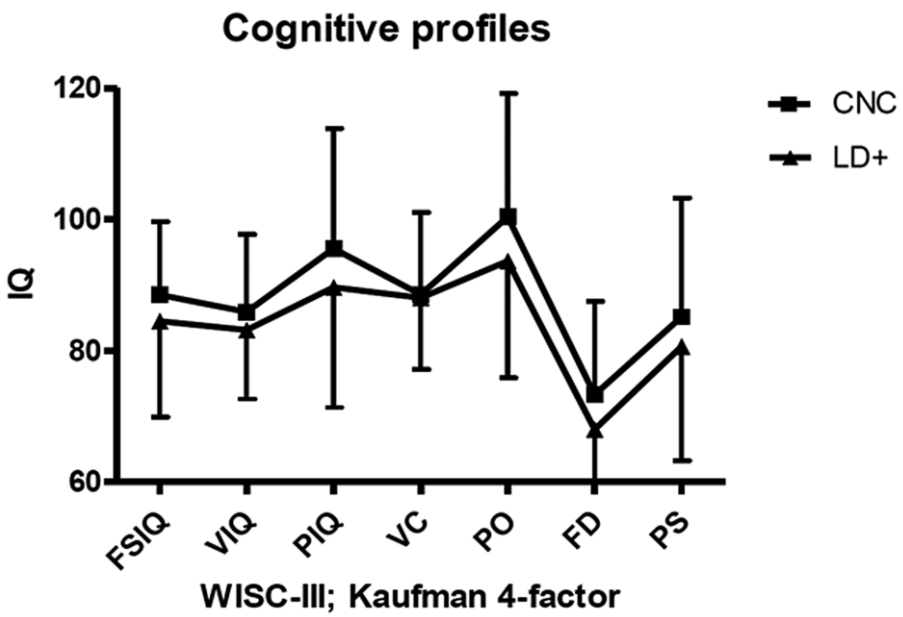
Table 2. WISC-III test profiles in 40 clinic children with ASD and/or ADHD

Diagnosis	FSIQ Mean (SD)	VIQ Mean (SD)	PIQ Mean (SD)	VC Mean (SD)	PO Mean (SD)	FD Mean (SD)	PS Mean (SD)
ASD (n=10[a])	89.5 (14.4)	87.6 (11.2)	98.4 (17.7)	90.5 (11.0)	102.4 (24.3)	78.6 (11.1)	85.2 (16.2)
ASD/ADHD (n=21)	88.0 (15.4)	90.0 (15.2)	88.4 (17.3)	94.1 (15.1)	91.8 (17.4)	78.9 (16.6)	88.8 (19.3)
ADHD (n=9)	89.5 (11.4)	93.0 (14.2)	87.8 (17.0)	95.1 (12.1)	91.0 (17.7)	88.3 (21.6)	88.6 (12.7)

Note. FSIQ=Full Scale IQ, VIQ=Verbal IQ, PIQ=Performance IQ, VC=Verbal Comprehension, PO=Perceptual Organisation, FD=Freedom from Distractibility, PS=Processing Speed.
[a]One child had not been assessed with the WISC-III due to intellectual difficulties. FSIQ was assessed with Griffiths Developmental Scales.
All differences non-significant.

4.1.3 Comparison of Verbal and Nonverbal Factors across Clinical ESSENCE and Community LD Groups

Thirteen children in the clinical ESSENCE group had been in contact with SLP at an early age (2.5 years). This subgroup was compared with 13 community children who had screened and tested positive for LD at 2.5 years of age and who were later diagnosed as having ASD or/and ADHD. When they were tested at about age 7 years no differences were found on WISC-III cognitive profiles in the two groups (Figure 1). Both groups had lower results on FD and PS whereas the highest result was in the perceptual domain (PO). VC was lower than nonverbal PO and lower than in the general population.



Note. All differences non-significant

Figure 1. Cognitive profiles in clinic and community children matched for SLP-contact

4.2 The Child Narrative Study

Participants in this study included both the original clinically diagnosed group with ESSENCE and the community children with LD from Study I. Five children were excluded due to actual tested FSIQ below 70 and one due to physical disability. We found no significant differences between the two groups on any of the three BST measures and therefore we collapsed them into one sample.

The mean score on the three measures (Sentence Length and Subordinate clauses, Information) fell slightly below average according to age appropriate norms. The group scored low on Information (-1.5 SD) which mirrors the narrative skill.

Two verbal/language tests, TROG and the subtest Vocabulary from the WISC-III, were combined into a language factor in order to provide a reliable measure that combines impressive and expressive language. Information in the BST was predicted by the verbal/language factor but also by the subtest Picture Arrangement (WISC-III). This subtest is a nonverbal narrative sequencing test. However, Sentence Length and Subordinate Clauses were only predicted by the verbal/language factor, indicating that these measures are more loaded with language.

Table 3. Verbal and nonverbal predictors of narrative abilities – regression analysis

	Information			**Sentence length**			**Subordinate Clauses**		
	R^2 / F	***t***	***ß***	**R^2 / F**	***t***	***ß***	**R^2 / F**	***t***	***ß***
Verbal/ Language factor		**2.30**	**0.29***		**3.81**	**0.46****		**3.66**	**0.45****
Nonverbal/ Picture arrangement		**2.59**	**0.32****		**1.66**	**0.20**		**0.51**	**0.06**
	0.21/ 6.80**			**0.27/ 9.55****			**0.22/ 7.15****		

Note: N=55, *p<.05, **p<.01

When dividing the total group into two subgroups, one “poor” group scoring “low” (≤7 scale score) on Picture Arrangement (n=14) and one “good” group scoring “high” (>7 scale score) (n=41), a difference between the subgroups was found on BST Information (p<.001). No differences were found between

the two subgroups on the verbal/language skills factor, or on the BST Subordinate Clauses or BST Sentence Length scores. The results indicate that narrative retelling is not only influenced by language skills but also by nonverbal temporal sequencing skills.

4.3 The Adult AS Neuropsychology Study

4.3.1 Verbal and Nonverbal Test Findings

This adult study group of young men with AS had been tested in childhood and they all had FSIQ within normal range (above IQ 70) at that time. At follow-up, all still had FSIQ in this range. About half of the group had an IQ profile associated with NLD (VIQ>PIQ) at the original diagnosis. At follow-up, approximately 10 years after original testing, slightly under half of these still had a VIQ>PIQ indicative of NLD, whereas the remainder had "changed" to a much more even cognitive profile. Fifty-three percent in the persistent P-NLD group had a VIQ-PIQ difference score in excess of 30 at original test compared with 22% in the "recovered" CO-NLD group. In the CO-NLD group, mean VIQ had decreased from 113.7 (SD=13.1) to 106.7 (SD=13.5, p<.01), and PIQ had increased from 89.5 (SD=14.1) to 104.7 (SD=14.1, p<.0001) between time 1 and time 2 (Table 4). The FSIQ in this group had also increased, from 102.1 (SD=14.5) at time 1 to 106.4 (SD=14.5, p<.05) at time 2.

Table 4. FSIQ, VIQ, and PIQ in AS subgroups – time 1 and time 2

INTELLECTUAL ABILITY Wechsler Scales	P-NLD Mean(SD) n=15	CO-NLD Mean(SD) n=18	NO-NLD Mean(SD) n=36	P-NLD vs CO-NLD	P-NLD vs NO-NLD	CO-NLD vs NO-NLD
***Time 1* FSIQ**	**96.5(18.3)**	**102.1(14.5)***	**100.8(19.1)**	**n.s.**	**n.s.**	**n.s.**
VIQ	**110.6(17.7)**	**113.7(13.1)****	**99.2(18.0)**	**n.s.**	**p=0.040**	**p=0.003**
PIQ	**80.6(15.4)**	**89.5(14.1)*****	**102.1(17.6)**	**n.s.**	**p=0.001**	**p=0.010**
***Time 2* FSIQ**	**100.7(17.2)**	**106.4(14.5)**	**103.9(15.3)**	**n.s.**	**n.s.**	**n.s.**
VIQ	**110.9(17.1)**	**106.7(13.5)**	**101.9(16.6)**	**n.s.**	**n.s.**	**n.s.**
PIQ	**86.5(14.9)**	**104.7(14.1)**	**105.9(14.4)**	**p=0.001**	**p=0.001**	**n.s.**

* p<.05 time 1 versus time 2 ** p<.01 time 1 versus time 2 *** p<.001 time 1 versus time 2

EF problems were documented in the P-NLD group. Their scores were significantly lower on several TOL measures (total correct score, total move score and total executive time) (Table 5). The two other subgroups, CO-NLD and NO-NLD performed in the average range according to available norms. Thus, there were greater problems with EF (such as with planning and processing speed) in the P-NLD group. Another EF test was the copying part of the ROCF. All AS subgroups scored equally low (considerably below average) on this task.

The ROCF also includes a visual memory part. All subgroups performed poorly on this task with no differences across subgroups.

Results of auditory learning from the Claeson-Dahl test fell within the average range but performance on the auditory recall task was below average (no differences across subgroups).

All three AS subgroups performed in the average range on the Gottschaldt Hidden Figures Test measuring central coherence (no differences between subgroups).

Table 5. Planning, central coherence, learning and memory in AS subgroups - time 2

	P-NLD Mean (SD) n=15	CO-NLD Mean (SD) n=18	NO-NLD Mean (SD) n=36	P-NLD vs CO-NLD	P-NLD vs NO-NLD	CO-NLD vs NO-NLD
			PLANNING ABILITY Tower of London			
Total move score	**83.7 (13.7) n=12**	**100.8 (13.0) n=12**	**105.4 (15.6) n=26**	**p=0.005**	**p=0.0003**	**n.s.**
Total correct score	**87.7 (11.4) n=12**	**100.7 (15.5) n=12**	**106.9 (16.9) n=26**	**p=0.040**	**p=0.002**	**n.s.**
Total rule violation score	**92.8 (19.0) n=12**	**98.8 (15.2) n=12**	**102.1 (10.1) n=26**	**n.s.**	**n.s.**	**n.s.**
Total time violation score	**85.7 (16.8) n=12**	**98.7 (12.0) n=12**	**99.5 (14.2) n=26**	**n.s.**	**p=0.020**	**n.s.**
Total initiation time	**108.8 (20.2) n=12**	**108.3 (20.6) n=12**	**101.7 (10.2) n=26**	**n.s.**	**n.s.**	**n.s.**
Total execution time	**80.8 (12.3) n=12**	**92.8 (14.8) n=12**	**96.9 (14.3) n=26**	**p=0.040**	**p=0.002**	**n.s.**
Total problem solving time	**80.7 (12.9) n=12**	**90.8 (14.3) n=12**	**95.3 (14.6) n=26**	**n.s.**	**p=0.006**	**n.s.**
			CENTRAL COHERENCE Gottschaldt Hidden Figures			
Gottschaldt Hidden Figures	**4.93 (2.1) n=14**	**5.69 (1.8) n=16**	**6.30 (1.7) n=30**	**n.s.**	**n.s.**	**n.s.**
			LEARNING AND MEMORY Claeson-Dahl and Rey Complex Figures			
Claeson-Dahl recall	**56.8 (8.3) n=12**	**58.8 (5.5) n=13**	**55.5 (9.0) n=25**	**n.s.**	**n.s.**	**n.s.**
Claeson-Dahl recall 30min	**39.6 (14.3) n=12**	**37.7 (9.8) n=13**	**43.5 (11.7) n=25**	**n.s.**	**n.s.**	**n.s.**
Rey Complex Figure Test copy	**1.79 (0.89) n=14**	**2.28 (0.83) n=18**	**2.23 (0.9) n=30**	**n.s.**	**n.s.**	**n.s.**
Rey Complex Figure Test recall	**1.43 (0.51) n=14**	**1.44 (0.62) n=18**	**1.68 (0.72) n=28**	**n.s.**	**n.s.**	**n.s.**

4.3.2 Adaptive and Global Functioning

The total composite scores (including the subdomains Communication, ADL and Socialization) in the three subgroups were significantly lower than average. When analysing subdomains there were no differences regarding Communication and ADL, but the mean Socialization scores differed across subgroups (NO-NLD mean=55.2, SD=15.0, CO-NLD mean=70.7, SD=21.5, and P-NLD mean=54.6 SD=17.6, p=.03 between CO-NLD and NO-NLD and p=.04 between P-NLD and CO-NLD).

The GAF-scores in the three subgroups were below 70. The mean total GAF score was 59. The P-NLD group had a significantly lower mean score than the CO-NLD group (p=.04).

Table 6. VABS- and GAF- results in AS subgroups – time 2

	P-NLD Mean (SD) n=15	**CO-NLD Mean (SD) n=18**	**NO-NLD Mean (SD) n=36**	**P-NLD vs CO-NLD**	**P-NLD vs NO-NLD**	**CO-NLD vs NO-NLD**
			SOCIAL AND ADAPTIVE BEHAVIOUR Vineland Adaptive Behavior Scales			
Communication	**84.1 (18.8) n=11**	**85.4 (20.4) n=18**	**82.4 (19.3) n=32**	**n.s.**	**n.s.**	**n.s.**
ADL	**74 (19.6) n=11**	**86.1 (28.2) n=18**	**75.7 (23.3) n=32**	**n.s.**	**n.s.**	**n.s.**
Socialization	**54.6 (17.6) n=11**	**70.7 (21.5) n=18**	**55.2 (15.0) n=32**	**p=0.04**	**n.s.**	**p=0.03**
Composite	**66.5 (16.5) n=11**	**77.6 (21.0) n=18**	**66.3 (14.1) n=32**	**n.s.**	**n.s.**	**n.s.**
			GLOBAL FUNCTIONING Global Assessment Functioning			
GAF	**56.1 (10.6) n=15**	**62.4 (10.6) n=18**	**58.2 (7.8) n=35**	**p=0.04**	**n.s.**	**n.s.**

4.4 The Adult AS Reported Problems Study

The DISCO interview with a parent was used in order to gather information about symptoms defining AS (Gillberg and Gillberg criteria). The majority (about or above 90%) of the participants (independent of subgroup) were reported to show impairments in reciprocal social interaction, impairments in interaction with peers, inappropriate social behaviour, and repetitive routines. Speech and language problems were reported to a much lesser degree in the three subgroups, affecting 41-65% of the group. “Inappropriate response to the emotions of other people” was less often reported in the CO-NLD group (58.8%) compared to the P-NLD (91.7%) and NO-NLD (96.9%) groups. The difference between CO-NLD and NO-NLD was significant (p=.003).

No differences in respect of parent-rated ADHD symptoms (SNAP-IV) were found. Quite a number of inattention symptoms were reported but cut-off criteria for ADHD “diagnostic level” were not met in any of the subgroups.

The CO-NLD group self-reported less dysexecutive functions, as measured by the DEX, than both the other groups (Table 7). These results were consistent with the neuropsychological test in the Adult AS Neuropsychology Study. The P-NLD group scored far above the cut-off for Abnormal EF (33.1) whereas the CO-NLD group scored under this cut-off (19.4) (Figure 2).

Table 7. DEX- results in AS subgroups – time 2

DEX	P-NLD n=15 Mean(SD)	CO-NLD n=18 Mean(SD)	NO-NLD n=34 Mean(SD)	Overall p-value (Kruskal Wallis)	P-NLD vs CO-NLD p-value	P-NLD vs NO-NLD p-value	CO-NLD vs NO-NLD p-value
Total score	**33.1(17.2)**	**19.4 (8.7)**	**28.6(11.3)**	***0.010***	**0.013**	**0.291**	**0.009**
			Area				
Cognition	**1.6 (0.8)**	**0.9 (0.5)**	**1.5 (0.7)**	***0.019***	**0.020**	**0.494**	**0.011**
Emotion	**1.8 (1.0)**	**1.4 (0.7)**	**1.7 (0.6)**	**0.167**	**0.180**	**0.840**	**0.063**
Motivation	**1.7 (1.1)**	**1.0 (0.7)**	**1.4 (0.7)**	**0.067**	**0.060**	**0.327**	**0.048**
Behaviour	**1.6 (0.8)**	**0.8 (0.3)**	**1.2 (0.6)**	***0.004***	**0.006**	**0.173**	**0.007**
			Subdivision factor				
Inhibition	**1.7 (0.8)**	**0.9 (0.3)**	**1.3 (0.7)**	***0.006***	**0.005**	**0.155**	**0.013**
Intentionality	**1.7 (0.9)**	**1.1 (0.7)**	**1.5 (0.7)**	**0.06**	**0.040**	**0.273**	**0.067**
Executive Memory	**1.5 (0.9)**	**0.7 (0.5)**	**1.3 (0.8)**	***0.008***	**0.020**	**0.478**	**0.004**
Positive Affect	**1.5 (1.0)**	**0.6 (0.5)**	**1.2 (0.8)**	***0.011***	**0.020**	**0.432**	**0.007**
Negative Affect	**1.8 (1.1)**	**1.6 (0.7)**	**1.8 (0.8)**	**0.520**	**0.529**	**0.811**	**0.246**

Note. Cut-off for *Abnormal EF*=21.8 for DEX total score

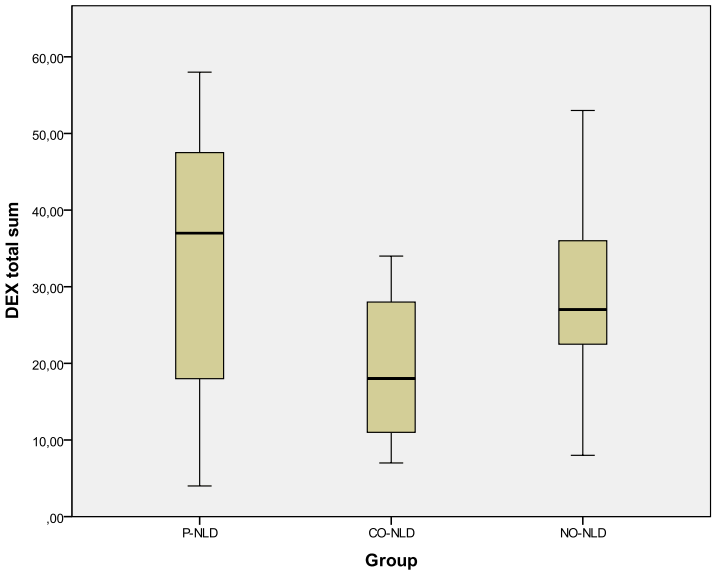


Figure 2. Boxplot of the DEX total sum with median value, upper and lower quartiles (75%-25%) of the data distribution and maximum and minimum extreme values across the P-NLD, CO-NLD and NO-NLD groups.

4.4.1 Outcome Predictors

In order to study background factors, age at diagnosis, VIQ, and PIQ at time 1 (childhood) were selected as independent predictors of three types of outcomes (DISCO, SNAP-IV and DEX results at time 2 (adulthood)). There were no significant correlations between age at AS diagnosis, VIQ, or PIQ respectively, at time 1, on the one hand, and the results obtained at DISCO-interview or on the SNAP-IV at time 2.

In the univariate analysis, VIQ and PIQ at time 1 were found to be associated with DEX total score at time 2. However, when using stepwise multiple regression and entering all predictors into the model, VIQ and age at diagnosis were the only independent predictors of DEX total score at time 2 (lower VIQ and older age at diagnosis of AS predicting more DEX EF dysfunction).

5 DISCUSSION

5.1 General Findings

Two of the four studies focused on school age boys and girls with ESSENCE (ASD, ADHD, and language delay), and the remaining two referred to adult men with ASD (Asperger syndrome).

The first two studies included a group of non-referred children from the general population with preschool concern about language delay. They were compared in early school age with a group of similarly aged children referred to a neuropsychiatric clinic where they were diagnosed with ASD, ADHD, or the combination of the two. We found that the two groups had similar verbal and nonverbal and early language developmental profiles, and both groups had usually had contact with SLPs during the preschool years. Both groups had low scores on the Freedom from Distractibility indicating attention problems. We also found that early concern about language delay was associated to lower IQ and ASD. Study I underscored the need for early diagnosis, and, in particular, the possibility to uncover the whole range of ESSENCE (e.g. ASD, ADHD, *and* language disorder) already before age 3 years in children presenting at community screening with language delay. - In Study II we reported that narrative retelling is linked with verbal/language skills *and* nonverbal temporal sequencing which supports the association between children's ability to nonverbally organise a picture story and their ability to convey story information during oral narrative retelling.

In the two remaining studies, Study III and IV, we demonstrated that young men with AS, as a group, had a stable FSIQ. The AS group showed problems on visual learning tasks (that are vulnerable to planning deficits), but, on average, they performed well on tasks measuring auditory learning. The AS group as a whole had a low GAF score and their adaptive functioning was lower than would be expected given the relatively high FSIQ. The P-NLD group showed poorer neuropsychological test outcome, and, on parent- and self-reported measures, they showed more EF problems than the other Non-P-NLD subgroups. The P-NLD group was slower, and had more planning problems. On a self-report questionnaire pertaining to EF, the P-NLD group experienced similar problems as they had objectively demonstrated on the neuropsychological tests. The CO-NLD group changed over time with a more even profile at follow-up than at the time of diagnosis. This group had the best outcome on socialisation and according to self-report. – Young men with AS constitute a heterogeneous group, but careful assessment of verbal and

nonverbal skills, beyond the establishing of the diagnosis of AS per se, will contribute highly important information for realistic prognosis and individualised intervention plans.

On the basis of the findings obtained in these two child and two adult longitudinal studies of ESSENCE (ASD, ADHD, and LD), it is suggested that early and repeated assessment of verbal and nonverbal skills, in addition to the formal behavioural ESSENCE diagnoses, is important in clinical practice.

5.2 Discussion of the Results Obtained in Each of the Four Studies

5.2.1 Verbal and Nonverbal Profiles at Primary School Age and Their Relationship to Preschool Indicators of LD

Sixty percent of the clinic children with ASD and/or ADHD in Study I had been in contact with SLP services during their preschool years. These results confirm those of earlier studies (Baker et al, 1980; Bishop and Edmundson, 1987; Dahlgren and Gillberg, 1989) showing language delay to often be a signal of a general neurodevelopmental lag in different developmental or behavioural areas. Our research group has shown a very high rate of neuropsychiatric and/or neurodevelopmental disorders at primary school age in an already published study of the children who had previously been shown to have LD at 2.5 years of age after community screening (the same group that is included also in the present Study I and Study II). Sixty-two percent of all children with LD at 2.5 years in that study had ASD, ADHD, or a combination of the two, and another 10% had borderline IQ (Miniscalo et al, 2006). The results of Study I showed that these children with LD at 2.5 years had very similar verbal, nonverbal, and developmental profiles at primary school age as those who had come to attention at a clinic for ASD and/or ADHD at the same age. A majority of this latter clinic group had actually screened positive for LD long before they came to attention at the neuropsychiatric clinic. Taken together, these data imply that it would usually be possible to identify many children with ESSENCE (probably both ASD and ADHD) already at the time of the language screening at 2.5 years, if only a multidisciplinary approach to assessment is taken from the very beginning. Currently, in many parts of the world, language screening is performed with a view to recognising and intervening for LD. This is all fine and well, but it appears that it is not a sufficient goal in itself. Screening for LD and then

assessing for all ESSENCE even in very young children appears to be a realistic goal, and one which could contribute towards minimizing the academic failure, social exclusion, and family problems that we know will often be the effects of unrecognised ADHD and ASD.

Examples of how such a screening programme can be translated into good clinical practice are provided by other recent studies performed in Gothenburg after 2005. In a population based study of 2-year-old children, a screening for LD and ASD at all child health centres in Gothenburg, Sweden, was conducted. The prevalence for diagnosed ASD was 0.8% (Nygren et al, 2012). A comprehensive neuropsychiatric/ESSENCE-type assessment was conducted in the cases that raised any suspicion of ASD. All children screening positive for ASD were referred from child health centres to a neuropsychiatric clinic. Cases "only screening positive for LD" were referred to SLP services (several of these were later referred to the neuropsychiatric clinic because suspicion had been raised about ESSENCE problems other than LD). The neuropsychiatric evaluation at the clinic included clinical psychiatric and medical examination, neuropsychological tests, child observation, and language assessment made by a multidisciplinary team (Nygren et al, 2012). This procedure agrees well with the concept of ESSENCE under which it is important to look for any early signs of impairing child behavioural, social, or developmental problems/symptoms before age 3-5 years not just in the field of language but also in areas of social communication, motor coordination, attention, activity, behaviour, and general development. This means that it is important for psychiatrists, psychologists, education specialists, occupational therapists, and SLPs and other professionals working with children with ESSENCE (ASD, ADHD, LD, DCD, tic syndromes, and a variety of learning disorders/intellectual developmental disorders), to work in close collaboration in order to focus, from the start, on all possible symptoms, to make the correct diagnosis, to plan for appropriate interventions and follow up assessments.

IQ is often a good predictor of learning ability and school achievement and it is also known that low cognitive level can be the cause of delayed language onset. Individuals with FSIQ below 70 are considered to have learning disability or an intellectual impairment. In the present study children with IDD had been excluded from study from the beginning. Even so, those 60% of the clinically referred sample in Study I who had been in contact with SLP services had lower FSIQ than those who had not had any contact at all. For the children who were referred at 2.5 years of age to SLPs services, the mean FD score was significantly lower compared to the children who had had no SLP contact. FD consists of the Arithmetic and Digit Span subtests on the

WISC, and both of them measure attention and working memory. Inattention and working memory problems are often seen in children with ESSENCE regardless of the categorical behavioural diagnosis made, and the results from EF testing alone cannot be used as guide for differential diagnosis (Sinzig et al, 2008a).

5.2.2 Narrative Retelling

Few studies have examined narrative retelling among children with ESSENCE. Reports indicate that narrative retelling effectively clarifies precisely the verbal/linguistic peculiarities that are characteristic of this group of children. One study described how people with ASD termed what they saw in the story´s images rather than getting together the events of the images into a logical coherent story (Norbury and Bishop, 2003). Other studies show that children with ADHD exhibit problems with using pronouns to reflect the characters and events in a way that allows the listener to know what is intended (Purvis and Tannock, 1997).

In Study II, we hypothesised that not only verbal/language skills play an important role in narrative difficulties but also narrative temporal sequencing is important, independent of basic verbal/language skills. BST Information was linked with verbal/language skills, as expected, but also with a nonverbal (Picture Arrangement) subtest from the WISC-III. Results suggested that narrative difficulty cannot only be verbal/language-based but is compromised also by more fundamental difficulties in expressive temporal sequencing. Other authors have reported different possible explanations for difficulties in narrative retelling. Bishop (1997) has highlighted attention problems as an important factor for difficulty in narrative retelling and in our study group we found low scores on the Freedom from Distractibility factor (closely related to attentional problems, and reported in Study I). On the other hand, Frith (1969) presented in her study of children with autism that this group was not helped by meaningful sentences (in contrast to scrambled words) in order to remember a string of words (Aurnhammer-Frith, 1969). Her interpretation was that children with ASD were less good at extracting meaning in general and that they have greater difficulties processing information in context. This finding has been replicated by other authors (Hermelin and Frith, 1971; Happé, 1997). In our study, we had a more heterogeneous study group and it is difficult to draw extensive conclusions but it is possible that in children with ADHD the attention factor is crucial in this task whereas for children with ASD, the ability to process information in context may play a more important role.

5.2.3 NLD and AS

Mean FSIQ was stable over time in our total study group of young men with AS from original study to follow-up. In a recently published 40-years follow up study of IQ in cases with autism and with an IQ in the average range, IQ remained very stable (Howlin et al, 2013). On the other hand, other studies have reported changes in IQ in those with IQ below the average zone (Billstedt et al, 2005; Hedvall et al, 2013).

Several studies have found that a large sample of individuals with AS often have a neuropsychological profile of nonverbal deficits and perform cognitively within normal range (Ehlers and Gillberg, 1993; Klin et al., 1995). In our study (III), half of the individuals with AS had an IQ profile with VIQ>PIQ of 15 points or more at time of original diagnosis. At follow-up, approximately 50 percent of the original uneven group still had this discrepancy. Our results confirmed the hypothesis that persistent NLD had poorer outcome in planning and processing speed compared to the other two subgroups, one with childhood NLD and one with never NLD. However, no differences were found between groups regarding visual and auditory memory. You would expect that the P-NLD group, with a superior verbal ability compared with performance ability, would score higher on auditory memory tests, but the plausible explanation for this is probably that the verbal IQ is equal over the three groups. Neither performance on central coherence test was found to differ between the subgroup. The P-NLD group had worse results on planning and they were slower on neuropsychological tests than the other groups. Late onset of unsupported walking and late onset speech were noticed in the P-NLD group but not in the group that had developed an even profile. The CO-NLD group strikes out as the group with best outcome. This group had a significantly better outcome regarding social skills (measured by the VABS) and less inappropriate response to others emotions (measured by the DISCO) than the two other groups. This group also self-reported less EF problems (DEX questionnaire). This result raises a central question. What is the underlying mechanism in this subgroup of AS that at some point has an uneven cognitive profile, which later evens out and parallel to this also exhibits fewer EF problems and better adaptive behaviour than would be expected compared to others with this condition? Does this group have less severe EF problems early in life and could they therefore be better equipped to develop in a more positive fashion? We found no difference between the groups regarding support in school (which might have been an explanation for the good outcome).

In study IV we used self-report questionnaire with the young men with AS in order to gather information about EF deficits. Burges and colleagues (1998) have reported that self-report in adults and adolescents with normal verbal ability and neurodevelopmental problems is a reliable tool to describe their strengths and weaknesses. We also used parental interviews about autism features and attention deficits. The persistent NLD group reported more EF problems than the two other subgroups. This was consistent with the findings from study III showing that this group also scored lower on neuropsychological EF tests.

The overlap between AS and NLD with deficits in social functioning, pragmatic language, and motor skills has been described by several researchers (Klin et al, 1995; Rourke, 1995; Gunter et al, 2002). Semrud-Clikeman and colleagues (2010) suggested that AS and NLD are related social disorders (Semrud-Clikeman et al, 2010). AS has emerged from the psychiatric literature, is defined by its behavioural symptomatology, and it has a psychiatric diagnosis in the DSM-IV (but not a separately coded one in the DSM-5 where it is subsumed under ASD). NLD, on the other hand, is "explained" from neuropsychological assessment and neurology. In our study we chose to use the VIQ-PIQ difference as the defining feature of NLD. This is also the definition that was used in the original study of Cederlund and Gillberg (2004). In our studies, we demonstrated that P-NLD in the context of AS infers greater tested *and* reported problems with EF as compared with cases with NO-NLD or CO-NLD.

5.2.4 AS and ADHD

Co-existence of AS and ADHD has been reported in several studies (Ghaziuddin et al, 1998; Nyden et al, 1999; Gillberg and Billstedt, 2000). At least 30 (maybe up to 50) percent of individuals with AS have impairing ADHD symptoms, including inattention and hyperactivity (Gadow, 2006). Neuropsychological studies have found that children with ASD have similar types of attention deficits that are seen in children with ADHD (Nyden et al., 1999). Severe hyperactivity is often seen in young children with ASD and some of this appears to abate over time (Gillberg and Billstedt, 2000). In our study of adult men with ASD (AS) we found a negative correlation between PIQ at time of original diagnosis and ADHD symptoms at follow-up. ADHD symptoms were also significantly more prevalent in cases with self-reported EF problems. However, there were no significant differences between the P-NLD group and the other two AS subgroups regarding SNAP-IV ADHD problems (as rated by a parent).

5.2.5 Gender Aspects

The number of girls was limited in study I and II, and in study III and IV there were none. This is a reflection of clinical realities. In the first two studies the children had been diagnosed in the 2000s. The original clinical group from which the examined cohort was derived (n=109, male:female ratio 4.2:1) was representative of groups of children with ESSENCE coming to clinics at a young age, even though it is likely that a number of girls with ADHD and/or ASD will come to clinical attention for ESSENCE a few-several years later. The community group of children with LD recognised at age 2.5 years (n=21, male: female ratio 4.3:1) is believed to be representative of the general population with LD, even though the total number of girls (n=8) included was so small that it is difficult to take a strong stance in this respect. As regards the men with AS in Study III and Study IV, they had all been diagnosed in the 80s and 90s, at a time when fewer girls with ASD were identified. It was very difficult to find any females at all during the recruitment process for the original diagnostic study of AS (Cederlund and Gillberg, 2004). Recent population surveys of autistic traits have confirmed that males do have more autistic traits than females (Posserud et al, 2006; Skuse et al, 2009). Other studies have shown that males have more of systemising capacity and females show more empathy, from the early years up to adulthood (Baron-Cohen and Wheelwright, 2004; Auyeung et al, 2009). These male personality traits are more associated with the phenotype that we associate with ASD. Regarding ADHD, girls more often than boys tend to be diagnosed with the inattentive subtype (Biederman et al, 2002; Rucklidge, 2010). Boys are more acting-out in school than girls, and that could be one explanation why girls are referred for assessment later, or not at all. Many studies report that girls are referred to clinics when they are older compared to boys and that problems are identified in school age (Kato et al, 2001; Biederman, et al, 2002; Quinn 2008). Kopp, in her study of 100 girls with social and/or attention deficits, found that they had been recognised as having depression, anxiety, developmental, motor, language, or family relationship problems long before a correct neuropsychiatric diagnosis within the ESSENCE group was finally established. Parents had been worried about their child´s development usually from preschool years even though the diagnosis was often not made until the teenage period (Kopp, 2010).

5.3 Strengths and Limitations

The clinical samples in all four studies are likely to be representative of clinically referred cases (of males) with ASD/AS and ADHD. In Studies I and II, a rather small group of clearly community representative cases with

LD was also included. The sample sizes, generally, were relatively small and any conclusions based only on the findings obtained here have to be tentative. The number of girls was very limited in Study I and II, and in Study III and IV there were only males. It has to be said, though, that this is a reflection of clinical realities. In the first two studies (of children) diagnosed in the 2000s, the number of girls included reflects the current clinical prevalence rates of ASD and ADHD, whereas in the study of men with ASD, diagnosed in the 1980s and 1990s, potentially very few females with ASD were recognised. There were only seven girls who were found meeting the inclusion criteria of the original study, and due to lack of power they were excluded in the original study. The studies might - from the design point of view - have appeared to be of higher quality had comparison groups of typically developing individuals been included. However the main focus has been on verbal and nonverbal abilities in ESSENCE and on the developmental trajectories of problems subsumed under this umbrella term. In studies III and IV several of the original group of cases with AS did not participate in the follow-up study. The follow-up period in itself - of approximately 10 years - is one likely reason for the attrition. We had no indications, though, that those who participated differed in any clear way from the beginning from those who did not. Another limitation, of course, given the size of the group studied, was that when the AS group was broken down into subgroups, the samples became small indeed.

The major strength of the studies is that all cases included were extremely thoroughly assessed, neuropsychiatrically and neuropsychologically. The fact that they had been followed longitudinally for five (children) and ten (adults) years adds extra weight to the findings. Furthermore, all 130 individuals included in studies I-IV were seen and tested by one and the same psychologist (the author of the thesis).

5.4 Conclusions and Implications for Clinical Practice and Research

The main conclusions from the present thesis were:

- The majority of school age children with ESSENCE have a previous history of SLP service contact during the preschool years, (particularly those with lower FSIQ and those with a diagnosis of ASD).

- Children with ESSENCE (ASD and/or ADHD) and children with LD at 2.5 years of age exhibit very similar verbal and nonverbal profiles at about 7 years of age.

- Oral narrative retelling difficulties in children with ESSENCE are associated with verbal/language level and with nonverbal temporal sequencing.

- Males with AS and P-NLD have a poor outcome in terms of neuropsychologically tested EF and as regards social adaptive functioning in early adult life.

- Males with AS and P-NLD (and their parents) report a high level of EF problems.

- In men with AS, very good verbal skills (high VIQ) early in life are a predictor of good EF outcome.

School age clinic children with ASD and ADHD had a similar verbal, nonverbal, and early language development profile as children with LD from the community. Concerns about early language delay in the preschool age need to be taken seriously; any assessment of their problems needs to be multidisciplinary, taking the whole ESSENCE concept into account, and include screening for other ESSENCE conditions. Further assessments should include psychiatric and cognitive evaluations, preferably in a multidisciplinary setting. Early language delay should also be taken as a signal that intellectual functioning *might* be in the low average range, even though *some* children with such delay later have high IQs. Reassessment of IQ in these cases is necessary.

Narrative difficulties in young children do not appear to be verbal/language-based only but are associated with more fundamental difficulties in expressive temporal sequencing. The results indicate that narrative production also requires an underlying set of cognitive processes that transfer across modalities for their expression. This result indicates the need for not only stimulating verbal/language skills but to also combine language and visual stimuli, and that listening to a story that is accompanied by a picture sequence, probably increases the ability to retell it.

According to the results of study III and IV the NLD profile changes over time in a subgroup of males with AS, and the outcome is different

depending on whether or not there are other factors such as lower cognitive ability and problems with EF. It is clear that males with AS constitutes a heterogeneous group with different verbal and nonverbal profiles that can change over time, meaning that it is impossible to draw diagnostic – or prognostic - conclusions based upon IQ and/or EF results obtained at only one time point. It is interesting to note, in this context, that in Study I, of children, the averaged verbal and nonverbal profiles were similar across different ESSENCE diagnoses.

The clinical implications based on the AS studies are that males with AS continue to need support in adult life and even though they have "normal" FSIQ their adaptive behaviour is far below what could be expected. They continue to have severe social interaction problems. Just as in young children with ESSENCE, the perspective in reassessment in adolescents/adults needs to have a broad focus, always including the possibility of a whole range of neuropsychiatric and neuropsychological "comorbidities". Reassessment of verbal and nonverbal skills (including FSIQ) might be recommended in individuals with a poor social and EF outcome and also in those with low FSIQ from the beginning; our results indicated that those with FSIQ (particularly VIQ) above average have a better outcome, at least as regards self-reported EF. Verbal and nonverbal testing has its natural place in all neuropsychological assessments, and should be seen as a *necessary part of all* ESSENCE/neuropsychiatric assessment. Testing cannot be replaced by rating scales/self report. However, rating scales/self reports have their advantages, capturing difficulties not always found in current neuropsychological tests. It is important to stress that the interpretation of results of tests, interviews, rating scales, questionnaires, and overall clinical evaluation have to remain in the hands of experienced clinicians.

5.5 Future Research

There is now a need for large research cohort studies of ESSENCE following children (boys *and* girls) from a very young age, making use of state-of-the-art neuropsychiatric *and* verbal and nonverbal psychological assessment and diagnostic methods. Children raising developmental or behavioural concern, perhaps particularly those screening positive for LD, together with (preferably blindly examined) children who appear to be developing typically, should be assessed in a multidisciplinary setting with a broad ESSENCE perspective in the choice of assessment tools. Randomised controlled trials of interventions (aimed at ADHD, LD or

ASD) should be included within the larger framework of such – population-based – studies of ESSENCE. Genetic and neurophysiological studies could easily be added to the protocols.

It is important to emphasise that findings need to be replicated in such studies, not just in other clinical groups but in much larger community-based cohorts of children with and without ESSENCE. For example, the association that we found between narrative and nonverbal temporal sequencing might also be found in typically developing children. It is also important to examine if different formats for narrative assessment place different demands on the child's skills in language, temporal sequencing, and other neuropsychological functions.

There is clearly also a need for more longitudinal studies of NLD, not just in AS, but regardless of behavioural neuropsychiatric diagnosis. Here too, such research would probably best be designed as nested case-control studies within the larger context of population-based cohort studies as outlined above.

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