Autism in preschool children: Cognitive aspects and interventions

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ABSTRACT

Aim: The overarching aims of this thesis were to (a) gain further insight into the developmental/cognitive aspects of autism spectrum disorders (ASD) in young children, and (b) assess outcome after interventions of varying intensity. **Methods**: In a prospectively designed longitudinal naturalistic study, 208 preschool children with ASD were comprehensively assessed - including with a variety of cognitive tests and other structured neurodevelopmental/adaptive interviews, observation schedules and questionnaires - before start of intervention and at the end of intervention after two years. Interventions given were based on principles of applied behaviour analysis (ABA) and were classified as intensive or non-intensive. The primary outcome variable was change in Vineland Adaptive Behavior Scales (VABS) composite scores. Subgroups with Good outcome and Poor outcome were identified by ≥15% positive/negative change in VABS composite scores. **Results**: Considerable changes with regard to ASD type, general cognitive level, adaptive behaviour and expressive speech were found, especially in children with atypical autism and in those with developmental delay/borderline intellectual functioning at the first assessment. About half the total group met criteria for intellectual disability (ID) at the two-year follow-up. Adaptive behaviour levels corresponded well with the level of intellectual functioning. Low processing speed negatively affected general adaptive skills, including in the domains communication, daily living skills, and motor skills. There was no difference in outcome between the intensive and non-intensive intervention groups. The single most important outcome predictor was cognitive level when dichotomised into IQ<70 vs >70. **Conclusions**: Development profiles changed considerably in many children over the two-year period. Low

processing speed - possibly indicative of executive dysfunction - was common even in relatively high functioning children. There was no significant difference between the intensive and non-intensive groups with regard to outcome; instead the child´s general cognitive level seemed to be the most important factor for prognosis. Children who are diagnosed with ASD at a very young age need to be followed up prospectively over several years. The naturalistic findings do not provide support for the use of very intensive as compared with less intensive ABA intervention in a community-based group of children with ASD.

Keywords: Autism Spectrum Disorders, cognition, intervention, children

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SAMMANFATTNING PÅ SVENSKA

Syfte: Syftet med studien var att få ökad kunskap om autism hos små barn; om barnens utveckling under förskoleåldern och om effekter av tidiga insatser. **Metod:** I studien, som är naturalistiskt utformad, har 208 barn i åldrar från 20 till 54 månader, med olika undergrupper av autismspektrumtillstånd (ASD), följts upp. Samtliga barn var vid studiens genomförande inskrivna vid ett specialiserat habiliteringscenter för barn med ASD. Barnen deltog i neuropsykologisk och utvecklingsneurologisk bedömning vid studiestart och två år senare. Kognitiva bedömningar gjordes vid uppföljningen med hjälp av antingen Griffiths´ utvecklingsskalor eller Wechsler Preschool and Primary Scale of Intelligence–III. Kognitiva resultat relaterades till adaptiv funktion mätt med Vineland Adaptive Behavior Scales (VABS). Interventionen klassificerades som intensiv respektive icke-intensiv och var baserad på tillämpad beteendeanalys. Forskar-gruppen var blind för typ av given intervention. Förändring i VABS- poäng var primär effektvariabel. En grupp med ökad respektive minskad VABS poäng (≥15% förändring) identifierades. **Resultat**: Barnens utvecklingsprofiler förändrades över tid, särskilt hos barn med atypisk autism och för dem med utvecklingsförsening vid den första bedömningen. Cirka 50 % av barnen visade sig ha en utvecklingsstörning. Adaptivt beteende var relaterar till intellektuell nivå. Låg bearbetningshastighet påträffades hos 78 % av de 85 barn som kunde genomföra snabbhetstest, vilket kan vara ett tecken på exekutiva svårigheter. Bearbetningshastighet förutspådde en betydande del av variansen avseende adaptiv förmåga. Det fanns ingen effektskillnad mellan intensiv och icke-intensiv interventionsgrupp, vid uppföljningen efter två år. I gruppen som ökade sin adaptiva förmåga signifikant återfanns den grupp barn som hade mindre allvarlig ASD och den grupp som hade en begåvningsnivå inom genomsnittet. **Slutsatser**: Uppföljning av förskolebarn med ASD visade att det för många skedde förändringar inom olika utvecklingsområden under den studerade två-årsperioden. Ungefär hälften av barnen hade en samtidig utvecklingsstörning. En relativt stor andel uppvisade i test tecken på låg bearbetningshastighet, indikerande exekutiv dysfunktion. Det kunde i denna studie inte påvisas att intensiva insatser gav bättre resultat än icke-intensiva, riktade insatser. Den viktigaste faktorn för prognos var barnets intellektuella funktion.

LIST OF PAPERS

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

I. Hedvall, A., Westerlund, J., Fernell, E., Holm, A., Gillberg, C., Billstedt, E. (2014). Autism and developmental profiles in preschoolers: stability and change over time. *Acta Paediatrica*, *103*, 174-81.

II. Hedvall, A., Fernell, E., Holm, A., Asberg Johnels, J., Gillberg, C., Billstedt, E. (2013). Autism, processing speed, and adaptive functioning in preschool children. *Scientific World Journal*, 2013; 20; 158263.

III. Fernell, E., Hedvall, A., Westerlund, J., Höglund Carlsson, L., Eriksson, M., Barnevik Olsson, M., Holm, A., Norrelgen, F., Kjellmer, L., Gillberg, C. (2011). Early intervention in 208 Swedish preschoolers with autism spectrum disorder. A prospective naturalistic study. *Research in Developmental Disabilities*, *32*, 2092-101.

IV. Hedvall, A., Westerlund, J., Fernell, E., Barnevik Olsson, M., Höglund Carlsson, L., Kjellmer, L., Norrelgen, F., Eriksson, M., Billstedt, E., Gillberg, C. Clinical characteristics of good and poor outcome in preschool children with Autism Spectrum Disorders. *Submitted.*

CONTENT

ABBREVIATIONS

ABA	Applied Behaviour Analysis
ABC	Autistic Behavior Checklist
ACYC	Autism Centre for Young Children
AD	Autistic Disorder
ADHD	Attention-Deficit/Hyperactivity Disorder
AIF	Average Intellectual Functioning
AS	Asperger Syndrome
ASD	Autism Spectrum Disorder
BIF	Borderline Intellectual Functioning
CAMHS	Child and Adolescent Mental Health Services
CDI	Communicative Development Inventory
DLS	Daily Living Skills
DQ	Developmental Quotient
EAB	Experimental Analysis of Behaviour
EF	Executive Functioning
EIBI	Early Intensive Behavioural Intervention
ESSENCE	Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations
FSIQ	Full Scale IQ
GLS	Global Language Composite

ICD	International Classification of Diseases
ID	Intellectual Disability
IQ	Intellectual Quotient
LEAD	Longitudinal Experts All Data
MID	Moderate Intellectual Disability
ODD	Oppositional Defiant Disorder
PARIS	Paris Autism Research International Sib pair Study schedule
PECS	Picture Exchange Communication System
PIQ	Performance Intellectual Quotient
PSQ	Processing Speed Quotient
SID	Severe Intellectual Disability
Ss	Standard scores
T0	Primary assessment
T1	Research assessment
T2	Research reassessment
TEACCH	Treatment and Education of Autistic and Related Communication Handicapped Children
ToM	Theory of Mind
VABS	Vineland Adaptive Behavior Scales
VIQ	Verbal Intellectual Quotient
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

1 INTRODUCTION

Autism Spectrum Disorder (ASD) when manifested and clearly symptomatic in the first few years of life is usually a severely disabling neurodevelopmental condition (Ozonoff et al. 2011) with a clinical picture that overlaps with that of certain other disorders during preschool years. ASD or Pervasive Developmental Disorder (PDD) is an ICD-10/DSM-IV umbrella term for autistic disorder (AD), Asperger´s disorder/syndrome (AS) and PDD-Not Otherwise Specified (PDD-NOS) (plus Childhood disintegrative disorder, and Rett syndrome). ASD was first delineated as a syndrome through descriptions made by Kanner and Asperger in the 1940s. Autism was introduced as a childhood diagnosis in the international classifications of psychiatric disorders in the 1960s. From the 1980s ASD was depicted as an umbrella PDD (DSM-III, American Psychiatric Association (APA) 1980) category, and from 2013 as one "disorder", viz. ASD (DSM-5, APA 2013).

The ASDs, also increasingly referred to as the "autisms" (Coleman and Gillberg 2012), nevertheless, constitute a heterogeneous group of neurodevelopmental conditions that are behaviourally defined. They are characterised by difficulties with reciprocal social interaction/ communication and by a restricted range of interests and behaviours. AD is usually still considered to be the most severe form with clear symptom onset before three years of age. PDD-NOS (also in older nomenclature referred to as atypical autism) required fewer criteria and thus was considered less severe, with an atypical symptomatology and/or with later onset. AS has been variably defined (Gillberg and Gillberg 1989, Szatmari 1989, APA 1994), but all existing criteria require significant social impairment, restrictive and repetitive interests and behaviour. Some criteria excluded cases with significant delay in language or in cognitive development, but others, in accordance with Asperger´s own writings and clinical experience, made no such provision.

With the publication of the Fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), (APA 2013), diagnostic criteria changed, and there was also a reduction from three to two categories of problems, viz. social/communication impairment and restricted interests or behaviours. Symptoms must be present in early childhood but may not become fully manifest until social demands exceed limited capacities. The DSM-5 also requires specification of additional information including severity level of ASD, level of adaptive functioning, and occurrences of

intellectual disability. One single umbrella term is used; ASD, subsuming the categories AD, AS and PDD-NOS, which are no longer separately coded.

The biological aetiology of ASD is complex but in a majority of cases a result of genes or biological environment or a combination of genetic and environmental factors. A genetic cause is identified in about 10-20% of all ASD (Abraham and Geschwind 2008; Coleman and Gillberg 2012). Several prenatal and perinatal risk factors have been associated with ASD but also associated with other neurodevelopmental and psychiatric disorders. The individual risk of ASD increases with increasing genetic relatedness (Sandin et al. 2014). There is evidence of the existence of a broader cognitive phenotype of autism (Baileys et al. 1998), also referred more recently to as "autism pure" or "autism only" (Gillberg and Fernell 2014).

1.1 ESSENCE

ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations) is a concept that takes into account that symptoms of developmental disorders overlap. The concept of ESSENCE also includes that changes of symptoms/developmental profiles may occur during the child's preschool age. ESSENCE includes symptoms pertaining to disorders such as intellectual developmental disorder, ASD, ADHD, oppositional defiant disorder (ODD), tic disorders, speech and language disorders, and developmental coordination disorders (Gillberg 2010).

Until now, the vast majority of all ASD studies have been conducted on school age children. There have been relatively few studies of preschool children that highlight cognitive and adaptive development during the preschool years. Furthermore, new types of interventions have been introduced, often with preschool children, but only rarely have these been clinically evaluated over more than a brief period, and usually only in small scale studies.

1.2 Conceptual framework

A cognitive approach to understanding ASD - as well as several other neurodevelopmental disorders - emerged in the 1980s, suggesting, at least, a three-level framework, linking biology and behaviour with an intermediate cognitive level (Frith 1991). Cognitive factors may play a primary role in one disorder and have a secondary associated role in another because several

pathways are involved and there are shared processes at the etiological, neural, and cognitive level (Pennington 2006).

1.3 Prevalence

The *reported* prevalence of ASD has been rising over the past thirty years. More children are being diagnosed at young ages, and this is probably due to increased awareness in public health care and an increased availability of assessment teams. Today the ASD prevalence rate is about 0.6% - 0.8% in preschool children and about 1% in school children (Fernell and Gillberg 2010; Nygren et al. 2012). Boys are believed to be affected more often than girls (male-to-female ratios of 3:5:1 are common) but reports suggest under-recognition of ASD in females due to less obvious social problems, less aggression and hyperactivity, than in males (Carter et al. 2007; Kopp et al. 2010; Mandy et al. 2012).

The American Academy of Pediatrics recommended that all children should be screened for possible ASD at 18 and at 24-30 months of age (Johnson and Myers 2007). The following "red flags" are suggested as indications for immediate evaluation: no babbling or pointing or other gesture by 12 months; no single words by 16 months; no 2-word spontaneous (not echolalia) phrases by 24 months; loss of language or social skills at any age (Filipek et al. 2000).

1.4 Diagnostic assessment

Recommended "best practice" in clinical setting is assessment by a multi professional team using LEAD procedure (Longitudinal, Experts, All, Data) (Spitzer 1983). Assessment includes, besides clinical interview and evaluation, also systemised collection of information from different informants and from different settings using parent and teacher for questionnaires. Standardised diagnostic instrument are also often used as guidelines but not for decision-making as regards diagnosis/no diagnosis. An ASD diagnosis should never rely only on any "autism-specific diagnostic" tool (NICE 2013). Diagnostic criteria are met when information gathered correspond to the diagnostic manual. The degree to which the child meets the criteria is determined and alternative diagnoses assessed and ruled out. Other conditions are considered such as hearing and vision impairment, intellectual disability, developmental language disorder, reactive attachment disorder, attention-deficit/hyperactivity disorder, epilepsy, neuromuscular disorder, and specific genetic or environmentally caused behavioural phenotype

syndromes (such as Fragile X syndrome, Rett syndrome or Fetal alcohol syndrome).

1.5 Diagnostic stability

The stability of an ASD diagnosis in young children is roughly consistent both in the short-term (i.e., from two or three to four years of age), with a stability of 72-87% (Cox et al. 1999; Eaves and Ho 2004) and in the longer term (i.e., from two to seven or nine years of age) with stability of 85 to 89% (Charman et al. 2005; Lord et al. 2006). A higher stability for diagnostic assessment after 30 months has been reported (87%) compared to assessment at 30 months or younger (52%) (Turner and Stone 2007). Toddlers presenting milder symptoms consistent with PDD-NOS may continue to display less severe social disabilities later on (Chawarska et al. 2009). Only a minority of toddlers who exhibit extreme delays in communication combined with a dysfunctional social behaviour will "catch up" cognitively and socially, once they understand the intentions and meaning of spoken language (Stone et al. 1999; Chawaraska et al. 2009).

1.6 General cognitive/intellectual function

Cognitive levels in ASD range from severe intellectual disability (ID) to an intellectual functioning above average. ID (IQ below 70) frequently co-exists in children with ASD although in the last decades more children with ASD and an IQ above 70 are identified (Rice 2009). This comorbidity is well established, about 40 to 75% of children with ASD diagnosis also have ID**.** There is a strong tendency for uneven intellectual/developmental profiles regarding verbal and performance abilities measured by IQ tests (Carr 2006). Several studies have demonstrated that individuals with ASD (particularly those with AD) perform better in visual – spatial nonverbal tests than verbal tests.

Assessment of behavioural, intellectual, and cognitive function in children with ASD is a complex task influenced by the child´s ability to interact, verbal- and non-verbal communication capacity, adaptive behaviour and flexibility, all taking into consideration the general cognitive level.

Infant cognitive tests ability to predict later IQ is moderate. Since early age is characterised by rapid change – both in abilities per se and in co-operation –

developmental quotients (DQ) are used. DQ tests are also used for assessment of children at a low-functioning level. From approximately a mental age of three years abilities are considered stable enough for using intelligent quotes (IQ).

The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III, Wechsler 2005) is widely used in clinical practice by psychologists for the evaluation of specific and general cognitive abilities. WPPSI-III yields information of general cognition based on a model that places full-scale IQ as an index of overall intelligence including verbal and performance IQ underneath reflecting verbal and visual - spatial abilities together with a processing speed index. The Wechsler scales include tests measuring both "fluid intelligence" or fluid reasoning, capacity to think logically and solve problems in novel situations, independent of acquired knowledge and "crystallised intelligence", the ability to use skills, knowledge, and experience capacity (Cattell 1963).

1.7 Adaptive behaviour

Adaptive skills refer to capacities involved in every day-functioning. While intelligence reflects the *maximum* performance, adaptive behaviour refers to *typical* performance in everyday, behaviours that are possible to influence to a certain degree by training. Four central domains in adaptive function have been identified; (1) communication which includes skills in language, reading, writing, reasoning, (2) social which covers empathy, social judgment, interpersonal communication skills, the ability to make and retain friendships, (3) practical with focus on self-management in areas such as personal care, recreation, and organising school activities, and (4) motor consisting of both fine and gross motor function.

In individuals with ASD, adaptive behaviour generally lags behind IQ and remains problematic throughout the lifespan (Loveland and Kelley 1991; Venter and Lord 1992; Eaves and Ho 2004). Cognitive functions higher than adaptive functions have been reported in children with an average or borderline IQ whereas low functioning children with ASD had adaptive skills higher than IQ (Perry et al. 2009).

Research on adaptive behaviour profiles in individuals with ASD has produced somewhat inconsistent result because of samples of varying ages and cognitive levels (Carter et al. 1998; Fenton et al. 2003). Toddlers with non-autistic developmental delay might have similar presentations as toddlers with ASD regarding impaired or delayed language, social interaction, and

pretend play skills. But in ASD these impaired skills go along with a delay in joint attention, imitation and interest in other children. Young children with ASD also use fewer conventional gestures and are less likely to initiate and respond to verbal communication; thus in ASD characteristics are related to early-emerging social skills normatively acquired at or before the age of 8 months (Ventola et al. 2014). Perry and colleagues (2009) reported Socialization and Communication domain scores to be lower in AD compared to non-spectrum children with ID. Paul et al. (2014) found children diagnosed with ASD, before the age of two, to be more impaired on all scales of Vineland Adaptive Behavior Scales (VABS, Sparrow et al. 2005) compared to toddlers with no ASD but with developmental delay. However, when matched after age and verbal and non-verbal development, the only differences found were on receptive communication (not expressive communication) and daily living skills (such as feeding, dressing and bathing) and not as expected in the Socialization domain.

The presence of routines, resistance to change, fascination of certain objects, repetitive questioning and abnormal responses to sensory stimuli were found in a group of children with intellectual disabilities (six years of age and older), some at a relatively high level of adaptive functioning. In a lower functioning group disruptive behaviour in public places (Soenen et al. 2009).

Deficits in both intellectual functioning *and* adaptive behaviour are central to intellectual disability. While autism is synonymous with delay and deviance, intellectual disability is characterised by global delay. DSM-5 (2013) emphasises the need to use both clinical assessment and standardised testing of intelligence when diagnosing intellectual disability, with the *severity* of impairment based on adaptive functioning rather than IQ test scores.

1.8 Executive function

Executive function (EF) is a cognitive construct used to describe goal or future-oriented behaviours, including planning, inhibition of responses, flexibility, organised search and working memory functions necessary to disengage from the immediate environment or external context and guide action instead by mental models or internal representations. The capacity of executive functioning occurs as a result of an interaction between the maturity of the individual's neurological capacity and the individual's interaction with his social world around. This EF category is considered broad-band and depending on the magnitude of the cognitive dysfunction of output in problem solving (Ozonoff 1997). Three different attentional functions (related and underpinning, but not equivalent to, EF) have been

conceptualised*; the alerting network* responsible for an increased sensitivity for incoming information, *the orienting network* defined as disengaging, shifting and reengaging attention, responsible for the selection of information from sensory input and *the executive control network* a multidimensional attentional system responsible for inhibition, conflict resolution, planning and cognitive flexibility. The orienting, but not alerting or executive control, networks may be impaired in children with ASD while decreased alerting efficiency is associated with greater socio-communicative impairment (Keehn et al. 2010). Executive dysfunctions are supposed to be central in ASD – but also, and perhaps even more so in ADHD - and literature on executive control abilities suggests impaired cognitive flexibility and a relationship between executive abilities and IQ in individuals with ASD (Liss et al. 2001; Lopez 2005).

1.8.1 Processing speed

Processing speed index in WPPSI-III includes the subtests Coding, which taps psychomotor speed, and Symbol Search which taps speed of mental operation. There is a correlation between processing speed and elements measured in general cognitive ability such as visual memory, quick and correct scanning of visual stimuli attention, visual motor coordination, sequencing, and discriminate simple visual information. Processing speed is also correlated to mental flexibility/set shifting capacity, which is considered an important factor for sustaining attention.

Processing speed is reported to have an impact in for example ADHD and learning disabilities (Donders 1997; Mayes et al. 2008). Children with specific processing speed deficits have been found to have deficits in basic psychological processes that interfere with learning and academic achievement, and according to teacher behaviour ratings, exhibit major psychosocial and adaptive impairment. Findings suggest processing speed deficits to be behind the cognitive and psychosocial disturbances found in what has been termed "nonverbal" learning disability (Backenson et al. 2013).

1.9 Other social/cognitive psychological functions in ASD

1.9.1 Theory of mind

Theory of mind (ToM) refers to the automatic attribution of mental states to self and others in order to predict and explain behaviour important to social

interaction and communication including understanding and enjoying pretend play (Frith 2003). The infant's understanding of attention in others has been found by 7 to 9 months of age, being a precursor to the development of ToM. Attention can be directed and shared by the act of pointing, a joint attention behaviour that requires taking into account another person's mental state (Baron-Cohen 1991). An important milestone in ToM development is gaining the ability to recognize that others can have beliefs about the world that are diverging. Deficits in ToM have been taken as a key feature of autism, also when children are matched for verbal skills (Happe 1995). It has been speculated that ToM exists on a continuum and recent evidence has point to the factor of coping mechanisms (Dapretto et al. 2006).

1.9.2 Central coherence

Another cognitive function in ASD is the theory of weak central coherence, a specific information processing style, described as a limited ability to understand context or to "see the bigger picture". This can often be at the expense of not understanding the actual meaning and nature of a situation or context of interactions with the environment (Happe´1994; Baron-Cohen 1995).

1.9.3 Procedural learning

Procedural learning, involves knowledge about how to do something (to use or apply) or about the sequence of steps necessary to accomplish a goal, commonly described as “knowing how”. Procedural memory allows us to learn both simple and complex skills to work automatically. Implicit procedural learning is essential to the development of any motor skill or cognitive activity. Faulty procedural memory has been proposed to play a role in ASD (Romero-Munguía 2013).

1.9.4 Mirror neurons

Scientists speculate about the possibility that the mirror system plays a role in our mentalising ability and language skills. The discovery of the “mirror system” function by neurons, both when the individual performs a certain action and when the individual sees the same action performed by another individual, could be important for an understanding other people´s actions and for learning by imitation. Mirror neuron dysfunction in ASD has been reported (Perkins et al. 2010).

1.9.5 Imitation

Deficits in the ability to imitate have been found among children with autism compared to children with a typical development both in nonspeaking and speaking children (Strid et al. 2013). In young children with ASD impairment in imitation predicted the rate of acquisition of communication skills (Munson et al. 2008; Toth et al. 2006).

1.10 Early intervention: Parental training and education

Information to parents about their child´s diagnosis, prognosis and how to help to develop skills or to compensate for communicative, cognitive and behavioural deficits, are included in almost all intervention programs aimed for children with ASD. Parents may also receive education in how to cope with challenging behavior (Nydén et al. 2000).

1.11 Early intervention: ABA

Early intervention is linked to the recent discoveries in neurosciences regarding the importance of experiences in early years; that exposure to diverse and complex input will increase and support developmental of desirable behaviors in children with ASD (Kuhl et al. 2003; Lewis 2004).

Applied Behavior Analysis (ABA) based intervention is an approach based on Experimental Analysis of Behavior (EAB), i.e., a systematic investigation of what stimuli and reinforcement is fundamental in governing behavior. Human behavior in this context also comprises thinking and feeling. ABA is the clinical application of EAB and requires, for analysis and design of interventions, understanding of links between event and behavior. Assessment of a behavioural function gives insight into modification strategies and identifies the conditions that need to be altered. Early Intensive Behavior Intervention (EIBI) emphasise early start, preferably before 3½ years-of-age, and consider the amount of training hours given to the child, to be crucial. EIBI initially includes one-to-one teaching and later on training together with other children in different settings. EIBI is considered more effective when parents are involved in training (Dawson et al. 2010).

Operant conditioning, is the process of strengthening a behaviour by given a stimulus closely in time to increase the frequency of the desirable behaviour. Another key element is discrete trial training, which is a structured technique

that breaks down skills into small, "discrete" components. Systematically, the trainer teaches these skills one by one. Along the way, trainers use tangible reinforcements for desired behaviour, operant response. For a child, this might include a candy or small toy.

In EIBI there are manual-based programs made in order to cover a range of abilities, and with the intention to influence a spectrum of behaviours, both more general behaviours such as collaboration with others and more specific training in the basic steps in development of social communication is also given; such as to jointly share interests, interaction in a social context, imitation and play (Swedish Council on Health Technology Assessment, SBU 2013).

In a recent published systematic review of studies between 1966 - 2012, the effect of EIBI and the eclectic approach was found to have no evidence (SBU, 2013).

1.12 Early intervention: Other

Treatment and education of autistic and related communication handicapped children TEACCH (Schopler et al. 1995), Structured teaching, Picture exchange communication system (PECS) (Bondy and Frost 1994) and Social Stories are other commonly used interventions. These methods all emphasise the adaptation of the environment and educational efforts, in supporting family and preschool staff.

1.13 Pharmacological treatments

Today there is no definite pharmacological treatment for ASD per se, but some of the often coexisting disorders, such as ADHD, may be treated pharmacologically with stimulants or with atomoxetine and sleeping disorders may be treated with melatonin.

A diuretic, bumetanide, that reduces intracellular chloride and reinforcing GABAergic inhibition, is a new promising therapeutic agent to treat autism. Positive effects have been demonstrated and larger trials are needed (Lemonier et al. 2012). Preliminary findings from clinical trials using the hormone oxytocin, a key regulator of social behaviour, in children with ASD have shown encouraging improvements in social cognition, but larger studies are needed (Canitano 2014).

1.14 Outcome in ASD

Development of speech before age 5 and IQ within the "normal range" has been reported to be predictors of good outcome with regard to adaptive functioning in older age (Billstedt et al. 2007). The importance of IQ regarding outcome has also been demonstrated in follow-up studies of preschool children (Howlin et al. 2004; Magiati et al. 2007; Howlin et al. 2014). Individuals with a performance IQ above 70 have been reported to have a significantly better outcome than those with an IQ below this level (Howlin et al. 2004). However, the degree of autism might not be crucial for outcome, but other factors such as low general cognitive function, executive dysfunctions, slow processing speed or coexisting epilepsy and other medical condition might be more important (Gillberg and Fernell 2014).

In a large and long prospective study, following individuals with AD or PDD-NOS from childhood to adulthood where the majority also had ID, poor outcome was found in 78%. In this low functioning ASD group childhood IQ-level was positively correlated with better outcome, as was the existence of some communicative phrase speech at age six years (Billstedt et al. 2005).

In a prospective follow-up study of males with AS and IQ above 70, initially diagnosed at an age of 5-24 years, outcome after more than five years was good in 27% and poor in 26% and intermediate for the remaining. The overall IQ in this AS group was stable over time in contrast to the low functioning AD/PDD-NOS group where there was a decline of intellectual ability over time (Cederlund et al. 2007). In a second follow-up of the AS group there is significant increase in individuals no longer meeting criteria for an ASD diagnosis (about 20%). Individuals with a stable diagnosis showed significantly more core ASD symptoms in adolescence/young adulthood. Early speech development and IQ did not predict diagnostic stability (Helles et al. Submitted).

2 AIM

The purpose of the study was to gain further insight into autism in young age, to enhance knowledge of developmental progress and outcome of early intervention in a representative group of 208 preschool children. More specifically, the aims were to:

1) examine stability and change in ASD diagnosis as well as trajectories in developmental/intellectual levels, adaptive functioning and expressive speech in these children
2) explore cognitive levels and profiles, including processing speed and its relation to adaptive functioning, in a relatively large and representative group of preschool children diagnosed with ASD
3) relate the outcome for these children over a two-year period in relation to the intensity of the early ABA intervention that they had been given
4) identify prognostic and associated factors in good and poor outcome cases in the cohort.

3 METHODS

An overview of all subjects participating in the studies is presented in Table 1.

Table 1. Study group and methods used in study I-IV

Study	I	II	III	IV
Object of study	Developmental trajectories	Processing speed	Intervention study	Good/poor outcome
Target group	n=208	n=208	n=208	208
Group examined	n=196	n=190	n=198	53
Attrition	n=12	n=18	n=10	
Male : female	169:27	164:26	169:29	41:12
ASD diagnoses	AD=118 AS=9 PDD-NOS=51 Autistic traits=17 Type of ASD not assessed n=1	AD=100 AS=12 PDD-NOS=56 Autistic traits=21 Type of ASD not assessed n=1	AD=112 AS=9 PDD-NOS=52 Autistic traits=17 Type of ASD not assessed n=1	AD=29 AS=3 PDD-NOS=17 Autistic traits= 4
Measurements	WPPSI-III Griffiths´ Developmental Scales I and II VABS-II PARIS	WPPSI-III Griffiths´ Developmental Scales I and II VABS-II	WPPSI-III Griffiths´ Developmental Scales I and II VABS-II ABC	WPPSI-III Griffiths´ Developmental Scales I and II VABS-II PARIS ABC CDI

WPPSI=Wechsler Preschool and Primary Scale of Intelligence, VABS=Vineland Adaptive Behavior Scale, PARIS=Paris Autism Research International Sib pair Study, ABC=Autistic Behavior Checklist, CDI=MacArthur-Bates Communicative Developmental Inventory

3.1 Procedure

Stockholm county, with a population of about 2 million inhabitants and about 27.000 births per year (2006), provides services through a specialised habilitation centre for families with children, one to six years-of-age, with ASD. All but the most severe disabled children with ASD (intellectual dysfunction in addition to physical disabilities) are referred to the Autism Centre for Young Children for intervention (ACYC). The participants included in this thesis are drawn from ACYC.

Referral assessments (T0) of the study group had been performed at the Child and Adolescent Mental Health Services (CAMHS) (83%) or at

neuropaediatric clinics in Stockholm County (17%) by professional teams consisting of psychologists, physicians, pedagogues and often also a speech and language therapist. Most frequent reason for referral was concerns regarding development of speech.

Research assessment took place at ACYC (T1) at onset of intervention, with reassessment after two-year (T2) following LEAD procedure. Children were prospectively followed in a naturalistic way and no exclusions were made (for example regarding severe learning disability, epilepsy or underlying medical disorders). Psychological reports from T0 were analysed and used at T1 while at T2, psychological assessments were carried out by research psychologists who also were experienced clinical psychologists.

The research team consisted of two neuropsychologists, four physicians (paediatrician, neuropaediatricians and psychiatrist) and two speech and language pathologists, all with long termed clinical practice assessing childhood developmental disorders. The research team remained blind to the type and intensity of intervention provided by the centre.

3.2 Participants

In year 2008, a total of 313 children (births years 2002-2006) in Stockholm county aged 20 months to 4:6 years had received a clinical diagnosis of ASD (during 2005-2008). Of these 313 children, 25 were directly referred to general habilitation centres due to more severe medical conditions and syndromes in combination with ASD. The cohort comprised of children admitted and registered at the ACYC (n=288). Of these 288 children, 24 had been referred during the first months of 2005. They could not be included due to limited research resources during the first year. Two children were referred from the ACYC to general habilitation centres due to medical conditions in combination with ASD while two families moved abroad. Two-hundred and sixty children out of a total of 313 children (figure 1), were invited. Since the intention was to do a follow-up after a period of two year (T2) no child older than four and a half years-of-age was included. Of the 260 children invited, 15 were excluded due to parental communication difficulties (not enough skills in the Swedish or English language) and 37 families declined participation, leaving 208 children to be included at T1. All together 79% of the cohort was included. A reduction of 10 families at T2 made 198 participants in the intervention study (article IV). Two families declined reassessment leaving 196 children to participate in the developmental study (Article I) while in the processing speed study (Article II) 190 children participated.

The group of 208 included 176 boys and 32 girls (ratio 5.5:1) with no significant differences in age at referral. Mean age at referral (T0) was three years and two months (SD=8.5 months, range 18-53), at T1 three years and 9 months (SD=8.2 months, range 24-60) and at follow-up (T2) five years and six months (SD=8.7 months, range 44-81). Medium time elapsing between T0 and T1 was 4.3 months (SD=3.9 months, range 0-25) and between start of intervention and follow-up 25 months (SD=2.8). The distributions in ages are shown in Table 2.

Table 2. Age at referral (T0), first follow-up (T1) and second follow-up (T2)

Age	T0 n=	T1 n=	T2 n=
≤1:11	9	-	-
2:0-2:11	66	27	-
3:0-3:11	100	93	6
4:0-4:11	33	87	45
5:0-5:11	-	1	88
≥6:0	-	-	59
Total	208	208	198

Of the 208 children, 121 (58%) had two Swedish-born parents, 32 (15%) had one Swedish-born parent, 53 (26%) children had both parents born outside Sweden and two children (1%) were adopted.

Ninety-three children (47%) received high to moderate intensive intervention (AD n=65, PDD-NOS n=23, AS n=3, ASD-traits n=2) and 105 children (53%) received non-intensive targeted intervention of moderate or low degree (also including when no intervention was given) AD n=55, PDD-NOS n= 29, AS n=6, ASD-traits n=15). The ACYC also provided education for parents and the children´s preschool staff.

3.2.1 Attrition

In the Developmental trajectories study, 12 families did not participate at T2; 10 children with AD and 2 with PDD-NOS (2 with AIF, 3 BIF and 7 ID).

In the Processing speed study, 18 families did not participate at T2; 13 with AD and 5 with PDD-NOS (2 with AIF, 8 BIF and 8 ID).

In the Intervention study, 10 families did not participate at T2; 8 with AD and 2 PDD-NOS (2 with AIF, 3 BIF and 5 ID)

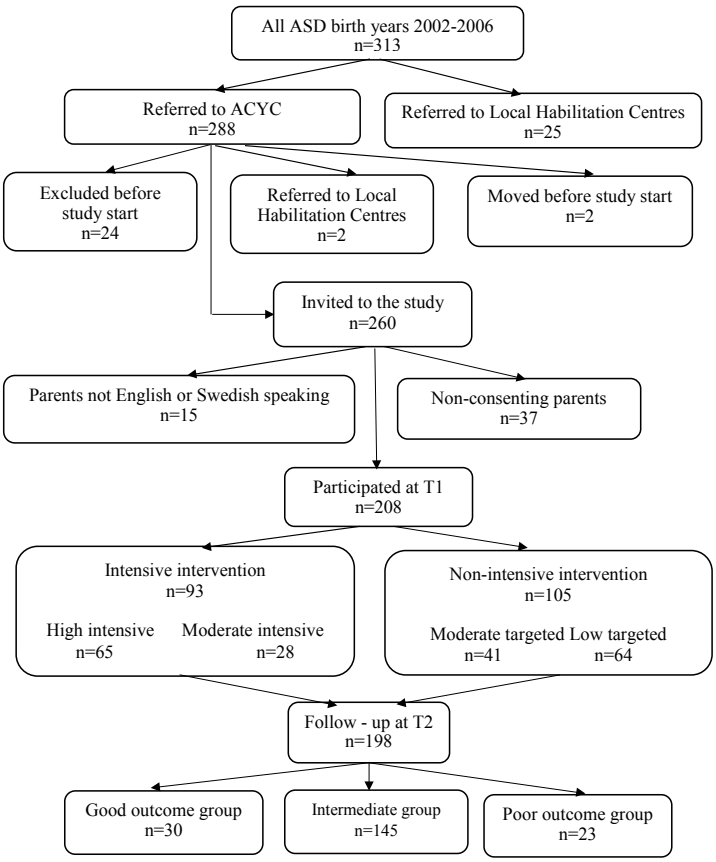


Figure 1. Flowchart demonstrating the inclusion procedure and groups of intervention

3.3 Instruments

3.3.1 Griffiths´ Developmental Scales

The result from the Griffiths scale Hearing and Speech (the C scale) and for those children with a cognitive age >24 months also the Practical Reasoning scale (the F-scale) were merged to Verbal Function whereas Eye and Hand Coordination scale (the D scale) and Performance scale (E) were merged to Performance Function. Global Cognitive Function is the average value of all

scales used (3 or 4 scales in Griffiths) and which DQ is obtained. DQ were converted to IQ equivalents.

3.3.2 WPPSI

Wechsler Preschool and Primary Scale of Intelligence-Third edition (WPPSI-III) is a well-established IQ test providing full scale IQ (FSIQ), scores of verbal (VIQ) and non-verbal performance IQ (PIQ), scores from Processing Speed Quotient (PSQ) and General Language Composite (GLC). VIQ, PIQ and FSIQ are referred to as Verbal, Performance and Global Cognitive Function, respectively. VIQ score measures acquired knowledge, verbal reasoning and comprehension and attention to verbal stimuli. PIQ score measures fluid reasoning, spatial processing, attention to details and visual-motor integration. FSIQ score is considered to be the score most representative of *g,* the general intellectual functioning (WPPSI-III, 2002).

At T1, DQ/IQ, according to complete tests or parts of tests, were found for 57% of the children. In order to establish the level of overall cognitive function, psychological records were studied by the research psychologists for the remaining 43%. The Swedish versions of Griffiths` Developmental Scales I and/or II (Alin-Åkerman and Nordberg 1980) were used as a "template" for the construction of developmental levels. Broad DQ/IQ ("cognitive group") status was assigned in the following manner: Average intellectual functioning =DQ/IQ>84 **(**AIF), developmental delay/borderline intellectual functioning DQ/IQ 70-84 **(**BIF**)**, intellectual disability =DQ/IQ<70 **(**ID) which was divided into mild intellectual disability (MID) = DQ/IQ 50 - 69, and severe intellectual disability (SID) =DQ/IQ <50.

At T2 a DQ/IQ level/profile and adaptive behaviour level/profile were evaluated for diagnosis such as mild, moderate/severe intellectual disability. An uneven profile (verbal versus nonverbal) was considered when there was a difference of 15 points or more in Griffiths Developmental Scales (DQ) (M=100) or 15 points in WPPSI (IQ) (M=100).

3.3.3 VABS

The English version of Vineland Adaptive Behavior Scales, Second Edition, Survey Interview Form (VABS-II) (M=100, SD=15) was used at T1 and T2 and also as outcome variable. It is a well-established and often used parent interview, individually administered measure of adaptive behaviour from birth to adulthood. Results from VABS composite scores are classified into five groups: low ability (20-70 Standard scores (Ss)), below average ability

(71-85 Ss), average ability (86-114 Ss), above average ability (115-129 Ss), and high ability (130-160 Ss).

Adaptive behaviour in four domains are investigated; Communication, Daily living skills, Socialization and Motor skills (M=100, SD=15). More precisely the Communication domain includes receptive, expressive and written subdomain including how the individual listen, pay attention and understand, what he/she says and how words and sentences are used to gather and provide information. Socialization domain measure interpersonal relationship, how the individual interacts with others, leisure and demonstrates sensitivity to others. Domains and subdomains (M=15, SD=3) allow for better understanding of an individual´s strengths and weaknesses.

Outcome measurement for the Good and Poor outcome group is defined as 15 % or more of increase or decrease in VABS composite/total score at T2 in comparison to T1. Change in total score is calculated and individually set for each child.

VABS correspond to adaptive behaviour specifications identified by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM – IV – TR, APA 2000).

3.3.4 PARIS

The PARIS (Paris Autism Research International Sib pair study) schedule includes levels of expressive speech development classified into 5 categories i) no words ii) a few words iii) a few sentences iv) some speech with or without echolalia v) much speech in sentences, mostly communicatively (Phillipe et al. 1999).

3.3.5 ABC

The Autistic Behavior Checklist (ABC) (Krug et al. 1980) is a questionnaire pertaining to core symptoms of autism. High ABC scores indicate a marked degree of autistic behaviour such as aggressive behaviour, echolalia speech, stereotypic behaviour and non-responsive behaviour. The maximum possible score is 158 and a score of 67 and above is strongly indicative of an autistic disorder and a score between 53 and 67 indicates a high probability of ASD.

3.3.6 CDI

The Swedish version of the MacArthur-Bates Communicative Development Inventory (CDI) was sent to parents of all children at T1. The result of the subscale Words Produced (with a maximum score of 370) from the Words

and Gestures is presented (Fenson et al. 1993; Fenson et al. 1994; Berglund and Eriksson 2000).

3.3.7 Intervention groups

Parents had the possibility to either choose a curriculum manual-based program (with the aim to influence a spectrum of behaviours such as communication, speech and language, social interaction/corporation, play abilities, daily living skills and motor performance) or to choose training of a specific domain (one at the time) such as compliance, problematic behaviour (phobias, disruptive- and self-harming) or different daily living skills (such as playing, communicating, toileting, sleeping, eating, dressing, gross-motor training, fine-motor training). Independent of type of intervention all parents were invited to an introduction course and supervision was handed out on a regular basis to parents together with assistants, in the intensive program 2-4 times/months during the first year and 1-2 times/months during the second and in the non-intensive program mostly at 1-5 occasions/domain. An overall evaluation of intervention given to each child took place semi-annual and was carried out by the supervisors.

The assistants, employed by the preschools, were approximately one third preschool teachers, one third trained preschool nurses while one third had no formal education in the field.

3.4 Statistical methods

All data analysis was conducted with the IBM Statistical Package for the Social Sciences (SPSS) Version 19. An alpha level of .05 was used for all statistical analysis.

In the developmental trajectories study, a $2 \times 3 \times 4$ mixed ANOVA with Time (T1, T2) and VABS domain (Communication, DLS, Social, Motor) as within-subject factors, General cognitive ability (AIF, BIF, ID) as a between-subject factor and VABS scores as the dependent variable were performed. This analysis was followed up with three separate two times four repeated measures ANOVAs, one for each general cognitive ability subgroup. Correction of the degrees of freedom with the Greenhouse-Geisser method was used.

In the processing speed study, Person´s *r* was used to investigate the relationship between PSQ and VABS. Those variables that were significantly

correlated with the criterion variable (VABS domains) were entered as predictors into a multiple model using the standard (enter) method.

In the intervention study, differences between the two treatment groups and between cognitive levels in terms of change in VABS composite scores, between T1 and T2 were analysed with a mixed analysis of variances (ANOVA), eta-squared (η^2) was used as a measure of effect size. The ANOVA was followed up by separate paired-samples *t*-test in order to study the degree of change in VABS composite scores between T1 and T2 for each of the treatment subgroups and for each of the cognitive level subgroups separately.

In the Good and Poor outcome study, Mann-Whitney *U*-tests were used for group comparisons of continuous variables. Group frequencies were made using chi-square tests (with Yates´s correction) whenever appropriate. Those variables that were significantly difference between groups were entered as predictors into a multiple model. Due to multicollinearity with IQ, speech and ASD diagnosis were left out of the model leaving age, ABC score, passing developmental milestones at 18 months, regression, and cognitive level. Logistic regression was performed to assess the impact of possible predictors.

3.5 Ethics

The study was approved by the Ethics Committee at the Karolinska University Hospital, Stockholm.

4 RESULTS

4.1 Study I: Developmental trajectory study

4.1.1 Stability and change in ASD category

For the 195 children who had been assessed both at T0, T1 and T2 the referral diagnosis (at T0) was AD in 121, PDD–NOS in 68, and AS in six cases. At T1, 118 were considered to meet criteria for AD, 51 for PDD–NOS and 9 for AS (type of ASD diagnosis had not been assessed in one child). Specific ASD subgroup remained the same for 112/195 children from T0 to T2. In 17 children the clinical research team (T1) found a somewhat lower level of autistic symptoms ("the autistic traits group") than had been reflected in the T0 clinical diagnosis of ASD. This group had been considered clinically to meet criteria for AD (n=8) or for PDD-NOS (n=9) at T0. For the overall category of ASD, the diagnosis was stable in about 90% from T1 to T2. Stability in ASD category is shown in figure 2 with solid straight line indicating stability of diagnosis.

At T2, 104 children (53% of 198) met criteria for AD, 57 (29%) for PDD-NOS and 13 (7%) for AS. The group with "autistic traits" comprised 21 cases (11%) at T2. AD and AS were the most stable diagnostic subtypes. Only one in three with PDD–NOS at T0 remained in the same diagnostic category at T2. Several of those with PDD–NOS at T0 but with no ASD diagnosis at T2 had other developmental problems including attention deficits, activity regulation problems, language delay, or ID/BIF.

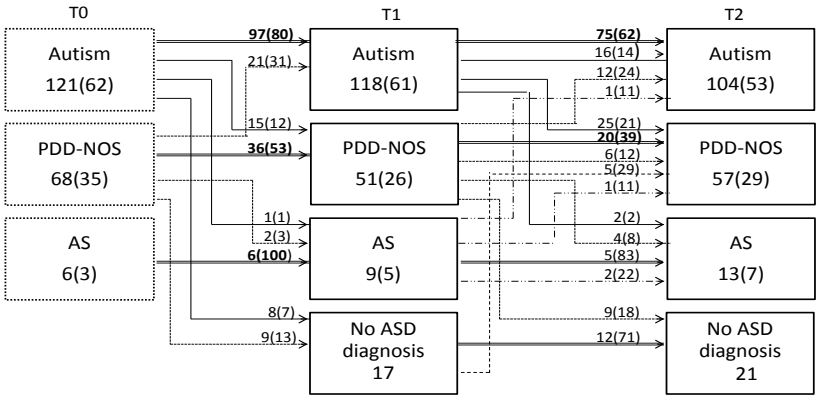


Figure 2. Stability and change in ASD category from T0, T1 to T2 (%)

4.1.2 Stability and change in developmental/intellectual function

At T0/T1, 45 of 196 children (23%) were classified as AIF, 78 (40%) as BIF and 73 (37%) as ID. The corresponding numbers at T2 were 52 (27%) with AIF, 51 (26%) with BIF and 93 (47%) with ID. Children with AIF and children with ID at T0/T1 more often had the same intellectual level at T2 (about 70% and 90% respectively) compared to those with BIF (about 40%). No child "went from" AIF to ID. The BIF group (n=78) was less stable; 29 (37%) had ID, 19 (24%) had AIF, and only 30 (39%) continued to have BIF at T2.

Sixty-four of 73 children with ID at T0/T1 (88%) continued to have ID at T2 of whom 44 (60%) had severe ID, and 20 (27%) had mild intellectual functioning (MID) at T2. Two children at T0/T1 ID level improved in intellectual functioning and met criteria for AIF at T2.

4.1.3 Stability and change in adaptive function

At T1, 15 of 191 children (8%) had average adaptive ability (86-114, Ss), 66 (34%) had below average adaptive ability (71-85) and 110 (58%) had low adaptive ability (20-70). No one had above average or high adaptive ability (115-129; 130-160). At T2 the "average group" increased to 30 children (16%), the low ability group to 64 (33%) and low average group to 97 (51%).

Adaptive function level was stable in 128 out of 191 children (67 %), whereas 44 children (23%) improved and 19 children (10%) declined. The distribution of percentage change is shown in figure 3.

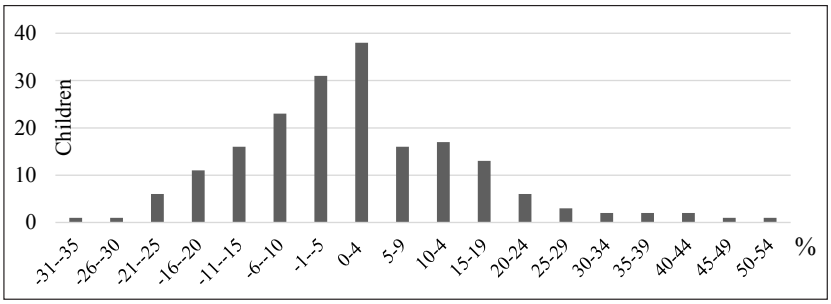


Figure 3. Distribution of change in VABS composite scores in relation to number of children

For children with AIF there was a significant improvement in DLS, Social and Motor domains. Children in the BIF group improved in Communication and Socialization domains scores from T1 to T2, while no changes were found on the DLS and Motor domains in this group. Children in the ID group had similar Communication scores at T2 compared to T1 but decreased in DLS, the Socialization domain and the Motor domains scores from T1 to T2. Change in adaptive domains scores in relation to cognitive level is illustrated in figure 4.

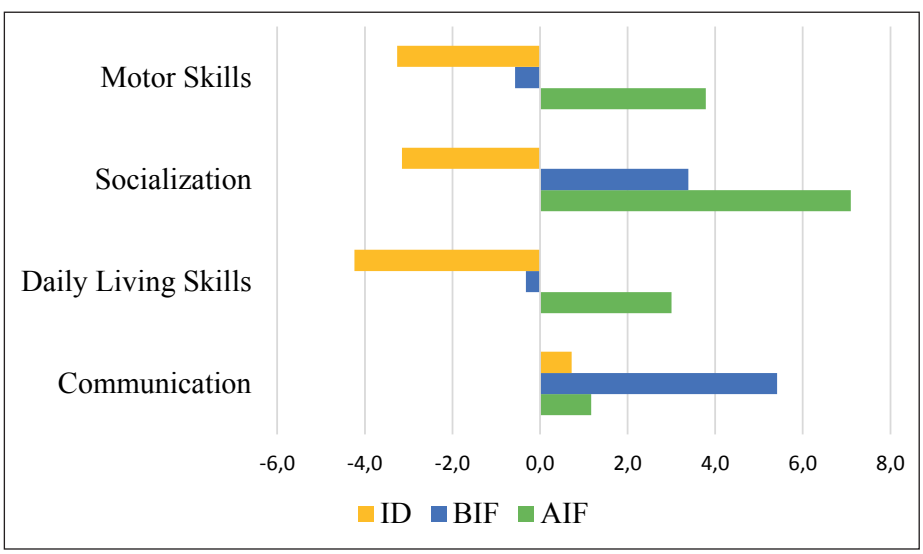


Figure 4. Change in adaptive domains scores in relation to developmental/intellectual level at T1

4.1.4 Stability and change in expressive speech in relation to DQ/IQ and ASD subgroups

Level of speech from T1 to T2 was stable in 85 of 196 children (43 %), improved in 99 children (51%) and declined in 12 children (6%) Ninety children had a level of speech characterised by using no words or only a few words or only a few sentences at T2 (figure 4). Seventy-one (79%) of these had ID, 19 (21%) had severe speech and language impairment in addition to ASD.

Table 3. Change in expressive speech in relation to DQ/IQ

	DQ/IQ level at T1				DQ/IQ level at T2			
	AIF	BIF	ID	Total n (%)	AIF	BIF	ID	Total n (%)
No words	1	8	18	27 (14)	-	-	19	19 (10)
Uses a few words	-	27	40	67 (32)	-	2	33	35 (17)
Uses a few sentences	6	23	19	48 (23)	4	6	26	36 (18)
Talks a great deal	12	14	4	30 (14)	2	3	8	13 (7)
Talks communicative	26	9	1	36 (17)	45	39	9	93 (48)
Total group n (%)	45 (22)	81 (39)	82 (39)	208 (100)	51 (26)	50 (25)	95 (49)	196 (100)

AIF= Average Intellectual Function, BIF=Borderline Intellectual Function, ID= Intellectual Disability

The difference between expressive speech subgroups in relation to intellectual functioning was significant both at T1 and T2 (p=.001 at T1 respectively T2).

The majority of children with low expressive speech level were found in the AD group (table 4).

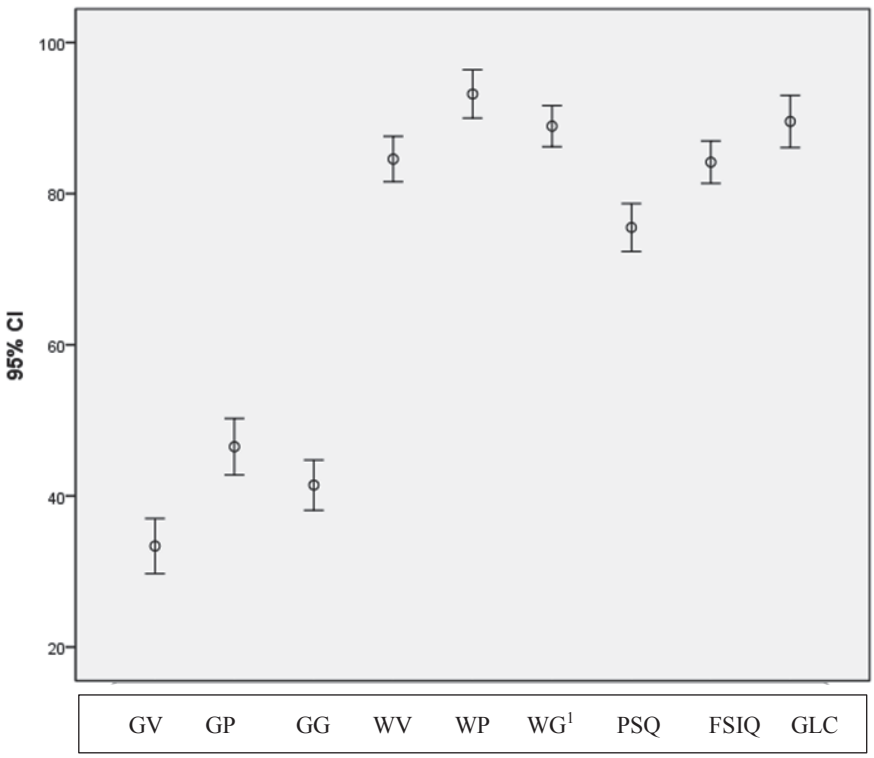
Table 4. Change in expressive speech in relation to ASD subgroups

	ASD subgroup at T1					ASD subgroup at T2				
	AD	PDD-NOS	AS	Autistic traits	Total n (%)	AD	PDD-NOS	AS	Autistic traits	Total n (%)
No words	25	2	-	-	27(13)	18	1	-	-	19(10)
Uses a few words	52	12	-	3	67(32)	30	3	-	1	34(18)
Uses a few sentences	31	13	-	4	48(23)	21	11	-	4	36(19)
Talks a great deal	16	10	2	2	30(15)	12	1	-	-	13(7)
Talks communicative	4	17	7	8	36(17)	23	41	13	16	93(48)
Total n=	128	54	9	17	208	104	57	13	21	195

AD=Autistic Disorder, PDD-NOS=Pervasive Developmental Disorder-Not Otherwise Specified, AS=Asperger Syndrome

4.2 Study II: Processing speed study

The cognitive profile was characterised by low verbal function in comparison to performance function in both Griffiths´ and WPPSI-III. Cognitive levels and profiles for 190 children at T2 are shown in figure 5.



G=Griffiths´ Developmental Scales, W=WPPSI, V=Verbal, P=Performance, G=Global, PSQ=Processing speed quotient, FSIQ=Full scale IQ, GLC=Global language composite, WG^1 = mean of verbal and performance scales in WPPSI

Figure 5. DQ/IQ levels and profiles at T2

For those children (77/190, 40%) who were evaluated with Griffiths´ Developmental Scales the mean for Verbal Function was 33.5 (SD=15.9), and 46.7 in Performance Function. For 113 (60% of the total sample) children WPPSI-III was used. FSIQ for this group was 84.5 (SD=14.7), VIQ

84.8 (SD=16.1), and PIQ 93.6 (SD=16.7). The mean value for PSQ (n=85) was 76.7 (SD=12.2) and for GLC (n=99) 89.9 (SD=17.1). The difference between VIQ, PIQ, FSIQ, PSQ and GLC was significant (p=.001).

4.2.1 Processing speed and adaptive behaviour

Low PSQ was found in 66 (78%) of the 85 children who were able to participate in the processing speed subtests. PSQ in relation to VABS-II was available for 84 of the 190 children. There were significant positive correlations between PSQ and the Communication domain (r=.422, p=.01), Motor Skills domain (r=.414, p=.01), Daily Living Skills (DLS) domain (r=.377, p =.01) and Adaptive Composite score (r=.438, p=.01).

A model (table 5) with VABS Communication scores as the dependent variable, a total of 35% of the variance was explained, with both speed and verbal IQ making a significant unique contribution. With VABS motor scores as the dependent variable, a total of 22% of the variance was explained with both speed and verbal IQ making a significant contribution. Using VABS DLS as the dependent variable, a total of 14% of the variance was explained with only speed making a significant contribution. Finally, in a model with the VABS total scores as the dependent variable, a total of 25% of the variance was explained with both speed and verbal IQ making a significant contribution. PIQ did not uniquely predict any of the VABS scores.

Table 5. Outcome of regression analyses (method: enter) with three VABS domain scores and VABS composite scores as dependent variables

	R^2	β	R^2	β	R^2	β	R^2	β
VIQ		.478**		.024		.241*		.277*
PIQ		-.095		.029		-.013		-.055
PSQ		.301**		.354**		.341**		.373**
	.35		.14		.22		.25	

*= p<.05, **=p<.01

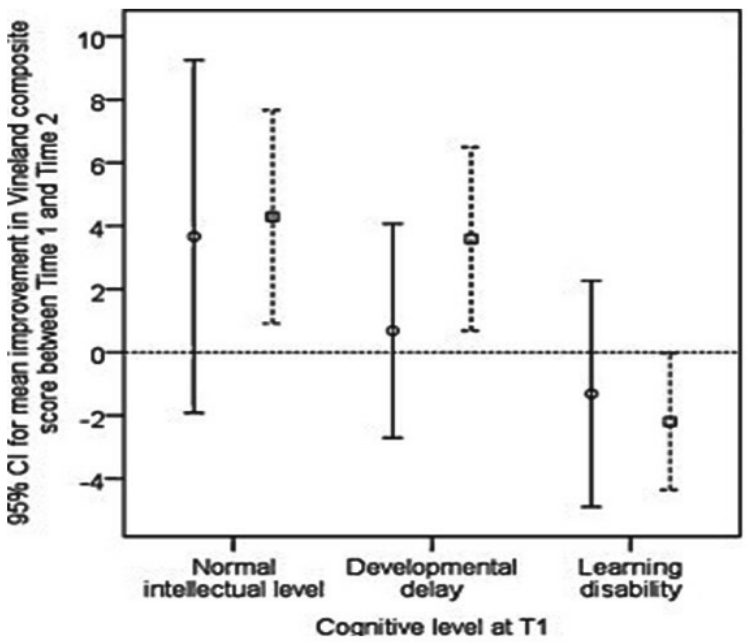
VIQ = Verbal Intellectual Quotient, PIQ = Performance Intellectual Quotient
PSQ = Processing Speed Quotient

Table 6. Comparison in IQ between PSQ and Non-PSQ group

WPPSI	PSQ group	Non-PSQ group (n=25) Mean	p-value
Verbal IQ	86.3 (15.4)	79.6 (17.4)	ns
Performance IQ	96.5 (15.3)	83.5 (17.8)	p=.002
Full Scale IQ	86.8 (13.8)	76.3 (14.9)	p=.003
Processing Speed	76.7 (12.2)	-	-

4.3 Study III: Intervention study

There was a significant improvement between T1 and T2 with respect to adaptive functioning (VABS composite score $F_{1, 186} = 3.90$, p=.050, η^2=.021) in the total group, and this was accounted for by the subgroup who had received *non-intensive intervention* ($t_{90=.28,}$ p=.783 for intensive intervention and t_{100}=2.07, p=.041 for non-intensive intervention). Intellectual functioning in relation to intensive and non-intensive intervention is illustrated in figure 6.



Intensive intervention = ———— Non-intensive intervention = - - - - - - - -

Figure 6. The 95% confidence intervals for the mean change in Vineland composite scores between T1 and T2 for the intensive and non-intensive groups and for cognitive levels

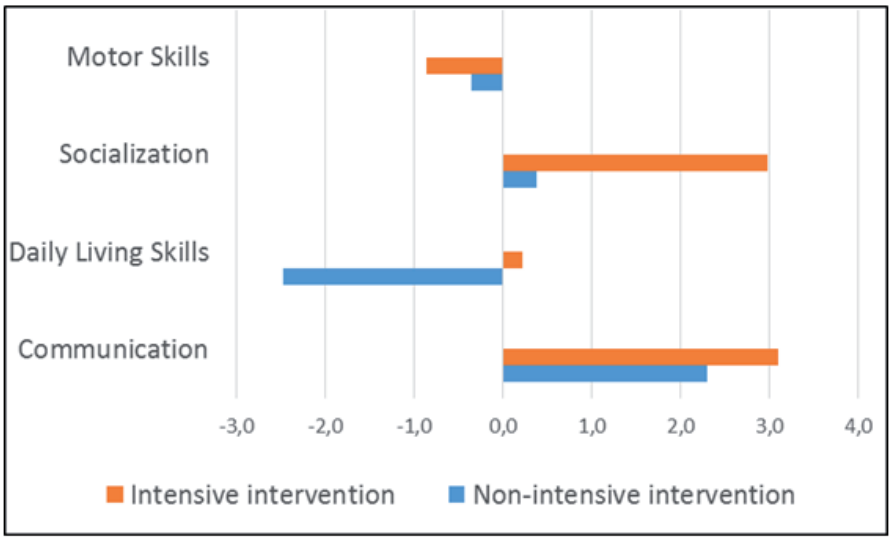


Figure 7. Change in VABS domain scores in relation to type of intervention

Differences in adaptive domain scores, between intervention groups, are illustrated in figure 7.

4.4 Study IV: Good and Poor outcome study

Intellectual functioning was found to be the best discriminator between the ASD Good and Poor outcome groups. A combination of five T1 factors: older age at diagnosis, lower level of "autistic" behaviour, having passed core developmental milestones at 18 months of age passed without problems, no regression and higher cognitive level (dichotomised into DQ/IQ≥70 or DQ/IQ<70), correctly classified 85% of Good versus Poor outcome cases at T2.

4.4.1 Adaptive functioning at T1

There was a significant difference in VABS composite score across the two groups at T1 with a mean of 71.2 (SD=8.6) versus 66.6 (SD=10.5, p=.023) in the Good versus Poor outcome group. When comparing domains and subdomains between Good and Poor outcome groups at T1, a difference was found in the Communication domain with a mean of 73.5 (SD=15.0, p=.009) in the Good and 63.3 (SD=14.8) in the Poor outcome group. In Motor skills domains the mean for the Good outcome group was 80.5 (SD=10.0) and for the Poor outcome group 73.7 (SD=12.7, p=.006). In the expressive

communication subdomain the mean in the Good outcome group was 9.8 (SD=2.6) compared to 8.0 (SD=2.6, p=.007) in the Poor outcome group. For pre-written skills the mean in the Good outcome group was 11.97 (SD=2.8, p=.005) and in the Poor outcome group it was 10.3 (SD=1.4). In the fine motor subdomain the mean in the good outcome group was 11.7 (SD=2.5, p=.009) compared to 9.9 (SD=2.6) in the Poor outcome group.

5 DISCUSSION

5.1 General findings

This thesis, reporting data from a pre-planned longitudinal prospective naturalistic study, has focused on different developmental/cognitive aspects and two-year outcomes for children who had an early clinical diagnosis of ASD. The children had all been assessed and diagnosed with ASD during the early preschool years and then been referred to a specialised autism centre for intervention. The study group was population-based and relatively large, about 200 children. All children had their individual – and, on a group-wise basis, highly variable – developmental/cognitive profiles and were in need of individualised support. The main finding was the broad variation with regard to (1) ASD type, (2) intellectual/cognitive functioning, (3) associated non-ASD co-existing disorders and problems, and (4) underlying medical factors.

The *Developmental trajectory study* showed that changes with regard to ASD type, general cognitive level, adaptive behaviour and expressive speech were considerable over time, particularly in those children who had been diagnosed with PDD-NOS and developmental delay/BIF at the first assessment. At the first assessment, 38% had definite or highly suspected ID, but at two-year-follow-up (at the end of intervention, non-intensive or intensive), half the total group met criteria for ID. Adaptive behaviour levels corresponded well with level of intellectual functioning. There was a strong correlation between AD and ID and between ID and low level of expressive speech capacity.

Uneven cognitive profiles, characterised by significantly higher performance than verbal skills, were reported in the *Processing speed study*. Low processing speed negatively affected general adaptive skills, including in the subdomains communication, daily living skills, and motor skills.

Results from the *Intervention study* did not find support for the notion that children with ASD generally benefit more from an intensive ABA intervention programme than from a non-intensive, targeted ABA intervention. Lower age at start of intervention did not predict better outcome after two years of intervention. The overall decrease in problematic autistic behavior was not associated with intensity of intervention.

The results of the *Good/Poor outcome study* (in which those with the very best adaptive outcomes were contrasted with those who had the least good outcomes) demonstrated that the level of intellectual functioning at first assessment was a clear predictor of outcome group status (more often IQ

below 70 in the Poor outcome group). Other important clinical associated factors were: age at referral due to a suspicion of ASD (younger in Poor outcome group), subtype of ASD (more often PDD-NOS in Good outcome group), developmental milestones at age 18 months (usually passed without problems in Good outcome group), speech and language development (relatively early in Good outcome group), degree of autistic behaviour problems (less severe in Good outcome group), and a history of regression (relatively more frequent in Poor outcome group).

5.2 Discussion of the results obtained in each of the four studies

5.2.1 Developmental trajectory study

Changes in developmental profiles were considerable. Major problems before the age of 3 (–5) years in the fields of general development, communication and language, social inter-relatedness and behaviour are often correlated. Co-existence of symptoms across disorders (comorbidity) is considered "the rule rather than the exception" in children with neurodevelopmental/ neuropsychiatric disorders (Gillberg 2010). About 90% of the children in our study continued to meet criteria for ASD during the two-year follow-up, a finding that accords with results from earlier studies following children from two years of age to four or nine years of age (Cox et al 1999; Eaves and Ho 2004; Charman et al. 2005; Lord et al. 2006). The PDD-NOS was the least stable ASD diagnosis and included some of the children who were later considered to have autistic symptoms rather than a "full" clinical diagnosis of ASD. In clinical practice, a "full" or "definitive" diagnosis of ASD might sometimes be preferred over diagnoses such as "BIF with autistic features", or "ADHD with autistic features", given that – for reasons that are neither based on science, nor on legal jurisdiction – it often opens doors to extra support in preschool/school compared to other diagnoses. The reports of a rise in the registered prevalence of ASD *diagnoses* in preschool children might be a reflection of this phenomenon. Recently (in 2007), a register based population study was performed in Stockholm County which estimated the ASD prevalence at 1.2% in children (Idring et al. 2012). UK and South Korea studies have reported even higher prevalence rates, about 2% and 3% respectively, when using screening followed by diagnostic assessment in population based groups (Baird et al. 2006; Kim et al. 2011). The DSM-IV category of PDD-NOS, which is not listed as a separate disorder in the new DSM-5, might have served as an "autism maybe?" category for some children, to allow for a "wait and see attitude as to how the child will develop and/or respond to early intervention and thus anticipating a label change" as

discussed by Daniels and colleagues (2011). Speculatively, the consequence of the new DSM-5 ASD criteria might be lower reported ASD prevalence rates, at least in the preschool years.

The study also showed stability in intellectual/developmental level in the AIF and ID groups, whereas (and perhaps not surprisingly) children with BIF at first assessment changed considerably compared to second assessment. The preschool ages are a difficult period for the assessment of IQ/DQ in children with ASD, not only because of the uneven cognitive development but sometimes also due to the child´s limited participation in tests, and this might influence the results. Adaptive level measured by VABS total composite score was most stable in the AIF and ID group but less stable in the BIF. Significant changes in domains were observed in all IQ/DQ categories both in the AIF (increased DLS, social and motor domain scores) and in the ID (decreased DLS, social and motor domain scores) group as well as in the BIF group (increased social and communication domains scores).

In general, the level of expressive speech was stable or increased in the total group with few exceptions in every speech category except for the group with no words at T1. Almost half of this group continued to have no words at T2. The majority of the children with no words, only a few words or only few sentences at T2 had ID. However, a substantial subgroup did not have ID indicating speech and language impairment in addition to ASD.

5.2.2 Processing speed study

At initial assessment it was possible to identify most children who at two-year follow-up where assessed as AIF or with ID. At follow-up it was found that every other child was considered to have ID, many of whom were moderately to severely affected. Only one child in the whole sample had above average intellectual functioning. These results are roughly in line with previous research reporting IQ ranges from severe ID to above average intellectual functioning. However, relatively more children with intellectual functioning within the normal range have been identified during the last decade (Rice 2009). Uneven intellectual/developmental profiles, with higher performance/non-verbal than verbal skills have often been reported in older children with ASD (Carr 2006). Our results confirm that this uneven profile is already present in preschool children with ASD.

We found that slow processing speed correlated with low levels of adaptive functioning. Processing speed tests measures a child´s ability to carry out a cognitive task under time pressure and demand the contribution of a number

of different functions including motor ability, memory and perception. Processing speed tests also require goal-directed behaviour, mental flexibility and sustained attention, all part of a set of processes often subsumed under the general heading of executive function. Assessment of executive functioning is difficult and partly impossible in preschoolers, particularly since the toolkit for this age group is limited and very young children are not able to exert higher order control of executive cognitive processes anyway. Preschool children show lack of inhibitory control, cognitive flexibility, and lack of strategic behaviour. However, it is possible that processing speed tests capture the *precursors* of executive function that are only evident later in childhood.

Processing speed tests also demand the abilities to perceive and integrate rapid information, functions that are also needed in order to integrate facial movements, speech flow and physical movements during social interaction. It has been suggested that "the social world might be changing too fast" for individuals with ASD, and that a slower speed would increase imitative, verbal and cognitive abilities particularly in low-functioning children with ASD (Gepner and Féron 2009). Impairments in the integration of visual processing and motor output have also been demonstrated; children with ASD and high average IQ perform at a similar level to those with no ASD on tasks with low motor demand (e.g. press one of two computer keys) but worse than children with no ASD on visual-motor integration tasks (e.g. when asked to draw a line, Kenworthy et al. 2013).

5.2.3 Intervention study

In the intervention study, the 2-year outcome in terms of adaptive functioning was related to type and intensity of intervention. Improvement in adaptive functioning was seen in the total group, both in the intensive and non-intensive group but the intensity of intervention did not appear as a factor related to outcome. That intensity of intervention lacks importance is supported by a recently published review (SBU. 2013). Instead improvement in adaptive functioning was significant in the non-intensive intervention group with AIF and BIF. Lower age at start of intervention was not associated with better outcome, a finding that contrasted with some previous studies (Kuhl et al. 2003; Lewis 2004). The child´s intellectual level has been found to be of importance for treatment effect; the initial intellectual level appears to have the strongest link to later outcome (Kraemer et al. 2002). In our study group children with the combination of a more severe form of ASD and ID had been referred for intervention at younger ages compared to children with ASD combined with AIF and BIF (Eriksson et al. 2013).

Our study was carried out in a naturalistic setting, investigating the outcome after different intensity of intervention "in real life". It has been proposed that naturalistic studies do not necessarily provide "lower-level/poorer quality evidence" than randomised controlled trials, and that in fact naturalistic studies are required to demonstrate that a form of therapy actually works in real life including complex and co-existing variants of disorders (Leichsenring 2004).

5.2.4 Good/Poor outcome study

In the fourth study the Good and Poor outcome groups were defined by 15% change up and down respectively in VABS composite scores between T1 and T2. Several clinical characteristics were compared between the two groups. A combination of five factors ((1) age at T0, (2) developmental delays at 18 months, (3) cognitive level and (4) ABC scores at T1 and (5) history of regression) correctly classified 85.4% of the children, as belonging to either group. Type of ASD diagnosis and the child´s development of speech and language were excluded from the analysis, due to their high correlation with intellectual/developmental level. There was no group difference between Good and Poor outcome groups regarding intensity of intervention. The single most important predictor was IQ>70; the probability was eighteen times higher that the child belonged to the Good rather than Poor outcome group at this IQ-level. IQ >70 (and also communicative phrase speech at age five) has been reported to predict outcome (Billstedt et al. 2005; Magiati et al. 2014).

The Good outcome group had moderately low adaptive function at T1 but the Poor group had an even lower adaptive function at T1, indicating that the Poor outcome group had more difficulties already at T1. When analysing adaptive profiles at T1 the Good outcome group was superior in communication and motor skills (but not social skills or daily living skills) compared to the Poor outcome group. Good communicative skills are strongly influenced by high intellectual capacity, which, as has been pointed out repeatedly, is an important predictor of outcome. Motor skills in children with ASD are influenced by the capacity for temporal control, which, in turn, is also important in turn-taking and for social reciprocity (Whyatt and Craig 2013) and often negatively correlated with autism severity.

5.3 Strengths and Limitations

The study group encompasses a relatively large and representative group of children aged 2.5-4 years. Only 25 children (out of 313) were excluded due to

being referred directly to habilitation centres specialising in children with multi-handicap but not specifically in autism. The majority of children excluded had an ASD diagnosis plus other severe disabilities and medical conditions. This means that our study has limitations regarding the representativeness of this multi-handicapped group. Furthermore, 15 children (out of 260) were excluded from the study because of insufficient skills in the Swedish or English on the part of the parents. At T1, not all of the children had had a *full* cognitive assessment; nevertheless, the cognitive estimation was based on comprehensive clinical assessment of the child, including both interviews of parents as well as observations of the child (including full or partial cognitive/developmental testing). A major strength was that very few and experienced/co-working clinicians were involved in the study and that this reduces measurement error. Strength of the intervention study was also that the research team was "blind" with regard to type of intervention the children had received. A limitation in the study was the lack of controlled randomisation. However, the study period extended over 2 years and many parents requested a specific treatment for their child, which meant that randomization, was not considered possible. Instead the study has a naturalistic design.

6 CONCLUSION AND IMPLICATIONS FOR CLINICAL PRACTICE AND RESEARCH

The rate of children with an early diagnosis ASD showing marked changes in their developmental profiles during the preschool years challenges the notion of ASD as a stable and clearly delineated diagnostic category, a diagnosis that will not need to be revisited once made after comprehensive expert assessment at age 2.5-4 years. Instead the findings underscore the need to take a more holistic ESSENCE approach already from the start (taking all possible neurodevelopmental disabilities and associated factors into account). They also provide pointers to the need for further follow-ups.

The results highlight the need for cognitive and medical assessment and reassessments for all children with ASD both in respect of planning for intervention in preschool and for educational school planning and for the provision of a realistic prognosis. In children with ASD who have had their first assessment during the preschool age there should always be a readiness for a new cognitive assessment before school start. The complete clinical picture may not have fully appeared in the very early years and it is important to follow the child during development and to assess the trajectories of different symptom domains, including of the often occurring co-existing disorders.

The impairments in ASD comprise a set of cognitive deficits that need to be elucidated and explained to parents and preschool/school staff in order to increase the understanding of the child´s difficulties and enable appropriate expectations and demands. Processing speed problems are possibly important to highlight given that they might predict executive dysfunction later on. However further follow-up of which cognitive mechanisms (executive functioning, memory, and attention) prevent or strengthen development is needed.

The intervention part of the study showed that children with ID on the one hand and children with BIF or AIF on the other differed with respect to outcome; those with BIF or AIF had the most favourable outcome. The overall group outcome did not differ between those who had had intensive or non-intensive ABA programs. In fact, if anything, the non-intensive group with BIF and AIF had better outcomes than the intensive group functioning at

these cognitive levels. Also, some of the children with ASD and ID decreased in adaptive functioning over time, particularly in the group receiving intensive intervention. Even though the study was not an RCT, the relatively large sample size, the pre-planned prospective longitudinal naturalistic design, the relatively long follow-up period (two years), and the relative blindness of the raters at follow-up are very considerable strengths, and the findings cannot be "thrown out" as uninformative just because randomisation did not occur. Instead the findings need to be taken seriously, as they could have implications for delivery of ASD services. In order to plan for the child´s intervention it will be very important to assess and to consider the child´s general (and more specific) cognitive functioning. Most current ASD interventions include elements of ABA, and these can be applied both with an intensive and a non-intensive approach, but they all have to be highly individualised and take into account all the "non-ASD" (read ESSENCE) factors that are important in all children with ASD.
In order to be able identify early predictors of negative outcomes it will possibly be important to pay more attention to the presence of documented developmental delay at 18 months, to documented regression (i.e. clear loss of skills), and to cases with identified clearly ASD/ESSENCE-associated medical disorders (such as Rett syndrome in girls, Fragile X syndrome and tuberous sclerosis) including epilepsy. Also, children who present very early and who meet full criteria for ASD at a very early age should be particularly in focus when it comes to immediately performing a full psychological/medical assessment, given that they are the most likely to have a multitude of ESSENCE problems and possible major medical disorders and a poor outcome. Their intervention program needs to take all their problems into account from the very beginning. Worldwide, there is still much too little emphasis on these aspects when it comes to assessment and intervention planning for children with ASD. It has almost come to a point where it is taken for granted that "all children with ASD need one kind of intensive ABA intervention". The findings of the present study lend little, if any support for such a stance.

The strongest predictor of good outcome is clearly IQ/DQ in the near normal or normal ranges. This again underscores the need to never consider an ASD diagnosis in itself "enough". The IQ/DQ-level, not the ASD diagnosis per se, is the most important variable in predicting outcome. Developmental assessments/IQ-tests must be part of the ASD assessment, both at original diagnostic assessment and at follow-up after one or more years.

In terms of future research there is a need for more prospective longitudinal naturalistic large-scale studies of ASD outcome, including a need to continue

to follow the children for much longer periods (including through adolescence and into adult age). Such studies need to always take a broad ESSENCE perspective from the start. Early developmental tests (including tests that tap into possible precursors of executive functioning) and detailed assessment of cognitive functioning (and adaptive functioning) should be included in all such studies as soon as the child is referred with a clinical diagnosis of ASD.

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