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Katja Jussila

ON THE AUTISM SPECTRUM?

RECOGNITION AND ASSESSMENT OF QUANTITATIVE AUTISM TRAITS IN HIGH-FUNCTIONING SCHOOL-AGED CHILDREN. AN EPIDEMIOLOGICAL AND CLINICAL STUDY

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
OULU UNIVERSITY HOSPITAL

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Recognition and assessment of quantitative autism traits in high-functioning school-aged children.
An epidemiological and clinical study

Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in the Leena Palotie auditorium (101A) of the Faculty of Medicine (Aapistie 5 A), on 1 November 2019, at 12 noon

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Abstract

Background: There is wide variability in the phenotypic manifestation of autism spectrum disorder (ASD). Recognizing autistic traits behind socio-emotional and adaptive problems in children with normal cognitive level can therefore be challenging.

Aims and methods: The purpose of this study was to find tools for recognition of autism traits for clinicians working in primary/secondary settings. Two internationally used and empirically valid quantitative screeners, the Autism Spectrum Screening Questionnaire (ASSQ) and the Social Responsiveness Scale (SRS), were translated into Finnish and evaluated among high-functioning elementary school-aged children. An epidemiological target population of 8-year-old children (N=4,408) including 28 children with ASD was rated by parents and teachers using the ASSQ in order to assess cut-off scores for the Finnish ASSQ, and sensory abnormalities (SA) were determined in order to estimate the prevalence of SAs, and to investigate associations between sensory-perceptual problems and quantitative autism traits (QAT). The SRS was evaluated in a clinical ASD case (N=44)-control (N=44) study. It was also studied whether QAT of family members were associated with child QAT using the SRS.

Results: Collecting parent and teacher ASSQ ratings and a cut-off of summed 30 points are recommended for ASD diagnostic assessments. The Finnish SRS was able to differentiate children with ASD from a normative child sample. The prevalence of SAs was 8% in the general population and 54% in the ASD sample. Tactile, auditory and olfactory hypersensitivities were associated with an elevated risk for an ASD diagnosis and auditory hypersensitivity explained the variance in the ASSQ scores among the ASD sample. In the normative sample, mother-child SRS QAT were more strongly associated, whereas in the ASD sample, a stronger positive correlation was found between father and child SRS QAT.

Conclusions: In ASSQ screening, it is essential to collect both parent and teacher assessments. The SRS offers valuable information for determining the focal points of rehabilitation and evaluating treatment outcome. The SAs of the child as well as high QAT levels of male family members are indicators of an elevated risk for ASD.

Keywords: ASD, ASSQ, autism, autism spectrum disorder, QAT, quantitative autism traits, rehabilitation, screening, sensory abnormality, SRS

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Tiivistelmä

Tausta: Autismikirjon häiriön kliininen oirekuva vaihtelee henkilöstä toiseen. Tästä johtuen autististen piirteiden tunnistaminen lapsen sosioemotionaalisten ja sopeutumisvaikeuksien taustalta voi olla haasteellista.

Tavoitteet ja menetelmät: Tutkimuksen tarkoituksena oli etsiä kognitiivisesti hyvätasoisten peruskouluikäisten parissa työskenteleville kliinikoille apukeinoja autististen piirteiden tunnistamiseen. Kaksi kansainvälisesti käytettyä seulontamittaria, Autismikirjon seulontalomake (ASSQ) ja Sosiaalisen vastavuoroisuuden arviointiasteikko (SRS), käännettiin suomeksi ja niiden psykometrisiä ominaisuuksia arvioitiin. Lisäksi tutkittiin, olivatko aistipoikkeavuudet tai vanhempien autistismipiirteisyys yhteydessä peruskouluikäisen lapsen autismipiirteisyyteen. Vanhemmat ja opettaja täyttivät ASSQ:n 8-vuotiaista epidemiologisen kohderyhmän lapsista (N=4408), joista 28:lla oli autismikirjon häiriö, ja kohderyhmän lasten aistipoikkeavuudet kartoitettiin. ASSQ:n seulontarajat sekä aistipoikkeavuuksien esiintyvyys ja yhteys autismipiirteisyyteen määritettiin. SRS evaluoitiin ja perheen sisäisen autismipiirteisyyden vertailu tehtiin kliinisessä autismikirjo (N=44)-verrokki (N=44)-aineistossa.

Tulokset: Vanhempien ja opettajan ASSQ-arviointien yhteenlaskettu pistemäärä 30 oli parhaiten toimiva seulontaraja autismikirjon häiriön diagnostisia tutkimuksia varten. SRS erotteli autismikirjon lapset normiaineistosta. Aistipoikkeavuuksien esiintyvyys kokonaisväestössä oli 8 % ja autismikirjon lapsilla 54 %. Tunto-, kuulo- ja hajuyliherkkyys olivat yhteydessä kohonneeseen autismikirjon häiriön riskiin ja kuuloyliherkkyys selitti autismipiirteisyyden vaihtelua autismikirjon lapsilla. Normiaineistossa lapsen ja äidin autismipiirteisyys olivat vahvemmin yhteydessä toisiinsa, kun taas autismikirjon lasten perheissä lapsen ja isän autismipiirteisyys olivat vahvemmin yhteydessä toisiinsa.

Päätelmät: ASSQ-arvioinnissa on ensiarvoisen tärkeää kerätä tietoa lapsen käyttäytymisestä sekä koti- että kouluympäristöstä. SRS on käyttökelpoinen määriteltäessä kuntoutuksen painopistealueita ja kartoitettaessa sen vaikuttavuutta. Lapsen aistipoikkeavuudet sekä hänen miespuolisten perheenjäsentensä vahva autismipiirteisyys viittaavat autismikirjon häiriön mahdollisuuteen.

Asiasanat: aistipoikkeavuus, ASSQ, autismi, autismikirjon häiriö, autismipiirteisyys, kuntoutus, seulonta, SRS

And now here is my secret, a very simple secret:
It is only with the heart that one can see rightly.
What is essential is invisible to the eye.

- Antoine de Saint-Exupéry, The Little Prince –

To my precious children

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Seventeen years ago I called the head psychologist at the children's clinic of Oulu University Hospital, the deceased Terttu Tapio, MPsych, and inquired if she would have a job for me at the hospital. She asked me if I would be interested in joining a research project since one about to launch was in need of a research psychologist. I was, and haven't left since.

We keep moving forward,
opening new doors,
and doing new things,
because we're curious
and curiosity keeps leading us down new paths.

- Walt Disney –

It has been a long journey with this thesis. Inspiring, sometimes frustrating… I have had to step out of my comfort zone many times. For some reason I have done so.

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Oulu, Finland, September 6, 2019 *Katja Jussila*

Abbreviations

ADHD	Attention Deficit/Hyperactivity Disorder
ADI-R	Autism Diagnostic Interview–Revised
ADOS	Autism Diagnostic Observation Schedule
AS	Asperger syndrome
ASD	Autism spectrum disorder
ASSQ	Autism Spectrum Screening Questionnaire
AUC	Area under the curve
CI	Confidence interval
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders–Fifth Edition
EM	Expectation-maximization
ED	Executive dysfunction
FSIQ	Full-scale intelligence quotient
IQ	Intelligence quotient
LR	Likelihood ratio
M	Mean
md	Median
ns	Non-significant
NOHD	Northern Ostrobothnia Hospital District
OR	Odds ratio
ROC	Receiver operating characteristics
RSB	Reciprocal social behavior
SA	Sensory abnormality
sd	Standard deviation
Sn	Sensitivity
Sp	Specificity
SPSS	Statistical Package for the Social Sciences
SRS	Social Responsiveness Scale
ToM	Theory of mind
WCC	Weak central coherence
WISC-III	Wechsler Intelligence Scale for Children–Third Edition
QAT	Quantitative autism traits

Original Publications

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

I Mattila, M. L., Jussila, K., Linna, S. L., Kielinen, M., Bloigu, R., Kuusikko-Gauffin, S., Joskitt, L., Ebeling, H., Hurtig, T., & Moilanen I. (2012). Validation of the Finnish Autism Spectrum Screening Questionnaire (ASSQ) for clinical settings and total population screening. *Journal of Autism and Developmental Disorders, 42*(10), 2162–2180. https://doi.org/10.1007/s10803-012-1464-5

II Jussila, K., Kuusikko-Gauffin, S., Mattila, M. L., Loukusa, S., Pollock-Wurman, R., Joskitt, L., Ebeling, H., Moilanen, I., Pauls, D., & Hurtig, T. (2015). Cross-Cultural differences in the parent rated Social Responsiveness Scale (SRS)? Evaluation of the Finnish version among high-functioning school-aged males with and without autism spectrum disorder. *Research in Autism Spectrum Disorders, 9*, 38–44. https://doi.org/10.1016/j.rasd.2014.09.008

III Jussila, K., Lyall, K., Kuusikko-Gauffin, S., Mattila, M. L., Pollock-Wurman, R., Hurtig, T., Joskitt, L., Bloigu, R., Ebeling, H., Moilanen, I., & Pauls, D. (2015). Familiality of quantitative autism traits. *Scandinavian Journal of Child and Adolescent Psychiatry and Psychology, 3*(2), 126–135.

IV Jussila, K., Junttila, M., Kielinen, M., Ebeling, H., Joskitt, L., Moilanen, I., & Mattila, M. L. (2019). Sensory abnormality and quantitative autism traits in children with and without autism spectrum disorder in an epidemiological population. *Journal of Autism and Developmental Disorders*. doi 10.1007/s10803-019-04237-0

Contents

1 Introduction

Autism spectrum disorder (ASD) represents the severe end of a continuum where autistic traits are continuously distributed in the general population and extend into normality. It is a pervasive neuropsychiatric disorder defined by early onset impairments in reciprocal social behavior (RSB) and stereotyped patterns of behavior (APA, 2013).

Reciprocal social behavior can be defined as "the extent to which an individual engages in emotionally appropriate, turn-taking social interaction with others. This requires the individual to be cognizant of the emotional and interpersonal cues, to appropriately interpret and respond to those cues, to be aware of others' perceptions or restrictions to his or her own behaviors, and to be capable of emotional engagement" (Constantino, Przybeck, Friesen, & Todd, 2000).

Atypical sensory processing has recently been suggested to be the earliest, primary characteristic of autism that possibly predicts and explains deficits in later social communication (Robertson & Baron-Cohen, 2017). Stereotyped patterns of behavior are more likely in children with ASD who experience atypical sensory processing (Chen, Rodgers, & McConachie, 2009; Gabriels et al., 2008) and might function as a soothing or stimulating mechanism for children with sensory dysfunction (Leekam, Prior, & Uljarevic, 2011). Atypical sensory processing may then cause avoidance of social stimuli and thereby impact the development of RSB and cognitive abilities (Ben-Sasson et al., 2007).

There is wide variability in the phenotypic manifestation of ASD. Recognizing autistic traits behind socio-emotional and adaptive problems in school-aged children with normal cognitive level can therefore be challenging, and yet, it is essential when making decisions concerning rehabilitation. When tailoring interventions for social deficits, it is necessary to be aware whether the deficits in a child's RSB capacity arise from deficits in social cognition and communication related to autism rather than impulsivity, for example. Due to the wide variability in the manifestation of ASD, it is essential to use quantitative instead of qualitative assessment methods when attempting to identify milder manifesting and/or subclinical autistic traits. A quantitative instrument yields a single total score indicating the severity of autistic traits, which can be referred to as quantitative autism traits (QAT).

In order to find tools for clinicians at the primary level to recognize children in need of comprehensive diagnostic evaluations of ASD, we imported two

internationally widely used, empirically sound, quantitative screening instruments to Finland: the Autism Spectrum Screening Questionnaire (ASSQ) and the Social Responsiveness Scale (SRS). Although an unofficial Finnish version of the ASSQ had been used in clinical settings since the 1990s, an official translation was lacking and normative data had not been collected. The SRS, which is more detailed than the ASSQ, is internationally widely used not only as a screener, but also as an aid in intervention planning and treatment outcome assessment. At the very beginning of our ASD research, there were no quantitative measures for ASD treatment outcome assessment in Finland. Hence we wanted to import these two instruments to Finland and study their psychometric properties.

It is known that there is a heritable component in ASD and autistic traits. In their recent review article, Waye and Cheng (2018) summed that parents who have a child with ASD have a 2–18 % chance of having a second child with ASD. During the epidemiological ASSQ study, some families reported "traitness" among the family members, and ASD family aggregation was also our experience from clinical practice. Therefore, we decided to investigate possible familial associations of phenotypic QAT in a clinic-based genetic study that was just about to launch in cooperation with Harvard University (Weiss et al., 2009).

The new revised diagnostic criteria of ASD have included atypical sensory processing, i.e., hyper- and/or hyporeactivity to sensory input and unusual interests in sensory aspects of the environment into the diagnostic criteria in the DSM-5 (APA, 2013). Only a few studies have addressed the association between quantitatively assessed autistic traits and atypical sensory functioning. In all these studies, sensory abnormality (SA) has been connected to an increase in QAT among both neurotypical and ASD adult populations (Horder, Wilson, Mendez, & Murphy, 2014); Mayer, 2017; Robertson & Simmons 2013; Takayama et al., 2014; Tavassoli, Hoekstra, & Baron-Cohen, 2014). To our knowledge, the prevalence of SA in an epidemiological child population had not been studied previously. We had a large epidemiological ASSQ-QAT data set, and the parents were also asked to answer questions concerning SAs in their children. This gave us an opportunity to study the prevalence of atypical sensory processing and the association between QAT and sensory functioning.

2 Review of the Literature

2.1 Psychological hypotheses of autism spectrum disorder

Prevailing psychological hypotheses of the deficits associated with ASD include the Theory of Mind (ToM) hypothesis, the Weak Central Coherence (WCC) hypothesis, and the Executive Dysfunction (ED) hypothesis. According to the ToM hypothesis, the social dysfunction in ASD results from disruptions in processes leading to the acquisition of the capacity for conceiving of other people's and one's own mind – that is, impairment in the ability to conceive mental states and to use mental state concepts to interpret and predict other people's (and one's own) behavior (Baron-Cohen, 1995). Deficits in ToM have also been hypothesized to underlie the abnormalities in communication of individuals with ASD. The ToM hypothesis thus builds on the assumption that the social cognitive domain is the core deficiency of ASD. The WCC and ED hypotheses, on the other hand, are built on the assumption that the social dysfunction defining these conditions is only part of a more generalized learning impairment. The WCC hypothesis states that individuals with ASD tend to process all stimuli focusing on details (localized processing) and thus have significant difficulties in configural processing, where achieving integrated and meaningful wholes are the focus of stimuli processing. The internal social world of individuals with ASD thus ends up appearing disjointed, lacking in the coherence that defines the social context and meaning (Happe, 1999). The ED account proposes that the rigid and repetitive behavior patterns and the impairments in communication and reciprocal social interaction defining the ASD are due to deficits in executive control processes – i.e. working memory, inhibitory control, mental flexibility, and planning (Ozonoff, 1997).

2.2 Autism spectrum disorder as a spectrum disorder and aggregation of autistic traits in family members of autistic individuals

Autism spectrum disorder was traditionally viewed as a categorical on/off condition. During the last 20 years, it has become evident that it is best conceptualized as a spectrum of related conditions on a continuum of social communication skills (Baron-Cohen, 1995; Constantino et al., 2000; Wakayabashi

et al., 2006; Wing, 1981) and that autism represents the extreme expression of a constellation of deficits on the continuum. Behavioral and cognitive characteristics qualitatively similar to those defined in the diagnostic criteria of ASD are common and continuously distributed in the general population, and the male to female ratio of these characteristics in general population seems to be in line with that in the clinical groups (Austin, 2005; Baron-Cohen et al., 2001; Constantino et al., 2000; Constantino & Todd, 2000; 2003; 2005; Kamio et al., 2012). It has been shown that autistic characteristics (i.e., deficits in social and communicative skills, repetitive behaviors and personality characteristics such as aloofness, shyness, hypersensitivity, anxiousness, rigidity, and tactlessness) aggregate in first- and second-degree relatives of autistic probands (Bölte, Knecht, & Poutska, 2007; Constantino et al., 2006; Murphy et al., 2000; Piven, 2001). This phenotypic profile consisting of subclinical traits qualitatively similar to those defining the ASD that manifest in relatives of autistic individuals has been referred to as the broader autistic phenotype (Bailey et al., 1998), or when measured by quantitative instruments, the QAT.

2.3 Repetitive behavior and atypical sensory behavior

Repetitive behavior consists of five subcategories:

1. repetitive sensory-motor/stereotypic behaviors,
2. ritualistic/insistence on sameness behaviors,
3. compulsive behavior,
4. restricted/circumscribed interests, and
5. self injurious behaviors (Bishop et al., 2013).

These repetitive behaviors are more likely to be present among ASD children who also experience SAs (Chen et al., 2009; Gabriels et al., 2008), and they might function as a soothing or stimulating mechanism for children with sensory dysfunction (Leekam et al., 2011). The role of sensory perception in autism is not yet fully understood, but recent research has acknowledged it as a core feature of ASD, possibly the most primary one. In a review article published in Nature Reviews, the sensory symptoms are recognized as the earliest, primary characteristics of autism which predict and explain deficits in later social communication (Robertson & Baron-Cohen, 2017). These atypical sensory symptoms can cause avoidance of social stimuli and thereby impact the development of social and cognitive abilities (Ben-Sasson et al., 2007).

2.4 Identification of autistic traits

Diagnosing ASD is a time-consuming task. There are several diagnostic and screening instruments for ASD. The most respected diagnostic tools include the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994) and the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000) that require a trained rater, are conducted in non-naturalistic settings, and may take up to several hours to administer, which obviously limits their utility in both the clinical field as well as in research. When using qualitative instruments, the informant or the trained rater has to estimate whether or not a certain autistic trait is present and in what degree of severity, and the child then either meets a set cut-off or falls below the threshold. With these instruments, there is often a risk for a false negative result when diagnosing milder manifesting ASD, and obviously, these instruments are not suited to identify the broader phenotype which is important when investigating the heritability of these conditions. Identifying the subclinical phenotypes is of great importance also due to the fact that even mildly manifesting autistic traits often lead to anxiety, depression, and isolation (Green et al., 2000; Kim et al., 2000; Muris et al., 1998). In primary settings where a school-aged child is referred to a health care provider (e.g., school nurse/psychologist/doctor) due to socio-emotional or neurocognitive problems, it can be challenging to identify children in need of more comprehensive tertiary level assessment by a clinician specialized in ASD.

There are also informant-based rating scales which use caregiver responses to assess information about the autistic symptomatology of a child. These instruments have some disadvantages over those mentioned above (for example, the informants might differ in the understanding and interpretation of a child's symptoms or presented questions, and have an opportunity to leave questions unanswered), but they also have many advantages: they offer information about the child's behavior in naturalistic settings, are easy and quick to administer, suited for screening large samples, and can be standardized, providing normative information.

2.4.1 The Autism Spectrum Screening Questionnaire

The ASSQ in a 27-item informant-based questionnaire that was developed in Sweden as a screener for ASD in higher-functioning (full-scale intelligence quotient [FSIQ] ≥ 50) primary school-aged populations (Ehlers and Gillberg,

1993). It has been validated in English (Ehlers and Gillberg, 1993), Lithuanian (Lesinskiene, 2000), Norwegian (Posserud, Lundervold, & Gillberg, 2006), Danish (Petersen et al., 2006), Korean (Kim et al., 2011), Mandarin Chinese (Guo et al., 2011), Hungarian (Jakab et al., 2013), Icelandic (Georgsdottir et al. 2013), Japanese (Kobayashi et al., 2013), and Turkish (Köse et al., 2017). Validation studies show variability of established cut-off scores in different languages and cultures (Ehlers, Gillberg, and Wing, 1999; Guo et al., 2011; Posserud et al., 2006). Additionally, a revised and extended version of the ASSQ, the Autism Spectrum Screening Questionnaire-Revised Extended Version has been developed in Swedish to better capture the female phenotype of ASD (Kopp and Gillberg, 2011), and a newly published study found the ASSQ also to be a reliable instrument for screening preschool children aged 4–6 years (Adachi et al., 2018).

The ASSQ was designed to measure 4 factors:

1. social interaction,
2. communication problems,
3. restricted and repetitive behavior
4. motor clumsiness and other associated symptoms including motor and vocal tics.

A three-factor solution has also been suggested:

1. social difficulties,
2. repetitive, stereotyped behavior and autism-associated problems
3. autistic style (a kind of social-cognitive and speaking style often seen in high-functioning individuals with autism/Asperger syndrome (AS), regarded, for instance, as “eccentric professor” by other children, or “old-fashioned”, or having “robot-like language”) (Posserud et al., 2008).

2.4.2 The Social Responsiveness Scale

The Social Responsiveness Scale (SRS; Constantino et al., 2000; Constantino & Gruber, 2005; 2012) is a 65-item informant-based questionnaire designed to be used both as a screener, as an aid to clinical diagnosis, and as assessment for treatment outcome. Originally developed and validated in the US, the SRS has since also been validated in the UK, Germany, Japan, Mexico, and the Netherlands (Royers et al., 2011; Bölte, Poustka, & Constantino, 2008; Kamio et

al., 2012; Wigham et al., 2012). The suggested cut-off score for screening has varied in different cultures and languages, and also between raters (parents/teacher). The SRS covers the dimensions of communication and behavior characteristic to ASD and quantifies autistic traits providing a total score representing the level of autistic impairment, as well as subscale scores for specific symptom domains: 1) social awareness, 2) social cognition, 3) social communication, 4) social motivation, and 5) restricted and repetitive behavior.

The SRS has been shown to differentiate children with ASD from those with other child psychiatric conditions (e.g., Attention Deficit Hyperactivity Disorder [ADHD]), conduct disorder, mood disorder), as well as from typically developing children (Bölte et al., 2008; Charman et al., 2007; Constantino and Gruber, 2005; 2012; Kamio et al., 2012; Reiersen, Constantino, Volk and Todd, 2007). However, it has also been found that non-ASD specific behavioral problems and psychiatric symptomatology can affect the scores (Hus, Bishop, Gotham, Huerta and Lord, 2013). Studies on the relationship of cognitive level and SRS scores have yielded inconsistent results. According to Constantino et al. (2000; 2003; 2007), SRS scores have been independent from FSIQ in children without ASD, and either inversely correlated or unrelated to FSIQ in ASD samples (FSIQ range 50-140). Kamio et al., (2012) found that SRS scores did not correlate with FSIQ in their sample of children with FSIQ at or above 70, but a subgroup with mental retardation tended to score higher on the SRS, and Hus et al. (2013) concluded that among children with ASD, lower cognitive lever was associated with higher SRS total scores. The SRS was recently updated to SRS-2, and there is now also a version available for preschool children (Constantino and Gruber, 2012). The psychometric properties of the SRS have been reported to be excellent (Constantino et al., 2000; Constantino and Todd, 2000; 2003; Constantino and Gruber, 2005; 2012; Murray, Mayes and Smith, 2011).

3 Aims of the study

The main aims of the present study were:

1. to validate the Finnish ASSQ and to determine the optimal cut-off score for screening in clinical settings among primary school-aged children with normal cognitive level or mild intellectual disability (Study I)
2. to evaluate the clinical utility of the Finnish SRS by examining the psychometric properties of the instrument in samples of elementary school-aged males with normal cognitive capacity with and without ASD (Study II)
3. to investigate whether autistic traits as a broader, subclinical phenotype aggregate in simplex ASD families, in which the child with ASD has an FSIQ at the normal level (Study III)
4. to estimate the prevalence of SA in a general total child population and in an ASD child sample, and to investigate whether SA is an indicator for an elevated risk for ASD (Study IV)

4 Subjects and methods

4.1 Procedure and participants

Prior to data collection, the study was approved by the Ethics Committee of the Faculty of Medicine, University of Oulu, and the Ethics Committee of the Northern Ostrobothnia Hospital District (NOHD). Data collection was conducted during the years 2000–2003 in the NOHD area. Individual participants and participating families were recruited from two large, partially overlapping studies: an epidemiological study (Mattila et al., 2007), and a molecular-genetic clinical study (Weiss et al., 2009). In sub-studies I and IV, the participants were recruited from the epidemiological study. In sub-studies II and III, the participants were recruited from the clinical study.

4.1.1 Epidemiological sample (n = 4 408) (Studies I, IV)

The target population of the epidemiological study included all 8-year-old children born in 1992 and living in the NOHD area during autumn 2000 (n = 5 484). The sample was recruited through schools. No exclusion criteria were used in the invitation phase. Approval was obtained from the school inspector and the chiefs of education of 43 municipalities. Principals of 329 schools were informed about the study and permission to gather data was requested.

Of 329 schools, 321 agreed to participate (5 319 children). Of these, nine schools had no pupils born in 1992, and eight schools did not return the study material. Finally, 304 schools with 5 242 children participated. The teachers of these children were given an informative lecture, after which the research material was given to them to be handed out to parents. The research material included an information sheet about the study, a written informant consent sheet, the ASSQ and a developmental questionnaire, in which SAs were inquired about. Parents of 4 424 children gave written informed consent to participate. However, two of those children did not return the parent or the teacher ASSQ ratings and were thus left out from the study group. Of the remaining 4 422 children, eight children were reported to have severe mental retardation, i.e., an FSIQ below 50. Of the 4 414 children with a reported FSIQ ≥ 50, the ones meeting selected cut-offs in the ASSQ (cut-offs selected on the basis of prior Swedish publications; high-risk n = 73, and medium-risk n = 52 [Ehlers et al., 1999; Kadesjö, Gillberg and

Hagberg, 1999]) were invited to the hospital for diagnostic (ADI-R and ADOS) and neurocognitive evaluations (WISC-III) (n = 125). Of the 125 children, 110 participated, and of these, six children turned out to have severe mental retardation (an FSIQ below 50) or disabilities so severe that they could not be included in the study sample. Finally, the high/medium risk group ended up consisting of 104 children, while the total population sample consisted of 4 408 children.

The hospital records of children in the high/medium risk group were checked. In addition, school day observations of 24 children were performed. Based on all gathered information, the diagnoses were then defined in detail according to DSM-IV (APA 1994) criteria (ASD n = 26). Two screened children had a clinically set diagnosis of ASD and did not participate in the diagnostic evaluations of our study, but returned the ASSQ and the developmental questionnaire filled by the parents. Thus, the ASD sample ended up consisting of 28 children.

Of the children with complete information about their sensory processing from the developmental questionnaire (4 397 children; 2 167 boys, 2 230 girls), 3 565 returned the parental ASSQ, 4 382 the teacher ASSQ, and 3 532 returned both ASSQ ratings.

4.1.2 Clinical sample (n = 44) (Studies II, III)

When collecting the clinical sample, the target population included all elementary school aged (7- to 16-year-old) children who were

1. outpatients diagnosed with ASD at the Oulu University Hospital,
2. had an FSIQ in the normal range, and
3. carried no additionally diagnosed speech or language disorders, hearing impairments or Fragile X syndrome.

Sixty children were invited to participate. When running a search in the hospital records, it became evident that the number of girls in our target population was so modest that any statistical analysis would not yield reliable/generalizable results, and we decided to include only boys in the analyses (57 boys). Invitation letters including a preliminary fact sheet about the study protocol and objectives were sent to the parents of the children. A time for a confirmatory phone call was also set in each letter. During the phone call, the families had the possibility to ask questions about the study, and they were also asked whether they had concerns

about their other children having ASD. Those siblings of ASD children were accepted to the proband group at this point as well. After the confirmatory phone calls, the proband group consisted of 59 children. The SRS and ASSQ questionnaires were sent to the parents of families willing to participate, and they were asked to fill out both questionnaires evaluating all their children and the SRS also evaluating each other. For the ASD outpatients, also developmental questionnaires were gathered. Written consent was obtained from parents and from all children over 12 years of age.

The families were then invited to the Oulu University Hospital outpatient clinic where confirmatory diagnostic assessments were performed, with one whole day reserved for every child's evaluation. The diagnoses were then redefined in detail based on all available data (ADI-R, ADOS, information from the patient records) according to the DSM-IV criteria. These diagnostic evaluations were also performed on all siblings of ASD outpatients of whom parents had reported concerns about possible ASD. The SRS ratings with more than 10 % of missing items were discarded from the analyses according to the publisher's recommendation. Finally, the proband group consisted of 44 boys.

4.1.3 Community sample (n = 44) (Studies II, III)

An age-matched control group for the clinical group was recruited from two mainstream elementary schools in Oulu. From each grade (1^{st} to 9^{th}), one class of students was randomly selected and invited to participate in the study with their parents (210 students). Families of 88 students participated (82 families). Controls were screened with the ASSQ (parental evaluation), and those exceeding 7 points were excluded to ensure there would be no ASD children among them (Ehlers et al. 1999). The hospital records were also checked to ensure that none of the control children were ASD outpatients of Oulu University Hospital. Of note, at the time of data collection, Oulu University Hospital was the only facility in the NOHD area where ASD diagnoses were set.

In study II, only the control boys were included in data analysis as we chose to leave the few girls with ASD out of data analysis.

4.1.4 Family samples (Study III)

In the family study of QAT (sub-study III), participants were recruited from the clinical and control samples described above. SRS data was received from 23

brothers and 20 sisters of children with ASD (closest-in-age siblings, parental evaluation) and from 44 fathers and 41 mothers of children with ASD, and 43 fathers and 38 mothers of control children.

4.2 Measures

4.2.1 The Wechsler Intelligence Scale for Children–Third Edition

The Wechsler Intelligence Scale for Children–Third Edition (WISC-III; Wechsler, 1991) is a performance scale designed for children from 6 to 16 years. It consists of verbal and visual performance subtests. Verbal subtests include

1. Information (factual knowledge, long-term memory, recall),
2. Similarities (abstract reasoning, verbal categories and concepts),
3. Arithmetic (attention and concentration, numerical reasoning),
4. Vocabulary (language development, word knowledge, verbal fluency),
5. Comprehension (social and practical judgment, common sense), and
6. Digit Span (short-term auditory memory, concentration).

The visual performance subtests include

1. Picture Completion (alertness to detail, visual discrimination),
2. Coding (visual-motor coordination, speed, concentration),
3. Picture Arrangement (planning, logical thinking, social knowledge),
4. Block Design (spatial analysis, abstract visual problem-solving),
5. Object Assembly (visual analysis and construction of objects),
6. Symbol Search (visual-motor quickness, concentration, persistence), and
7. Mazes (fine motor coordination, planning, following directions).

The WISC-III was administered to the "high-risk" sample of the epidemiological group (n = 110).

4.2.2 The Autism Spectrum Screening Questionnaire

The Autism Spectrum Screening Questionnaire (ASSQ; Ehlers, Gillberg and Wing, 1999) is a 27-item informant-based rating scale yielding a total continuous score ranging from 0 to 54, designed to screen ASD in higher-functioning (normal intelligence or mild mental retardation) children aged 7–16 years. It consists of 27 items, of which 11 regard impairment of social interaction, 6 communication

problems, 5 restricted and repetitive behavior, and 5 motor clumsiness, motor and vocal tics and other ASD related symptoms. An unofficial version of the ASSQ has been used in clinical settings in Finland for many years. In the beginning of this study, an official version was completed. The ASSQ was first translated from Swedish into Finnish by two clinical psychologists, then back-translated into Swedish by an official Swedish-Finnish translator, and after comparison of the original Swedish and the back-translated Swedish forms, the final Finnish version was completed. The ASSQ was collected from the epidemiological sample (parental and teacher evaluation), from ASD cases (parental evaluation), as well as from the controls in the clinical study (parental evaluation).

4.2.3 The Social Responsiveness Scale

The Social Responsiveness Scale (SRS; Constantino and Gruber, 2005; 2012) is an informant-based internationally widely used 65-item quantitative measure of autistic traits that yields a total continuous score (raw score range 0–195) that can be interpreted as a level of QAT, and also provides subscales representing different aspects of RSB: perception (Social Awareness; 8 items, raw score range 0–24), information processing (Social Cognition), capacity for reciprocal social responses (Social Communication), social anxiety/avoidance (Social Motivation), and characteristic autistic preoccupations (Restricted Interests and Repetitive Behavior). In the beginning of this study at 2003, the school-aged and adult versions of the SRS were translated from English into Finnish by two clinical psychologists, and back-translated into English by an official translator. Subsequently, the English versions were compared for inconsistencies by a native English-language speaking clinical psychologist. In addition, we discussed the English back-translation with the developers of the measure who evaluated and approved it (Constantino, 2003, personal contact). The SRS was collected from the ASD cases, their siblings and parents, and the control children and their parents.

4.2.4 The Autism Diagnostic Interview–Revised

The Autism Diagnostic Interview – Revised (ADI-R; Lord, Rutter and LeCouteur, 1995) is a standardized investigator-based, semi-structured parental interview developed to elicit a full range of the information needed when evaluating the diagnostic criteria of autism and related ASD. It covers the main symptom areas

associated with ASD: reciprocal social interaction, communication, and restricted and stereotyped behavior and interests.

4.2.5 The Autism Diagnostic Observation Schedule

The Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore and Risi, 2000) is a semi-structured assessment of social interaction, communication, and play or imaginative use of materials. It comprises four modules based on the verbal level of the subject being evaluated.

The ADI-R (Hogrefe Psykologisk Forlag, 2009) and ADOS-2 (Hogrefe Psykologisk Forlag, 2014) were translated from English into Finnish by a group of professionals in the field of ASD and then back-translated into English by an official English translator. After comparison, the final Finnish version was completed by a group of professionals, all of whom were extensively trained in the use of the ADI-R and ADOS.

Both the ADI-R and ADOS use diagnostic algorithms based on separate thresholds for ASD symptom domains (DSM-IV). Domain scores are sums of codings that indicate the severity of impairment based on symptom frequency and degree of interference with daily living (Lord et al., 2001). The diagnostic evaluations were administered to the "high-risk" group from the epidemiological sample and to all clinically diagnosed ASD cases in the clinical sample, as well as to the siblings their parents had concerns about.

4.2.6 The developmental questionnaire

At the time of this study, there were no standardized or even official Finnish translations of measures evaluating SAs. Thus, we developed a 14-item parental questionnaire that was used to gather information about the participants' early development and familial background, and also assessed sensory hyper- and hyposensitivity as follows: (1) "Does the child have sensory hypersensitivity in the area of one or more sensory modalities: auditory, olfactory, gustatory, tactile or visual?" (answer options no/yes), and (2) "Does the child have sensory hyposensitivity in the area of one or more sensory modalities: auditory, olfactory, gustatory, tactile or visual?" (answer options no/yes). Below the above-mentioned questions, the sensory modalities were listed individually and in case of the answer "yes" to either one of the above-mentioned questions, the parents were asked to check the modalities their child had abnormality in. In data analysis,

these variables acquired were thus dichotomous. The developmental questionnaire was collected from all children in the epidemiological sample.

4.2.7 Patient records

Early development was checked from the patient records of the University Hospital of Oulu for all individuals diagnosed with ASD in this study and also for screened subjects if verification was considered necessary after the ADI-R interviews. We also searched for all target-aged children with ASD from the patient records of Oulu University Hospital (Weiss et al., 2009). Note that at the time of the screening and diagnostics, all children with a suspected ASD in the NOHD area were referred to Oulu University Hospital for diagnostic evaluation. Thus, via the search conducted in the patient records, we could check if all registered ASD patients born in 1992 were identified in our screening, and the validity of the ASSQ in the total population sample could be assessed.

4.3 Statistical Methods

Analyses were performed with the Statistical Package for Social Sciences; SPSS for Windows, rel. 17.0. 2008 (Chicago; SPSS Inc.).

In sub-studies II and III, the expectation maximization (EM) algorithm imputation method was used for missing SRS data replacement, in cases where < 10 % of the SRS items was missing. Cases not meeting the publisher requirements for scoring of the SRS (more than 10 % missing items) were excluded, and only families with complete SRS forms from at least two family members (including the child with ASD/the control child) were used in the analyses.

In sub-studies I and II, Receiver Operating Characteristics (ROC) analysis was used to determine discriminant validity of the ASSQ and the SRS.

In sub-study II, parametric tests were used to study discriminative validity of the Finnish SRS (Student's t-test), and also to evaluate convergent validity SRS-ASSQ; Pearson's correlation coefficient). Reliability was assessed by calculating internal consistency (Cronbach's α).

To correct for skewed data regarding the SRS outcome measures in groups of ASD siblings and parents in sub-study III, non-parametric tests (Mann Whitney U-test and Spearman correlation coefficient) were employed to examine group differences and family level correlations.

To investigate how SAs were associated with an elevated risk of ASD (sub-study IV), a series of logistic regression analyses was used as a risk analysis.

Since the ASSQ scores in the epidemiological sample were not normally distributed, the non-parametric Mann-Whitney and Kruskal-Wallis tests for two or three independent samples were used to investigate the association between SAs and QAT. Eta square values were also calculated to determine, how many percent of the variation in the ASSQ scores were explained by a specific SA

Principal component analysis (PCA) with varimax rotation was used to evaluate, whether the SAs are associated with certain ASSQ subscale/s. PCA uses an orthogonal transformation to convert a set of observations of possibly correlated variables into a set of values of linearly uncorrelated variables (principal components).

5 Results

5.1 Screening with the Finnish Autism Spectrum Screening Questionnaire (Study I)

Discriminant validity of the ASSQ was assessed in the total population sample (n = 4 408) and in the high/medium risk sample (n = 104). The ROC was run separately using the ASSQ ratings of 1) parents and teachers, 2) the higher scores of parent/teacher ratings, as well as 3) the summed score of parents' and teachers' ratings. In the High/Medium risk sample (n = 104), the summed ASSQ scores of parents' and teacher's ratings showed the best discriminating ability between children with and without ASD (Area under the curve; AUC = 0.92, 95 % Confidence Interval; CI = 0.87–0.97). A summed score of 30 indicated the best balance between sensitivity (Sn) (89 %) and specificity (Sp) (82 %). Also, in the total population sample (n = 4 408), the summed ASSQ scores of parents' and teacher's ratings showed the best discriminating ability between cases with and without ASD (AUC = 0.998, 95 % CI = 0.997–0.999). A summed cut-off score of 28 was associated with a Sn of 100 % and Sp of 99 %.

5.2 Evaluation of the Finnish Social Responsiveness Scale (Study II)

Reliability of the Finnish SRS was assessed by estimating internal consistency in the total sample (n = 88). Internal consistency for the SRS total scale was $\alpha = 0.98$. Cronbach's alphas for the subscales were as follows: Social Awareness $\alpha = 0.76$, Social Cognition $\alpha = 0.91$, Social Communication $\alpha = 0.94$, Social Motivation $\alpha = 0.83$, and Restricted Interests and Repetitive Behavior $\alpha = 0.93$.

Convergent validity was established by examining correlations between the parent rated SRS total raw score and the parental ASSQ total score in the ASD and control groups. The correlation between the SRS and ASSQ total scores was 0.65 in the ASD group ($p < 0.0001$), and 0.78 in the control group ($p < 0.0001$).

The SRS demonstrated excellent ability to differentiate participants with ASD from control participants (AUC = 0.981, *SE* = 0.015, $p < 0.0001$, 95 % IC = 0.97 to 1.00). The best combination of Sn and Sp was found at a raw score of 46, which was associated with a Sn of 1.0 and Sp of 0.96, screening all outpatients with confirmed diagnoses and two control children (false positive rate 4.5 %).

The original published raw cut-off score of 75 for primary screening on the SRS manual was associated with a Sn of 0.71 and Sp of 0.98 for an ASD diagnosis in our sample (false negative rate 29.5 %).The SRS differentiated the ASD group from the control group on the total raw score as well as on all subscale scores statistically significantly. More precisely, the ASD group scored statistically significantly higher on all subscales. The results are presented in Table 1.

Table 1. Group differences on the ASSQ and the SRS total raw score (parental evaluations).

Group	ASD[3] group n = 44 M[4] ± (sd[5])	Control group N = 44 M ± (sd)
ASSQ[1]	26.6 (7.3)	2.9 (5.8)
SRS[2] Total	89.9 (21.2)	23.0 (17.3)
Social Awareness	10.6 (4.0)	4.7 (2.8)
Social Cognition	17.7 (6.4)	4.5 (3.8)
Social Communication	29.7 (8.2)	7.5 (6.2)
Social Motivation	13.4 (5.0)	4.2 (3.1)
Restricted Interests and Repetitive Behavior	18.5 (5.4)	2.1 (3.5)

[1] Autism Spectrum Screening Questionnaire, [2] Social Responsiveness Scale, [3] Autism Spectrum Disorder, [4] mean, [5] standard deviation.

- Student's t-test, ASD > control group, $p < 0.0001$ for all; sig. 2-tailed

5.3 Quantitative autism trait aggregation in first-degree relatives of children with autism spectrum disorder (Study III)

5.3.1 Within groups differences in quantitative autism traits (SRS total score)

Among children, gender differences in the SRS scores were found only in the group of siblings of children with ASD, but not in the groups of controls or probands with ASD. In the sibling group, brothers of children with ASD had higher SRS total scores than the sisters of children with ASD (23.9 ± 23.2 vs. 12.2 ± 8.0, $p = 0.032$). Brothers also had higher scores (than the sisters) on the subscales Social Cognition (4.3 ± 4.9 vs. 2.0 ± 1.3, $p = 0.042$), and Social Motivation (5.5 ± 4.3 vs. 2.9 ± 2.7, $p = 0.021$).

Among adults, fathers of children with ASD had higher SRS total raw scores than the mothers of children with ASD (38.2 ± 29.6 vs. 24.1 ± 21.7, $p = 0.014$).

Fathers also had higher scores on the subscales Social Awareness (5.2 ± 4.2 vs. 3.6 ± 3.0, $p = 0.041$), Social Communication (13.0 ± 10.8 vs. 6.0 ± 7.6, $p = 0.001$), and Restricted Interests and Repetitive Behavior (6.2 ± 6.7 vs. 3.7 ± 4.3, $p = 0.048$. In the control parents group, no gender differences were found.

5.3.2 Between groups differences in quantitative autism traits (SRS total score)

The brothers of the children with ASD scored statistically significantly higher on the Social Motivation subscale when compared to control boys (5.5 ± 4.3 vs. 3.1 ± 2.1, $p = 0.014$). Furthermore, although not statistically significant, the brothers of individuals with ASD had higher SRS Total Scores than did control boys (23.9 ± 23.2 vs. 17.1 ± 8.9), with a mean difference of 6.8 and an effect size of 1.7 (very large). The sisters of ASD probands and control children did not differ on the scales. See Table 2.

Table 2. SRS raw scores of unaffected siblings of ASD children and control children by gender.

SRS[1] Total and Subscale Scores	ASD[2] brothers n = 23	Control boys n = 26	ASD sisters n = 20	Control girls n = 25
	M[3] ± (sd[4])	M ± (sd)	M ± (sd)	M ± (sd)
SRS Total Score	23.9 (23.2)	17.1 (8.9)	12.2 (8.0)	18.1 (12.1)
Social Awareness	3.9 (3.3)	4.9 (1.9)	2.5 (1.7)	3.8 (2.1)
Social Cognition	4.3 (4.9)	3.4 (2.5)	2.0 (1.3)	3.2 (1.8)
Social Communication	7.7 (8.5)	5.6 (3.7)	4.0 (3.3)	5.9 (5.2)
Social Motivation	5.5 (4.3)	3.1 (2.1)	2.9 (2.7)	4.0 (3.2)
Restricted Interests and Repetitive Behavior	2.5 (4.3)	1.0 (1.2)	0.9 (1.3)	1.2 (1.7)

[1] Social Responsiveness Scale, [2] Autism Spectrum Disorder, [3] mean, [4] standard deviation

Mann-Whitney U-test.

- Brothers of children with ASD > Sisters of children with ASD for SRS Total Score, Social Cognition, and Social Motivation, $p < 0.05$ (sig. 2-tailed);
- Brothers of Children with ASD > Control boys for Social Motivation, $p < 0.05$ (sig. 2-tailed);
- Sisters of Children with ASD < Control Girls for Social Awareness and Social Cognition, $p < 0.05$ (sig. 2-tailed)

Among the parent groups, the total SRS scores of the fathers of children with ASD were significantly higher when compared to the fathers of control children, and similar differences were also noted on all subscales: SRS total score

38.2 ± 29.6 vs. 19.0 ± 13.4, $p < 0.001$; Social Awareness 5.2 ± 4.2 vs. 3.5 ± 2.2, $p = 0.019$; Social Cognition 7.2 ± 6.2 vs. 3.2 ± 2.8, $p = 0.001$; Social Communication 13.0 ± 10.8 vs. 6.5 ± 5.4, $p < 0.001$; Social Motivation 6.6 ± 5.3 vs. 4.2 ± 3.8, $p < 0.001$; Restricted Interests and Repetitive Behavior 6.2 ± 6.7 vs. 1.7 ± 1.6, $p < 0.001$. The mother groups did not differ on the scales.

5.3.3 Familial associations of quantitative autism traits

When investigating the familiality of QAT, statistically significant positive correlations emerged between the SRS scores of children and their parents in all child groups, although these correlations were moderate. Partial correlation coefficients between child-parent SRS scores are presented in Table 3. The SRS scale scores of boys with ASD and their brothers were statistically significantly associated in the subscale Restricted Interests and Repetitive Behavior ($n = 29$ brother pairs, $r = 0.39$, $p = 0.039$). No associations were found between the scores of the few ASD girls in our sample and their sisters.

Table 3. Spearman correlation coefficients between child-parent SRS scores.

SRS[3] score	ASD[4] proband[5]	ASD sibling[6]	control child[7]
SRS total			
father	0.55[2]	0.39[1]	0.43[2]
mother	0.17	0.42[1]	0.54[2]
Social Awareness			
father	0.59[2]	0.39[1]	0.43[2]
mother	-0.03	0.26	0.61[2]
Social Cognition			
father	0.59[2]	0.44[1]	0.35[1]
mother	0.12	0.46[1]	0.31[1]
Social Communication			
father	0.53[1]	0.33	0.40[1]
mother	0.23	0.43[1]	0.50[2]
Social Motivation			
father	0.20	0.22	0.17
mother	0.06	0.30	0.39[1]
Restricted Interests and Repetitive Behavior			
father	0.51[1]	0.40[1]	0.20
mother	0.07	0.29	0.39[1]

[1] $p < 0.05$ (2-tailed), [2] $p < 0.01$ (2-tailed), [3] Social Responsiveness Scale, [4] Autism Spectrum Disorder, [5] ASD probands n = 49 child-father pairs, 48 child-mother pairs, [6] Siblings of ASD probands n = 32 child-father pairs, 32 child-mother pairs, [7] Control families n = 47 child-father pairs, 44 child-mother pairs

Linear regression revealed that father SRS scores significantly predicted child SRS scores, and also explained the variance in the child scores in all child groups (children with ASD ß = 0.43, $t(46) = 3.30$, $R^2 = 0.19$, $F(1, 47) = 10.90$, $p = 0.002$; control children ß = 0.43, $t(44) = 3.20$, $R^2 = 0.18$, $F(1, 45) = 10.00$, $p = 0.003$, and siblings of ASD children ß = 0.37, $t(29) = 2.18$, $R^2 = 0.14$, $F(1, 30) = 4.75$, $p = 0.037$). Mother scores did not have statistically significant effect on child scores in the group of ASD children, but predicted child scores in the groups of control children (ß = 0.51, $t(41) = 3.83$, $R^2 = 0.26$, $F(1, 42) = 14.70$, $p < 0.001$) and siblings of ASD children ß = 0.44, $t(29) = 2.66$, $R^2 = 0.19$, $F(1, 30) = 7.06$, $p = 0.013$). Child gender and age did not predict child scores, nor did they statistically significantly explain the variance in scores.

5.4 Association between sensory abnormalities and quantitative autism traits (Study IV)

5.4.1 Prevalence of sensory abnormalities in total general population, autism spectrum disorder and non-autism spectrum disorder samples

Of the 4 397 children with sufficient data regarding sensory perception, 8.3 % (n = 364; 206 males and 158 females) were reported to have some form of sensory-perceptual abnormality. Among the children with ASD (n = 28), the prevalence of SA was 53.6 %, (n = 15, 11 males, 4 females), and among the non-ASD children, 8.0 % (n = 349; 195 males, 154 females) (Table 4).

5.4.2 Sensory abnormality as a risk factor for autism spectrum disorder

A series of logistic regression analyses revealed that the presence of any form of SA indicated a 13-fold risk for ASD diagnosis (OR = 13.3, $p < 0.001$). When analyzing the effect of individual SAs, tactile hypersensitivity raised the risk to 34-fold (OR = 33.7, $p < 0.001$), and auditory/olfactory hypersensitivity to 22-fold (OR = 22.0, $p < 0.001$).

Table 4. Prevalence (percentage) of sensory abnormalities (parental report).

Group	ASD group n = 28 %	males n = 17 %	females n = 11 %	non-ASD group n = 4 369 %	males n = 2 150 %	females n = 2 219 %
Any sensory-perceptual abnormality	53.6	64.7	36.4	8.0	9.1	6.9
Hypersensitivity						
Auditory	42.9	47.1	36.4	3.3	4.1	2.5
Visual	0.0	0.0	0.0	0.4	0.4	0.3
Tactile	17.9	23.5	9.1	0.6	0.8	0.5
Gustatory	7.1	11.8	0.0	0.9	1.2	0.7
Olfactory	25.0	29.4	18.2	1.5	1.7	1.3
Hyposensitivity						
Auditory	0.0	0.0	0.0	1.4	1.7	1.0
Visual	0.0	0.0	0.0	1.4	1.3	1.4
Tactile	0.0	0.0	0.0	0.1	0.1	0.1
Gustatory	0.0	0.0	0.0	0.0	0.0	0.0
Olfactory	0.0	0.0	0.0	0.1	0.0	0.1

5.4.3 Association of sensory abnormalities with quantitative autism traits (summed Autism Spectrum Screening Questionnaire total score)

The ASSQ (summed parents' and teacher's score) was able to differentiate the sample of children with SA (n = 296) from those without (n = 3 236) statistically significantly: $M = 9.4 \pm 12.4$ vs. 3.1 ± 5.2, $p < 0.001$).

When evaluating specific SAs within the child samples, it was found that among children with ASD, the ASSQ differentiated statistically significantly only the samples with and without auditory hypersensitivity (children with auditory hypersensitivity having higher ASSQ outcome measures than those without). **A**uditory hypersensitivity explained 28 % of the variance in the ASSQ scores among the ASD sample ($M = 48.8$, sd = 10.8 vs. $M = 37.8$, sd = 7.7, $p = 0.003$, $\eta 2 = 0.28$), whereas in the non-ASD sample, children with hypersensitivity in any sensory modality or hyposensitivity of auditory, tactile or visual perception had statistically significantly higher ASSQ total scores than children without. See Table 5 for more specific ASSQ outcome score differences between the child samples.

Table 5. Group differences of summed total ASSQ[1] scores in child groups.

Group		ASD[2] n = 28					non-ASD n = 3 506				
		N	M[4]	sd[5]	md[6]	p/ŋ²[3]	N	M	sd	md	p/ŋ²
Any sensory abnormality	no	13	37.4	7.8	36	0.017	3 223	2.9	4.8	1	< 0.001
	yes	15	46.9	10.8	49	0.2015	283	7.4	8.7	4	0.0374
Auditory hypersensitivity	no	16	37.8	7.7	36	0.003	3 386	3.1	5	1	< 0.001
	yes	12	48.8	10.8	52	0.2824	120	9.1	9.9	5.5	0.0256
Olfactory hypersensitivity	no	21	40.9	10.2	38	0.192	3 451	3.3	5.3	1	< 0.001
	yes	7	47.3	10.7	49	0.063	55	5.6	6.6	3	0.0042
Gustatory hypersensitivity	no	26	42.6	10.7	40	0.737	3 472	3.3	5.3	1	< 0.001
	yes	2	41	11.3	41	0.0046	34	8.2	9.5	4.5	0.0059
Tactile hypersensitivity	no	23	41.5	10.3	39	0.351	3 484	3.3	5.2	1	< 0.001
	yes	5	47	11.7	49	0.033	22	12.7	13.1	6	0.0071
Visual hypersensitivity	no	28	42.5	10.5	40	-	3 492	3.3	5.3	1	0.004
	yes	0				-	14	10.5	10.6	9.5	0.0022
Auditory hyposensitivity	no	28	42.5	10.5	40	-	3 463	3.2	5.2	1	<0.001
	yes	0				-	43	8.1	9.6	4	0.0045
Olfactory hyposensitivity	no	28	42.5	10.5	40	-	3 504	3.3	5.3	1	0.213
	yes	0				-	2	4.5	2.1	4.5	0.0005
Gustatory hyposensitivity	no	28	42.5	10.5	40	-	3 505	3.31	5.3	1	0.508
	yes	0				-	1	0	0	0	0.0004
Tactile hyposensitivity	no	28	42.5	10.5	40	-	3 503	3.3	5.3	1	0.001
	yes	0				-	3	21	14.2	26	0.002
Visual hyposensitivity	no	28	42.5	10.5	40	-	3 455	3.3	5.3	1	<0.001
	yes	0				-	51	6.5	7.7	3	0.0045

[1] Autism Spectrum Screening Questionnaire, [2] Autism Spectrum Disorder, [3] effect size (small > 0.01, moderate > 0.06, large > 0.14), [4] mean, [5] standard deviation, [6] median

The principal component analysis showed that the SAs were not related to any of the previously suggested ASSQ subscales (personal communication with Professor Cristopher Gillberg), but formed a distinct factor.

6 Discussion

6.1 Importing quantitative autism spectrum screening instruments to Finland for clinical use (Studies I and II)

Autism spectrum disorder is a spectrum disorder that manifests at different severity levels. Thus it is essential to use quantitative screening measures when assessing autistic traits. When we initiated our study, there was an obvious lack of Finnish screening and diagnostic instruments for ASD, and we imported two quantitative instruments, the ASSQ and SRS, for the present thesis. We completed the official translations into Finnish, determined the cut-off score for the Finnish ASSQ, and evaluated the usability of the Finnish SRS.

In clinical settings among Finnish primary school-aged children (7 to 12 years old, FSIQ ≥ 50), the optimal cut-off score with high Sn and Sp in the ASSQ was at the summed parents' and teacher's score of 30. Low agreement between informants regarding children's autistic features has previously been shown (Mattila et al., 2009; Posserud et al., 2006; Posserud, Lundervold and Gillberg, 2009; Szatmari, Archer, Fisman and Streiner, 1994). Compared with home, school requires more social and communication interchange, which is one of the defining symptom domains in ASD. Therefore, low agreement between parents' and teachers' assessments is partly explained by real differences in children's behavior at home and at school. Our own clinical experience also confirmed the low agreement between raters, and we sought to establish an alternative and more effective method to give points in order to screen cases with ASD by using the ASSQ. Thus, we combined information from school and home by using summed ASSQ scores of parents' and teachers' ratings. We tried out different scoring methods, and the ROC analysis showed that the summed scores of parents' and teachers' ratings worked best, yielding an optimal cut-off score with high sensitivity and specificity: a summed score of 30 points.

In the Norwegian Bergen Child Study, an optimal cut-off score of 17 with a Sn of 91 % and Sp of 86 % was indicated in a total population sample when using the higher of either parent-rated or teacher-rated ASSQ scores (Posserud et al., 2009). We tested the "Norwegian model" with a high validity at a cut-off score of 19 in our total population validation sample, but we achieved even higher validity using our "summed score model" with the cut-off score of 28.

Our high-/medium-risk sample can be considered comparable to a child-psychiatric clinical sample and our results are therefore more comparable with clinical studies conducted in Sweden (Ehlers et al., 1999) and in China (Guo et al., 2011). However, our summed score of 30 differs from the Swedish and Mandarin Chinese recommendations. In the Swedish study, a parent-rated ASSQ cut-off score of 19 and a teacher-rated ASSQ cut-off score of 22 were suggested for clinical settings (Ehlers et al., 1999). In the Chinese study, only parental ratings were collected and a cut-off score of 12 was recommended (Guo et al., 2011).

The various ASSQ cut-off scores could be partly explained by different samples and methods (e.g., clinic- vs. population-based, parent- and teacher-rated vs. parent-rated), but the variation also shows the importance of estimating valid cut-off scores when importing screening questionnaires from other languages and cultures. In addition, translations may end up differing from each other in some aspects even though the importing protocol is carefully followed (translation, back-translation and comparison of the versions).

Concerning the screening instruments, we also evaluated the Finnish version of the parent-rated SRS by determining its psychometric properties in the samples of school-aged high-functioning males with and without ASD. Our results indicate that the Finnish SRS is able to differentiate boys with ASD from community controls, and its internal consistency is high, in line with previous international research on the measure. The same holds true for convergent validity and the AUC of the ROC analysis (.98) (Constantino and Gruber, 2012). In our sample, a cut-off score of 46 showed the best combination of Sn and Sp. A cut-off score of 46 is considerably lower than the original raw cut-off score for screening reported in the SRS manual (Constantino and Gruber, 2005), and also lower than the cut-off scores derived from German and Mexican validation studies (Bölte et al., 2008, 2011; Fombonne, Marcin, Bruno, Tinoco, & Marquez, 2012), but, however, closer to the suggested cut-off for primary screening in Japan and Netherlands (Kamio et al., 2012; Roeyers, Thys, Druart, De Schryver and Schittekatte, 2011).

In screening measures for diagnostically challenging disorders, such as the ASD, a high Sn is desirable, and may arguably be a more important feature than high Sp, since their principal role is to correctly identify the greatest number of cases possibly meeting diagnostic criteria. After a case is identified in the screening phase, more specific, structured clinical examinations based on multi-informant sources need to be carried out in order to achieve high Sp for a

diagnosis. The few clinical examinations of miss-screened cases without ASD would still benefit from thorough neuropsychiatric/psychiatric examinations.

The SRS total raw mean score in our ASD sample ($M = 89.9$) was lower than in the original SRS validation studies conducted in the US ($M = 101.5$ (Constantino and Gruber, 2005), Germany ($M = 102.2$; Bölte et al., 2011), and Mexico ($M = 102.2$; Fombonne et al., 2012), but again, however, closer to the mean scores in Japan ($M = 87.3$; Kamio et al., 2012) and Netherlands ($M = 88.8$; Roeyers et al., 2011). In the SRS manual, studies using the SRS are reviewed (Constantino & Gruber, 2012, pp. 64), and group means for mixed ASD diagnostic groups vary between 85–101.5 total (raw) score. The SRS total mean scores in our community sample ($M = 23.0$) were also lower than the mean scores of typically developing children in the US ($M = 33.7$ for boys; Constantino and Gruber, 2005), but closer, however, to the mean scores in Japan ($M = 27.4$ for boys; Kamio et al., 2012), Germany ($M = 26.0$ for boys; Bölte et al., 2011). The lower mean scores of our ASD sample might be explained by the cognitive characteristics of our sample (normal intelligence). There is, however, evidence that the SRS scores are independent of intelligence quotient (IQ) in ASD children with normal intelligence (Kamio et al., 2012). Since our ASD participants were all outpatients of Oulu University Hospital, they all had some kind of rehabilitation ongoing (in most cases, occupational therapy), which may also explain the slight difference in scores between our sample and the clinical samples in other studies.

The differences of our results on the ASSQ and SRS compared to those from other countries might also reflect cross-cultural differences in what is considered normative or socially accepted behavior, and cultural values in social development. For example, cross-cultural differences in parental goals are likely to account for differences in the way parents assess their children. Lebra (1994) stated that American children are raised to be autonomous, independent, assertive and successful, which may lead to higher levels of extraversion, whereas Carbaugh (2005) reported that parents of Finnish children tend to promote patience, thoughtful speech, and proper reservation. Thus, it is possible that child characteristics assessed by, for example, the subscale Social Motivation of the SRS (clings to adults, does not join group activities, avoids starting social interactions, is tense in social settings etc.) are not viewed as problematic by parents of a Finnish child as by parents of an American child.

Interpretations of the items and answer options in different cultures may also explain cross-cultural differences in group means and suggested cut-offs. Finnish

and East Asian parents may tend to use milder expressions (e.g., "often true" instead of "almost always true") in their answers than, for example, American or Australian parents (Chen, Lee and Stevenson, 1995; Kamio et al., 2012). In cultural communication studies, cultures are divided into low and high context cultures, depending on a culture's communication style, that is, the culture's tendency to use high context messages/low context messages in routine communication. In low context cultures, communication is explicit, and a lot of words are used. In high context cultures, communication tends to be more implicit, formal, and fewer words are used. It appears that the Finnish culture belongs to the latter one in contrast to many other Western cultures (Jokinen & Wilcock, 2006). This may have a link to the findings of the SRS and ASSQ studies. For the Finnish version, the ASSQ rating expression of two points was toned down to "fits" instead of the original "fits definitely" used in the Swedish version, because Finnish parents prefer milder expressions regarding their child's behavior. The Finnish expression "fits" was also considered analogous to the English ASSQ rating expression of two points ("yes").

Our results indicate that the Finnish version of the ASSQ is a valid screening measure for ASD when using the summed score of parent and teacher ratings. The Finnish SRS should be validated in a larger sample including a female ASD sample, and also non-ASD clinical samples, and Finnish norms for both males and females should be determined before using it as a screener. Until then, the SRS is useful in acquiring a more detailed description of a child's problems in reciprocal social behavior ability and it is recommended to be used in designing therapeutic interventions and when evaluating treatment outcome.

6.2 Quantitative autism traits in family members (Study III)

The present study provides important information for clinicians, especially with regard to identifying novel ASD cases, but also with regard to communicating with the parents and siblings of children with ASD. The aggregation of autistic traits in the male family members of children with ASD was shown; more specifically, we found that the fathers and brothers (but not the mothers and sisters) of children with ASD present more autistic traits as measured by the SRS when compared to their control counterparts, and that in ASD families, father (but not mother) trait severity is associated with (proband) child trait severity. Thus, our results suggest that the brothers and sons of individuals with ASD should be screened if showing any signs of atypicality in their social development.

The brothers of children with ASD had significantly higher scores than the group of control brothers on the SRS subscale Social Motivation. In the SRS total score, the mean difference between ASD brothers and control boys was almost statistically significant, and it should be noted that the mean difference of the groups was 6.8 points with a very large effect size, suggesting a clinically meaningful difference. Previous studies have reported sibling trait aggregation in multiplex, but not in simplex families (Constantino et al., 2006; Virkud, Todd, Abbacchi, Zhang, & Constantino, 2009). Our results suggest that these characteristics aggregate in the male family members of children with ASD in simplex families as well.

The fathers of children with ASD showed higher levels of QAT than the brothers of children with ASD. In contrast to other groups in our study, the SRS scores were not normally distributed in these two groups but were shifted towards the subclinical end. Also, the standard deviation of SRS scores in both these groups was high, which suggests that there might have been undiagnosed individuals with ASD in these groups. As for the brothers, this possibility was taken into account in the beginning of the study by asking the parents if they or the school personnel had any concerns about the siblings, and then conducting diagnostic evaluations for all siblings regarding whom concerns were reported.

Interestingly, the sisters of children with ASD in our study sample had significantly lower scores (i.e., higher capacity) than the control girls on the subscales Social Awareness and Social Cognition. The low scores of the sisters of children with ASD might reflect the way parents assess their daughters with no special needs (as compared to a sibling with ASD), or could be due to chance given the small numbers, but it may also reflect a true gender-difference in the pattern of inheritance of QAT, and the ability of typically developing female siblings to adapt to a family system where there is a sibling with special needs.

Gender differences emerged in the parents of children with ASD as well as in the siblings of children with ASD, with males having higher QAT than females in both groups. Overall, these results support the findings that, similar to the gender ratio of the ASD, these subclinical traits assessed by the SRS manifest more frequently, or are more evident, in the male relatives of ASD probands (Constantino et al., 2006; Virkud et al., 2009; Schwichtenberg, Young, Sigman, Hutman, & Ozonoff, 2010).

Control parents did not differ on their SRS scores, and contrary to previous findings by Kamio et al. (2012) in their nationwide study including over 20 000 school-aged children, we found no gender differences in the SRS scores of

control children, which is likely due to our small sample size. The SRS scores were normally distributed in the control groups, which is in line with earlier findings in the general population (Constantino and Gruber 2012).

This study demonstrates that the fathers and brothers of children with ASD may have similar, though less severe, difficulties in the areas of social perception, cognition, communication and motivation as the diagnosed child with ASD. Subclinical autistic traits are associated with anxiety, internalizing problems, mood disorders (Kanne, Christ and Reiersen, 2009; Lundström et al., 2011; Pine, Guyer, Goldwin, Towbin, & Leibenluft, 2008), ADHD symptoms (Lundström et al., 2011; Reiersen, Constantino, Grimmer, Martin and Todd, 2008; Rommelse et al., 2009), conduct problems (Gilmour, Hill, Place and Skuse, 2004; Lundström et al. 2011), behavioral problems (Hoekstra, Bartels, Hudziak, Van Beijsterveldt and Boomsma, 2007; Hus et al., 2013), as well as problems with personal adjustment, lower self-esteem, and less self-reliance (Kanne et al. 2009). Therapists and clinicians should take this into consideration when devising family interventions. The broader autism phenotype is not a diagnostic entity, but especially in situations when there are problems in the interaction between family members, assessing parent/sibling QAT and offering support when needed could be a useful strategy in aiding families with a child with ASD.

6.3 Sensory abnormalities as correlates of autism spectrum disorder and quantitative autism traits (Study IV)

Sensory abnormalities seem to be a strong indicator of ASD traits. Based on our study, the prevalence of sensory-perceptual problems in the ASD sample was dramatically higher than in the general child population, and they are also associated to weaker RSB ability (i.e., higher QAT) among non-ASD children. To our knowledge, our study is the first to estimate the prevalence of SA in an epidemiological child population. We found the prevalence to be 8.3 % in the general population. This is in line with studies regarding sensory processing disorder in child samples, in which the prevalence has varied from 5 % to 13 % (Ahn, Miller, Milberger and McIntosh, 2004). Auditory, olfactory and tactile hypersensitivity were the most common forms of SA recognized by parents among both children with ASD and among non-ASD children in our study. Ben-Sasson, Carter and Briggs-Gowan (2009) estimated the prevalence of sensory over-responsivity to auditory and tactile sensations at 16.5 % among a general elementary-school-aged child population (n = 925). In clinical studies, SAs have

been estimated to affect as many as 69 % to 95 % of children with ASD (Baranek, David, Poe, Stone and Watson, 2006); Tomchek and Dunn, 2007). We found a slightly lower prevalence of 53.6 % among the children with ASD. The difference in results between clinical studies and our epidemiological study is most likely explained by differences in the degree of severity of autistic symptomatology in the child samples. Clinical study participants with ASD usually have more severe symptoms than participants who are screened in epidemiological studies. In our study, SAs were more common among males in children with and without ASD. This finding differs from Ben-Sasson et al., (2009) who found no gender difference in sensory over-reactiveness.

The ASSQ was able to differentiate children with and without SA in the total epidemiological child sample as well as in the non-ASD sample. This indicates that SA has a strong impact on the behavior of a child. It is important to recognize that this is not merely an ASD-related issue; SAs can also interfere with a child's everyday life and social functioning in the general population, and these children need help in regulating their sensory environment. According to Hazen, E., Stornelli, O'Rourke, Koesterer and McDougle (2014), sensory over-responsivity is the most often cited sensory correlate to increased anxiety in both general and ASD populations. In our study, only auditory hypersensitivity was found to be statistically significantly associated with higher QAT among children with ASD, explaining 28 % of the variance in QAT, but among the non-ASD sample, hypersensitivity in all sensory modalities and also auditory, tactile and visual hyposensitivity were statistically significantly associated with higher QAT, although the percentages of variance explained were modest.

Auditory hypersensitivity manifests as discomfort or painful response to noises, such as certain types of noisy environments (Kern et al., 2001; Rosenhall, Nordin, Sandström, Ahlsén and Gillberg, 1999). It is most acute if the noise level is high or if there are many different sources of noise, for example in restaurants (Kern et al. 2001). In school settings, the school cafeteria is an area where the different noises can cause problems for sensitive pupils. The noises there include people talking, sudden loud voices, noises from the kitchen, unpleasant sounds from eating and biting, clicking of cutlery, moving of seats and people walking around. A situation that is supposed to provide relaxation between lessons can turn into a very stressful situation.

Auditory hypersensitivity is suggested to be a result of abnormal brain processing in children with ASD. Differences in auditory sensory processing were described by Kern et al. (2006). This observation conforms to fMRT studies.

Gomot, Belmonte, Bullmore, Bernard and Baron-Cohen (2008) reported differences in brain activity mainly involving the right prefrontal-premotor and the left inferior parietal regions. These regions were more activated in the ASD sample than in controls when they were exposed to acoustic stimuli (Gomot et al., 2008; Rosenhall et al., 1999). Kwon, Kim, Choe, Ko and Park (2007) investigated the auditory ability of children with ASD by using auditory brainstem responses and reported that children with ASD have a dysfunction or immaturity of the central auditory nervous system. Furthermore, abnormal cortical auditory processing was observed in children with autism when measuring the regional cerebral blood flow with positron emission tomography while they were listening to speech-like sounds (Boddaert et al., 2004).

Among the non-ASD sample, tactile hypo- and hypersensitivity had the strongest effect on the ASSQ scores, suggesting that they may manifest as autistic-like features in a child's behavior. Tactile hypersensitivity often manifests as an avoidance of being touched or by a discomfort from wearing certain clothes (Baranek, Foster and Berkson, 1997); Kern et al., 2001) or as a resistance to hair brushing and washing (Kern et al., 2001). In school, daycare or other social situation, tactile hypersensitivity may manifest as a general avoidance of situations or marked discomfort in situations where physical contact with other children is likely. On a behavioral level, tactile hyposensitivity may present as an attempt to gain tactile sensations (by touching, pushing, bumping into things on purpose).

Quantitative autism trait level and SA were associated in the all three study samples and existence of SA explained the variance in the ASSQ scores, indicating that SA has a marked role in autistic behavior. Clinicians are reminded to assess SA not only in children who receive an ASD diagnosis, but also among children with elevated ASSQ outcome measures.

In the principal component analysis, the SAs did not load to any of the ASSQ subscales, but instead, correlated positively only with each other. This suggests that the SAs make up an independent component in ASD pathology and could be used as a very early "red flag" in clinical practice.

In school and daycare, auditory elements are usually taken into consideration when planning special education and support for children with ASD, but more knowledge of different SAs is still needed, especially among teachers in general education schools, where one or more students with ASD are integrated. SA affects also children without ASD, and many children benefit from learning environments with reduced sensory stimuli. The discomfort caused by sensory

overload raises the stress level of the child, which can lead to poorer adaptation and weaken the child's ability to concentrate in the learning environment. On the other hand, children with sensory under-responsiveness need activation and change of routine to keep them engaged.

6.4 Limitations

I In sub-studies I and IV, the children scoring either below nine in teachers' ratings and below seven in parents' ASSQ ratings or between 7 and 18 in parents' ratings and below nine in teachers' ASSQ ratings, or between 9 and 16 in teachers' ratings and below seven in parents' ASSQ ratings; (n = 4 304) (i.e., "low risk group") were not followed up, nor was a sample of randomly selected children from the low risk group of children, which can be considered as a limitation. However, we had previously (Mattila et al., 2009) shown that all 47 hospital-registered ASD patients met our inclusion ASSQ criteria for diagnostic examinations in the current study. In addition, based on previous results (Ehlers et al., 1999; Mattila et al., 2009) and the prevalence rates of ASD (Fombonne, 2009; Levy, Mandell and Schultz, 2009), we relinquished random selection of subjects at low risk because the probability of discovering ASD cases in that group was minimal in relation to the time-consuming effort and cost. For example, in their study, Posserud and colleagues (2009) detected only two cases with ASD with outcome measures below 17 in parents' and/or teachers' ASSQ evaluation, yielding a prevalence of 0.3 per 1 000 below the cut-off score of 17. In addition, remarkable similarity between the questions in psychiatric screening questionnaires and diagnostic interviews supports the decision not to investigate children in the "low risk group".

II In sub-study II, the proband data consisted of only high-functioning males, and therefore the results cannot be generalized to females or ASD probands with lower cognitive level. In addition, the study groups were not precisely matched for IQ. However, all the children in both the ASD and control groups attended mainstream schools, and our outcome measure of interest, the SRS, has been shown to be independent of IQ in typically developing children (Constantino et al. (2000; 2003; 2007). Furthermore, only parental evaluations were available. Previous research has found differences between parental/teacher SRS evaluations, but they have been strongly correlated (Constantino & Gruber 2012; Constantino et al. 2007). Finally, due to lack of

a non-ASD clinical sample, we were not able to critically evaluate the high Sp rate obtained.

III In sub-study III, the families were selected on the basis of their present status; the definition of a simplex family might thus have been biased as a result of potential changes with the addition of infant siblings with ASD. Reporter bias was also possible; the parents rated each other and also their children, and we had only parental, not teacher, evaluations of the children. However, Constantino and colleagues have reported strong correlations between teacher and parent ratings on the SRS ($r = 0.72$), which suggests that such bias in unlikely to drive robust statistical results.

IV In sub-study IV, SAs were assessed by inquiring about the presence/absence of auditory, tactile, visual, olfactory and gustatory hyper- and hyposensitivity. That is, we did not have the possibility to use validated measures of sensory perceptual problems. Again, the information regarding QAT and SAs was derived from proxy ratings (i.e., parents filled the developmental questionnaire and both parents and teachers filled the ASSQ). Hence, proxy biases are possible as always when analyzing informant-based data gathered from family members. It can be argued, however, that the parents are the best possible informants regarding a child's developmental history and characteristics.

7 Conclusions

The present study provides novel data and information for clinical guidelines on identification of autistic traits.

1. Collect parent and teacher evaluations. The Finnish ASSQ is a valid screening instrument for ASD, but clinicians should collect both parent and teacher ratings and use the summed score for screening. A child receiving a summed score at or above 30 points should be referred to more comprehensive diagnostic evaluations.
2. Detailed information enables effective intervention. The Finnish SRS is suggested to be used alongside with the ASSQ as a tool for acquiring more detailed information about the deficits a child has in his/her RSB abilities. The subscales offer valuable information for intervention planning and assessing treatment outcome.
3. It is crucial to identify early signs of autism. Since male family members have an elevated risk for a broader, subclinical phenotype of ASD, the development of social communication skills should be included into the routine developmental check-ups at child health clinics and in school health care if the family reports ASD diagnosis or high QAT among a child's male family members. Support/interventions and the use of screening instruments are essential without any delays if early signs of autism are identified. Further, clinicians, therapists and other professionals are reminded to take into account possible ASD or subclinical QAT in ASD families when planning interventions or adaptation training courses.
4. Atypical sensory processing is a red flag for ASD. It should be assessed early as part of the routine developmental check-ups. The development of social communication skills should be followed and support/therapy offered in an early stage to children with SAs.

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Original Publications

I Mattila, M. L., Jussila, K., Linna, S. L., Kielinen, M., Bloigu, R., Kuusikko-Gauffin, S., Joskitt, L., Ebeling, H., Hurtig, T., & Moilanen I. (2012). Validation of the Finnish Autism Spectrum Screening Questionnaire (ASSQ) for clinical settings and total population screening. *Journal of Autism and Developmental Disorders, 42*(10), 2162–2180. https://doi.org/10.1007/s10803-012-1464-5

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III Jussila, K., Lyall, K., Kuusikko-Gauffin, S., Mattila, M. L., Pollock-Wurman, R., Hurtig, T., Joskitt, L., Bloigu, R., Ebeling, H., Moilanen, I., & Pauls, D. (2015). Familiality of quantitative autism traits. *Scandinavian Journal of Child and Adolescent Psychiatry and Psychology, 3*(2), 126–135.

IV Jussila, K., Junttila, M., Kielinen, M., Ebeling, H., Joskitt, L., Moilanen, I., & Mattila, M. L. (2019). Sensory abnormality and quantitative autism traits in children with and without autism spectrum disorder in an epidemiological population. *Journal of Autism and Developmental Disorders*. doi 10.1007/s10803-019-04237-0

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