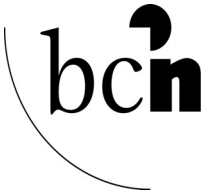
Autism Spectrum Disorders:
A study of symptom domains and weak central coherence



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Autism Spectrum Disorders: A study of symptom domains and weak central coherence

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1.
GENERAL INTRODUCTION

Autism is a behavior disorder with a neurodevelopmental origin. It is defined by its behavioral properties in the editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM). In the latest edition of the DSM, the DSM-IV-TR, autism is described by impaired functioning on three behavior domains: qualitative impairments in social interaction, qualitative impairments in communication, and the occurrence of stereotyped behaviors or restricted interests (American Psychiatric Association, 2000). These three behavior domains are based on the first descriptions of autism by Kanner (Kanner, 1943), and by the influential study of Wing and Gould (Wing & Gould, 1979), and are subsequently modified according to international field studies that investigated the clinical consensus of the necessary classification criteria.

In the DSM-IV-TR, autism is classified under the category of 'Pervasive Developmental Disorders' (PDD), a category consisting of five diagnoses: Autistic Disorder (AD), Asperger's Syndrome (AS), Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS), Rett syndrome, and Desintegrative Disorder. The first three diagnostic categories occur most frequently, and have the following diagnostic criteria: AD requires a minimum of six features from the three behavior domains, from which at least two from the domain of social impairments, one from domain of communication impairments, and one from the repetitive and stereotyped area. For PDD-NOS, a minimum of two features is required, of which one must be from the domain of social impairments and either one from the domain of communication impairments or repetitive and stereotyped area. For AS, no significant delay in language development is required, and subjects need to fulfil at least two criteria on the domain of social impairments and one of the repetitive and stereotyped area.

In the last decade, the interest in autism focuses on autistic individuals with intellectual disabilities, individuals with Asperger's Syndrome or individuals with autistic symptomatology with intelligence rates in the normal range, and family members with autistic traits. All these individuals with varying degrees of autistic behaviors are yet described by the concept of 'Autism Spectrum Disorders', emphasizing a continuum in symptom severity in the autism phenotype (Allen *et al.*, 2001; Prior *et al.*, 1998). Despite this continuity in autistic behaviors, individuals with autistic disorders still differ in their symptomatology to a great extent (e.g. shows a large heterogeneity in symptoms). This variety in symptomatology

between individuals with similar diagnostic classifications may also be associated with the discussion about the poor construct validity of the diagnostic categories PDD-NOS and AS (Klin *et al.*, 1995; Mahoney *et al.*, 1998; Sponheim, 1996).

Research on the etiology of autism, showed that autism has a biological base due to disperse structural and functional brain abnormalities (Rutter *et al.*, 1999; Rutter, 2000), and that the vulnerability to develop autism is largely genetically determined (Silverman *et al.*, 2002; Spiker *et al.*, 2002). However, the question of how the variability in autistic symptomatology is linked to etiological properties is still unclear. In addition, about 75% of subjects with autism show a comorbid intellectual disability (Dykens, 2000; Kraijer, 1997), and it remains also a question of how this comorbidity is related to etiology. Several studies showed that high cognitive and verbal intelligence skills are associated with a good prognosis in autism (Nordin & Gillberg, 1998; Stevens *et al.*, 2000). Nevertheless, these skills can not explain the phenotypical variation in autism fully, because higher-functioning individuals with autism still exhibit such disturbing behaviors that they remain seriously handicapped (Howlin *et al.*, 2000; Rutter *et al.*, 1967; Venter *et al.*, 1992). Questions thus remain about how autistic behaviors are genetically transmitted and how they are associated with neurodevelopment. In addition, questions remain about how the etiology can explain the high variability in symptomatology that is seen in autism.

Aims of the present thesis

The present thesis aims to gain more insight into the variability in autistic symptomatology. It tries to identify symptom domains that may underlie the autistic behaviors, and it examines the use of a particular cognitive processing style in autistic subjects, as predicted by the theory of a weak central coherence, that tries to give an explanation of why autistic subjects display these behaviors. First, the question arises whether the symptom structure of autism is represented by the triad of impaired behavior domains, as described in the DSM-IV-TR. Recently, studies suggested that the symptom structure that underlies the autism spectrum disorders differs from the triad of behavior domains of the DSM (Robertson *et al.*, 1999; Tanguay *et al.*, 1998; Szatmari *et al.*, 2002). These findings indicate that it is important to investigate symptom domains in autism further, in order to find out if the symptom structure differs from the DSM triad and if the symptom domains that are derived, can be replicated in a new and Dutch sample. Three studies in the present thesis focus on symptom domains in a large group of Dutch subjects with autistic symptomatology in varying degrees of severity.

Second, two other studies in the present thesis focus on the cognitive processing style of subjects with disorders in the autism spectrum. By means of the influential theory of a weak central coherence in autism, autistic subjects are hypothesized to process information in a detail-focused manner (Frith, 1989). Evidence for this theory is not well established yet. The present thesis therefore examines the hypothesized detail-focused processing style in two groups of subjects with autism spectrum disorders: a group functioning in the lower IQ ranges, and a group functioning in the mild-to-normal IQ range.

Before the studies in this thesis are presented, the construction of a database with information about the behavioral and cognitive functioning of Dutch subjects with minor to severe autistic symptomatology is described first. The studies that investigate symptom domains in autism and the studies that examine the theory of a weak central coherence are given next, along with a summary of the research questions, as presented in the separate chapters of this thesis.

The construction of a database of Dutch subjects with autistic symptomatology

The main goal of the construction of the database was to select as many subjects with autism spectrum disorders as possible, with substantial attention being paid to subjects with a comorbid intellectual disability. In 1998, a start was made with the construction of the database. Data of intellectually disabled children and adolescents of 4 to 20 years with minor to severe autistic symptomatology was collected in Friesland by means of an epidemiological study (De Bildt *et al.,* 2003a). Subjects were included when they were likely to fall within the spectrum of autistic disorders according to a screening questionnaire completed by teachers, the PDD-MRS (Kraijer, 1997). This questionnaire is specifically designed to detect pervasive developmental disorders in this population of individuals with an intellectual disability. In 1999, this database was enlarged with data from a population study on three schools for children with severe learning problems in Groningen, applying the same procedure as in Friesland. In addition, a clinical study on an Outpatient Clinic for patients with Autism Spectrum Disorders, covering patients from Friesland, Groningen and Drenthe was also conducted, to include children and adolescents with autism spectrum disorders of 4 to 20 years, with intelligence rates in the ranges of intellectual disability to borderline, normal and above normal IQ range (Van Lang, *this thesis*). The mean positive response rate was 68% in the schools or institutions for children with learning problems and 71% in the Outpatient Clinic for patients with Autism Spectrum Disorders.

Because of differences between the included subjects, in whether or not they were formerly diagnosed with an autism spectrum disorder or receiving clinical treatments, each subject was (again) classified by four experienced clinicians for the purpose of the present studies. The clinical raters based their classifications on the information obtained from two extensive classification instruments: the protocols of the Autism Diagnostic Interview Revised (ADI-R) (Lord *et al.*, 1994), a structured interview with subject's primary caregiver, and the videotapes of the Autism Diagnostic Observation Schedule (ADOS-G) (Lord *et al.*, 2000), a semi-structured play observation with the subject. These classification instruments were administered to each caregiver and to each subject by trained researchers, and yield extensive descriptions of subject's behavioral functioning, resulting in a DSM-IV based classification of Autistic Disorder in the ADI-R and Autistic Disorder or PDD-NOS in the ADOS-G (American Psychiatric Association, 1994). The four clinical raters were blinded to the classification outcomes of both instruments, and in case there was any doubt in classifying a subject, a consensus was reached with all four clinical raters (an acceptable interrater agreement with a weighted kappa of .68 was found on 40 subjects, De Bildt *et al.,* 2003b).

As a result, a database of N= 299 subjects was selected from 332 subjects, with information available about subject's behavioral functioning according to the ADI-R, an intelligence rate that was already known or was established, and with a clinical classification made by the four clinical raters (see Figure 1.1 for an overview of the selection of subjects). Of the N=299 subjects, 84% had additional an intellectual disability (i.e. an IQ<70). The clinical raters classified the 299 subjects as follows: 74 with an Autistic Disorder (AD), 84 with a Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), 3 with Asperger's Syndrome (AS), and 132 with autistic symptomatology, but not severe enough to warrant a disorder in the autism spectrum ('typically developing' subjects). In addition, 6 subjects were judged to have only minor autistic traits, and received no clinical classification diagnosis. This group, together with a group of 15 adolescents with no or minor autistic traits from schools for children with severe learning problems, and a group of 76 healthy children from elementary schools were treated as control groups for the studies that investigated the tendency for a weak central coherence in autistic individuals (Van Lang, *this thesis*).

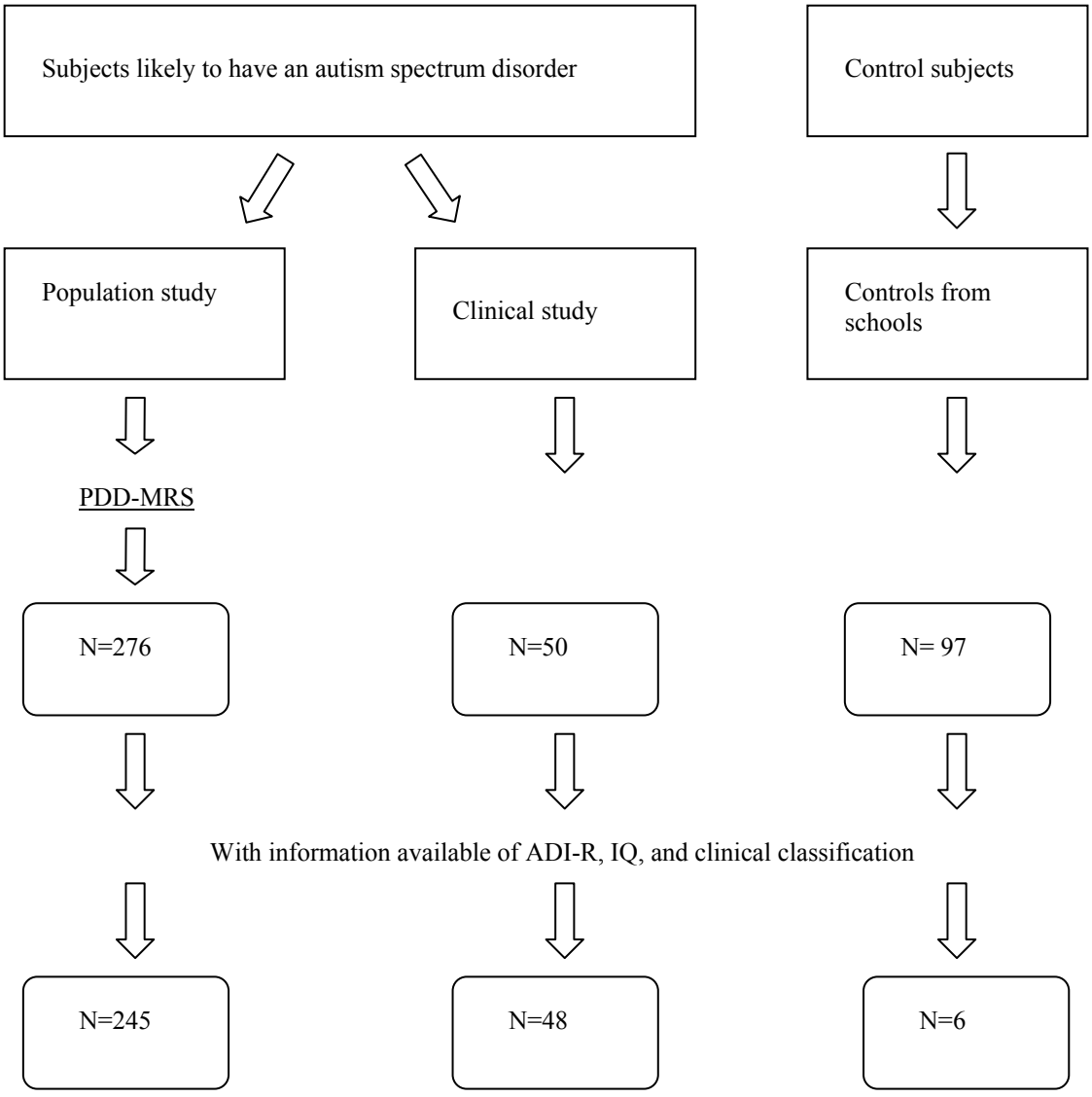

Figure 1.1

Schematic overview of the selection of subjects

Identification of symptom domains

Several studies revealed that the impairments on the three behavior domains as described in the DSM editions, occur frequently in people with autistic disorders and that the impairments are also highly correlated (Spitzer & Siegel, 1990; Volkmar *et al.*, 1994; Wing & Gould, 1979). Nevertheless, recent studies that investigated the structure of the autistic symptomatology showed that the symptom domains that may underlie the autistic

impairments differ from the three behavior domains of the DSM. For example, factor analytic studies on autistic core features revealed a symptom structure with factors 'joint attention', 'affective reciprocity' and 'theory of mind' (Robertson *et al.*, 1999; Tanguay *et al.*, 1998) or with factors 'autistic symptomatology' and 'level of functioning' (Szatmari *et al.*, 2002). These findings raise the question whether the three behavior domains as presented in the DSM represent the actual symptom domains in the autism spectrum.

In this thesis, the symptom domains underlying a group of subjects with varying degrees of autistic symptomatology is examined (see c*hapters 2 to 4*). First, the symptom domains in verbal subjects with autistic symptomatology is explored, by using the information about subject's behavioral functioning obtained from the ADI-R (*see chapter 2*) and from the ADI-R and ADOS-G (*see chapter 3*). Second, a hypothesized symptom model is constructed based on the explorative findings. The model is being tested with confirmatory analyses in a large group of verbal and nonverbal individuals with mild to severe autistic symptomatology (*see chapter 4*).

Chapter 2 starts with a description of the development of the criteria for autism, across the different editions of the DSM. It starts with the first descriptions of autism, made by Kanner (Kanner, 1943), and subsequently gives a brief overview of how the criteria for autism are firstly formulated in the category 'Pervasive Developmental Disorder' in the DSM-III (American Psychiatric Association, 1980) and changed into the criteria as formulated in the most recent DSM edition, the DSM-IV-TR (American Psychiatric Association, 2000). The study investigates the symptom domains, by using subject's ratings on the classification (or algorithm) items of the ADI-R, which pertain to the 4-5-age period of the subject. With these items, a comparison between empirically derived symptom domains and DSM symptom domains can be made, because these items are directly related to the DSM-IV criteria for Autistic Disorder. In addition, only items that pertain to verbal subjects are used. The study describes the structure in symptomatology in 87 verbal subjects with a disorder on the autism spectrum, with intelligence rates larger than 35.

Chapter 3 describes a study in which the symptom structure of autism is examined in more detail. It incorporates the ADOS-G additional to the ADI-R and examines the underlying symptom domains in a larger group of 156 verbal individuals with mild to severe autistic symtomatology, with intelligence rates larger than 35. Instead of ratings that pertain to subject's functioning in the 4-5-age period, this study included (algorithm) items of the ADOS-G and ADI-R, that are related to verbal subjects and that pertain to the current age

status of the subject. Based on the results from these explorative studies in chapters 2 and 3, a hypothesized symptom model is constructed in chapter 4.

Chapter 4 describes a study in which the hypothesized symptom model is being tested with confirmatory analyses in a large group of 255 verbal and nonverbal subjects with minor to severe autistic symptomatology, with intelligence rates larger than 20. The summary scores of ADI-R (algorithm) items that pertain to subject's current functioning are used, reflecting behaviors that may occur in verbal and in nonverbal autistic individuals.

Across the three studies, the derived symptom domains are contrasted to the three symptom domains of the DSM-IV. In addition, groups of individuals with autistic disorder symptoms are compared in whether their behavior structure showed differences in symptom profile or in symptom severity.

Weak central coherence

Recent studies that try to investigate why people with autism exhibit specific impairments, use cognitive theories that suggest qualitative differences in information processing styles. The theory of a weak central coherence in autism is an influential theory, which postulates hypotheses of why autistic individuals have impaired social and communication skills and why they display stereotyped mannerisms or have restricted interests (Frith, 1989). The theory supposes that people with autism process information in a local style, being more focused on details, and as a consequence make less allowance for the context in which the information is put in. Thus, as a result of the use of this particular cognitive processing style, autistic individuals are hypothesized to pay more attention to details in their communication, interests and play patterns, and experience difficulties in social contacts, because they do not take account for the social context during the communication.

In the last decades, the theory received empirical support from several studies, showing that people with autism performed better than controls on tasks where detail-focused processing was beneficial to global processing (Happé, 1999; Jolliffe & Baron-Cohen, 1997; Ropar & Mitchell, 2001; Shah & Frith, 1983; Shah & Frith, 1993). However, some studies failed to replicate these findings (Brian & Bryson, 1996; Ozonoff *et al.*, 1991; Ropar & Mitchell, 1999), and recent studies seem to limit their focus on higher functioning subjects with autism or subjects with Asperger's Syndrome only (Jolliffe & Baron-Cohen, 1997; Jolliffe & Baron-Cohen, 1999; Rinehart *et al.*, 2000; Ropar & Mitchell, 1999).

In this thesis, *chapters 5 and 6* describe studies about the tendency for a weak central coherence in autistic individuals. In *chapter 5*, the tendency for a weak central coherence is compared between adolescents with severe learning problems with and without a comorbid disorder in the autism spectrum. All adolescents attended schools for severe learning problems and were offered two visual-spatial tasks that measure weak central coherence: (adapted versions of the) Child Embedded Figures Test (Shah & Frith, 1983; Witkin *et al.*, 1971) and Block Design Task (Shah & Frith, 1993).

In *chapter 6*, the influence of age on weak central coherence is examined first in a group of healthy control children from elementary schools. Secondly, a group of subjects with autism spectrum disorders functioning in the mild-to-normal IQ range is compared to a selection of the healthy control children, matched on mental age, in the tendency for a weak central coherence. The same two visual-spatial tasks as in chapter 5 are used to measure weak central coherence. In both studies of chapters 5 and 6, the relationship between weak central coherence and autistic behaviors is additionally explored, because the theory hypothesizes that the autistic behaviors emerge from employing a detail-focused processing style.

Summary of the research questions as presented in the separate chapters

The studies in this thesis address the following questions:

Identification of symptom domains (chapters 2, 3 and 4):

- Which symptom domains can be identified in a heterogeneous group of individuals with autistic disorder symptoms?
- Do the derived symptom domains resemble the symptom domains of the DSM-IV?
- Do groups of individuals with clinical classifications of an autism spectrum disorder (i.e. with an Autistic Disorder or PDD-NOS or Asperger's Syndrome) or typically developing individuals differ in symptom profile or in symptom severity?

Weak central coherence (chapters 5 and 6):

- Are individuals with a clinical classification of an autism spectrum disorder characterized by a qualitatively different cognitive processing style, as predicted by the theory of a weak central coherence?
- Is the tendency for a weak central coherence associated with autistic behaviors?

In the final *chapter 7*, the findings of the studies are discussed in the light of the phenotypical variation in autism. In addition, limitations of the studies are given, together with suggestions for further research. The chapter ends with a conclusion and with clinical implications that may result from the findings of the studies.

2.

SYMPTOM DIMENSIONS IN VERBAL INDIVIDUALS WITH AUTISM: A TRIAD OR A DYAD?

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ABSTRACT

OBJECTIVE: The present study examined the underlying symptom dimensions in the autism spectrum, using the Autism Diagnostic Interview Revised (ADI-R). METHOD: Eighty-seven verbal subjects with a clinically established autism spectrum disorder were included (ages 4-20 years; IQ's above 35). Factor analysis and Mokken scale analysis were applied, and differences in behavioral profiles were verified. RESULTS: From the three-factor solution, socially impaired behavior, stereotyped language/behavior and impaired conversation were extracted. A two-factor solution had more face validity: socially impaired behavior and stereotyped language/behavior. No difference in profiles was observed. CONCLUSIONS: The three-factor solution found provided evidence for restructuring major DSM-IV criteria. A two-factor solution seemed more substantial however, and showed that subjects differed in severity rather than in profile.

INTRODUCTION

Autism is a neurodevelopmental disorder, described by a triad of behavior domains in the DSM-IV-TR (American Psychiatric Association, 2000). These domains are not empirically derived, but are based on the comprehensive descriptions of Kanner (Kanner, 1943), and followed by clinical consensus on the necessary classification criteria (Rutter, & Lockyer, 1967). However, for research into etiological mechanisms or effectiveness of training programs, empirically derived behavior domains are more valuable (Tordjman *et al*., 2001; Lord, Leventhal, & Cook, 2001). These behavior domains consist of manifest behaviors that are highly correlated and reflect possible underlying symptom dimensions. However, at present, it is unclear whether symptom dimensions in autism will equal the DSM triad of behavior domains.

In 1943, Kanner described autistic children as aloof, unable to relate to other persons, not communicating adequately, having an obsessive desire to keep things as they are and repeat the same actions constantly. After Kanner, studies were undertaken to identify children, who resemble the ones that Kanner had described (Rutter, 1999). For example, a study by Rutter, Lockyer and Greenfeld (Rutter, Greenfeld, & Lockyer, 1967; Rutter, & Lockyer, 1967) revealed that three behavior domains for autism were best at discriminating autism from other psychiatric conditions, even after a 10 year follow-up. These domains were (1) failure to develop social relationships with various specific abnormalities in interpersonal functioning; (2) language retardation with impaired comprehension, echolalia and pronominal reversal; and (3) ritualistic and compulsive phenomena associated with repetitive stereotyped play patterns. The authors described a large heterogeneity in symptoms and concluded that impairments in the three behavior domains persist, but the severity of these symptoms may change over the years.

These results led to the inclusion of autism as a new class of childhood onset disorders, formulated into the category 'Pervasive Developmental Disorder' (PDD) in the DSM-III (American Psychiatric Association, 1980). The aim of this category was to make clear that autism was a developmental disorder, manifested in multiple areas of functioning. In 1979, Wing and Gould (Wing & Gould, 1979) performed an influential study, in which they aimed at detecting any of the features of autism regardless of mental retardation. They drew attention to the high frequency of autistic-like symptoms, especially in children with mental retardation. The authors pointed out that subjects varied in the severity of their symptoms on a triad of behavior domains: impaired socialization, impaired communication and imagination, and

repetitive activities and interests. The importance of an autism spectrum disorder characterized by this triad of impairments was emphasized.

The effect of the study of Wing and Gould was to broaden the definition of autism. Their results and the attempt to resolve some problematic issues of the DSM-III (Szatmari, 1992; Volkmar, Cicchetti, Bregman, & Cohen, 1992) led to the development of the DSM-III-R criteria (American Psychiatric Association, 1987). While the criteria set in the DSM-III-R was now better defined so as to cover the entire spectrum of autism, taking into account the different manifestations of the triad, psychometric problems emerged. Results showed good sensitivity scores but low specificity scores (Spitzer & Siegel, 1990; Szatmari, 1992; Volkmar, Cicchetti, Bregman, & Cohen, 1992). As a result, the application of the DSM-III-R led to a high risk for false positives, compared to for example those described by the ICD-10 criteria (World Health Organization, 1993).

In the DSM-IV (American Psychiatric Association, 1994), in which the criteria became closer to the ICD-10, the concept of autism was narrowed. In the multinational field trial (Volkmar *et al*., 1994), the diagnoses of clinically assigned subjects with many disorders related to autism were again examined by field trial clinicians. They based their diagnoses on a standard coding system, with extensive criteria thought relevant to autistic features (inclusion of criteria from the ICD and from earlier DSM versions). Criteria were selected for maximum sensitivity and specificity to formulate a new set of criteria for the DSM-IV. New categories were introduced, such as Asperger's Syndrome, and fewer items per domain were found necessary to define Autistic Disorder (classic autism).

Currently, the spectrum of autism extends more widely. For example, genetic and imaging studies include not only subjects with an Autistic Disorder, but also those with Asperger's Syndrome or mild autism with IQ's in the normal range, and even extend the concept of autistic traits in family members (Folstein *et al*., 1999). Autism is supposed to be a part of a spectrum of autistic-like disorders (Prior *et al*., 1998; Allen *et al*., 2001; Wing, 1997) however, the construct validity of the whole spectrum is not yet clear-cut (Allen *et al*., 2001; Eisenmajer *et al*., 1996; Mahoney *et al*., 1998). Furthermore, the psychometric properties of Asperger's Syndrome and the category of Pervasive Developmental Disorder Not Otherwise Specified, PDD-NOS, are poor (Klin, Volkmar, Sparrow, Cicchetti, & Rourke, 1995; Mahoney *et al*., 1998; Sponheim, 1996).

Therefore, the phenotypic variation in the autism spectrum and the underlying symptom dimensions are studied through factor analysis on characteristic autistic behaviors

(Robertson, Tanguay, L'Ecuyer, Sims, & Waltrip, 1999; Szatmari *et al*., 2002; Tanguay, Robertson, & Derrick, 1998). The studies used different operationalizations of autistic behaviors, however the first results point towards an underlying symptom structure that is somewhat different from the DSM triad. The present study aims at contributing to a further identification of underlying symptom dimensions in the autism spectrum. It focuses on a verbal group of individuals with an autism spectrum disorder (ASD) and looks at the latent symptom structure underlying the DSM-IV criteria for an Autistic Disorder. Accordingly, the algorithm items of the Autism Diagnostic Interview Revised (Lord, Rutter, & Le Couteur, 1994) are used for factor analysis. Because many of the algorithm items are only applicable to individuals who are verbal, we examined the factor structure of a verbal ASD group only. Our aim was (1) to look for the DSM triad in a group of verbal individuals with ASD, (2) to investigate whether another factor solution besides the DSM triad would be appropriate, and (3) to see whether there is a difference in symptom profile or in symptom severity within the ASD group.

METHOD

Subjects

Two groups of verbal ASD subjects, all from three northern regions in the Netherlands, were recruited to this study: (a) from schools for children with mild to severe learning problems (N=56) and (b) from an Outpatient Clinic for patients with Autism Spectrum Disorders (N=31). The subjects selected at the schools were all likely to be on the autism spectrum on the basis of screening with a teacher's questionnaire, specifically designed to detect pervasive developmental disorder (PDD) in this population (PDD-MRS; Kraijer, 1997). Subsequently, both groups were examined for their diagnostic classification and behavioral profiles in more detail, with amongst others the Autism Diagnostic Interview Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994) and Autism Diagnostic Observation Schedule Generic (ADOS-G; Lord *et al*., 2000). Based on the ADI-R protocols and videotapes of the ADOS-G, four experienced clinicians provided a clinical DSM-IV-TR diagnosis of an Autistic Disorder (AD), PDD-NOS or Asperger's Syndrome (AS), or for any other disorder but PDD, to the subjects that were selected at the schools. The clinicians were blinded to the classifications according to both instruments. Consensus diagnoses were reached when there was any doubt in classifying a subject (weighted kappa of .68; 4 raters on n=40 subjects). For the subjects selected from the

outpatient clinic, the diagnoses known to the clinic were applied. With regard to subjects' cognitive abilities, if an IQ had been determined within 2 years of the study, that figure was used. If not, one of the following Wechsler scales were used, depending on age: Dutch versions of the WAIS-R (Uterwijk, 2000), WISC-R (Van der Steene *et al*., 1986), and WPPSI-R (Van der Steene & Bos, 1997). We excluded children and adolescents with profound and severe mental retardation (IQ≤ 35), children whose IQ-scores were obtained but deemed unreliable because they were untestable in a standard test situation, and children who were nonverbal. For the latter, we used the ADI-R item about overall level of language as criterion for verbalization. Only subjects with functional use of at least three word phrases and comprehensible language were included.

Measures

The ADI-R (Lord, Rutter, & Le Couteur, 1994) is a semi-structured and standardized interview with the principal caregiver, consisting of questions about the functioning of the child in the past and present. For all items, caregivers are asked to look back at the past corresponding to the 4-5-age period and then focus on the current status. The items in the ADI-R deal with the main characteristics of PDD, and more specifically with AD. The items concern reciprocal social interaction, language, communication and play and the restricted, repetitive and stereotyped behaviors and interests. Scores on each item range from 0-3, with 3 as the most severe condition. With an established algorithm based on the 3 domains of the DSM-IV, together with an age of onset before three (Lord *et al*., 1997) a classification of 'AD' versus 'no AD' can be made. For verbal subjects, the ADI-R algorithm consists of a total of 37 items relating to the DSM-IV/ICD-10 criteria for AD, of which 35 items cover the behaviors during the 4-5-age period and 2 items the present behavior in reciprocal conversation and social chat. Reported sensitivity and specificity scores are .86 and .91 respectively (Lord, Rutter, & Le Couteur, 1994). For children with mental ages below 2 years and for higher-functioning subjects, specificity and sensitivity are lower (Lord, Rutter, & Le Couteur, 1994). Interrater and retest reliability seem promising (Hill *et al*., 2001). In the present study, trained researchers who had established sufficient reliability for the administration of the instrument administered the interview.

Data Analysis

Exploratory factor analysis with principal component analysis (PCA) and varimax rotation was used on the ADI-R algorithm items for the identification of symptom dimensions. Two

conditions were used: items pertaining to (a) the 4-5-age period, and (b) the current status. A score of 3 on the items were recoded as 2. Mokken scale analysis, a polytomous nonparametric item response model, was then applied to examine the robustness of the symptom dimensions found by PCA, because the items were not normally distributed and the ratio items/subjects was not ideal (Stevens, 1996). The program MPS5, a stochastic cumulative scaling program with a stepwise search procedure, was used to construct one-dimensional Mokken scales: scales with a hierarchy of interrelated items ordered by difficulty (Molenaar & Sijtsma, 2000). The Loevinger's scalability coefficient H was used to test the deviation of the observed data structure from the perfect scalogram structure (Mokken, 1971). For the internal consistency of the extracted PCA factors, Cronbach's alpha was used. Differences in mean scores on these factors for various diagnostic groups, adjusted for IQ level, were studied with MANCOVA analysis. Finally, a latent class analysis (LCA) was applied to define ASD profiles in the PCA factors. The unrestricted ordinal model for polytomous data was used with the computer program LEM. The optimum number of latent classes was established based on the information criteria AIC and BIC to measure the 'goodness of fit'. Models were run with various sets of starting values to prevent solutions based on just a local maximum in iteration processes (Vermunt, 1977). The outcome of LCA might indicate the existence of different phenotypes if the latent classes show divergent profiles of relative frequencies on the scales. However, if the latent classes show comparable profiles of relative frequencies that only differ in symptom severity, the conclusion would be that PDD is a dimensional construct.

RESULTS

SUBJECT CHARACTERISTICS

The clinical raters classified the 87 verbal ASD subjects as follows: 26 with AD, 56 with PDD-NOS and 5 with AS. According to the classification following the ADI-R algorithm, 61 were judged to have AD at the age of 4-5 years. The majority was male: 72 male:15 female. The chronological ages varied between 4-20 years, with a mean of 11;10 years (SD 3;10). The IQ ranges varied between 36-129, with a mean of 68.1 (SD 22.4). About ninety percent (88.5%) of the subjects were attending schools for special education, of which 61% were following education at schools for children with severe learning problems. Table 2.1 shows the IQ distribution and mean IQ of the clinically established diagnostic groups.

Table 2.1

IQ distribution and mean IQ (SD in parenthesis) of N=87 subjects

	Autistic Disorder	PDD-NOS	Asperger's Syndrome	Total
IQ level:				
Moderate	8	10		18
Mild	11	29		40
Borderline I.F.	4	8		12
Normal	3	6	4	13
Above normal		3	1	4
Mean IQ	60.0 *(15.6)*	68.2 *(22.1)*	106.2 *(15.4)*	68.1 *(22.4)*
Total	**26**	**56**	**5**	**87**

Note: Ranges of the IQ levels, moderate (36-50); mild (51-70); borderline intellectual functioning (71-85); normal (86-115); above normal (116-129)

FACTOR ANALYSIS

Examining the DSM triad

Analyzing a three-factor solution on the ADI-R algorithm items related to the 4-5-age period, resulted in 34% explained variance, with factor 1 explaining 17% and factor 2 and 3 respectively 10% and 7% (data not shown). The first factor represented items about *socially impaired behavior*, like impairments in interaction in play situations, being interested in other children and responding to them appropriately. Moreover, items about nonverbal communication like impaired imitation skills and less use of gestures related to this factor. Factor 2 covered items about *stereotyped language and behaviors*. Stereotyped utterances, inappropriate questions and the use of idiosyncratic language were related to unusual sensory interests, repetitive use of objects, and motor mannerisms. Factor 3 was a factor consisting of items about *impaired conversation*. Analyzing a three-factor solution based on 29 items of the current status (eight items about play skills were excluded, because they were not applicable to subjects aged above 10), revealed a comparable factor structure explaining 27% of the variance. Because our data in the three-factor solution showed a different structure than the DSM triad and the third factor correlated highly to the first factor ($r = .703$, $p < .01$), we also examined the structure of a two-factor solution. This solution seemed to have more face validity.

Examining a two factor-solution

The PCA analysis with two factors revealed that the third factor from the three-factor solution merged into the first factor. In order to limit the number of items in the analysis, only those items with factor loadings above .40 from the correlation matrix (26 items) are used. In addition, because of the small sample size for the number of items that are used in the PCA analysis, items with loadings ≥ .60 are suggested to give a more reliable representation of factors and are therefore presented in Table 2.2 only.

Table 2.2

A two-factor solution on ADI-R algorithm, related to the 4-5-age period

Items from algorithm	Factor 1 Socially impaired behavior	Factor 2 Stereotyped language/behavior
Socialization		
Offers comfort	.711	
Social smiling	.706	
Response to children	.662	
Quality of social overtures	.657	
Appropriateness social response	.645	
Seeking to share own enjoyment	.639	
Interest in children	.619	
Communication		
Imaginative play alone	.721	
Imitative social play	.676	
Instrumental gestures	.604	
Stereotyped utterances		.669
Idiosyncratic language		.629
Repetitive stereotyped behavior		
Unusual sensory interests		.666
Hand finger mannerisms		.615
Variances explained, %	25	13

Note:

Principal Component Analysis with varimax rotation. Only loadings above .60 are shown

The two factors corresponded to the two symptom dimensions *socially impaired behavior* and *stereotyped language and behavior* which were also present in the three-factor solution. The two-factor solution explained 38% of the variance and included 14 items: factor 1 with 10 items about impaired socialization and play skills and factor 2 with 4 items about impaired language skills, unusual sensory interests and behavioral mannerisms. A PCA analysis with a

two-factor solution on the current status revealed a same structure (data not shown). In addition to the PCA, a Mokken scale analysis on the 37 algorithm items relating to the 4-5-age period gave additional support for the two-factor solution. With the MPS5 search method two Mokken scales were found: scale 1 with 17 items about socially impaired behaviors (with a medium scale coefficient H of .41) and scale 2 with 6 items about stereotyped language and behaviors (with a weak scale coefficient H of .35) (see table 2.3).

Table 2.3

Mokken analysis with two derived scales on 37 ADI-R algorithm items related to scores on the 4-5-age period (Mean = mean group score; Difficulties = max.score of 2 – mean score; H-i = goodness of fit for each item separately to the scale)

	Mean	Difficulties	H-i
Scale 1 (17 items):			
Nodding	.97	1.03	.38
Headshaking	1.00	1.00	.39
Response to children	1.14	.86	.50
Seeking to share own enjoyment	1.26	.74	.41
Appropriateness of social responses	1.26	.74	.42
Directing attention	1.30	.70	.37
Social smiling	1.32	.68	.47
Imitative social play	1.36	.64	.44
Quality of social overtures	1.37	.63	.47
Instrumental gestures	1.47	.53	.38
Offers comfort	1.48	.52	.45
Interest in children	1.52	.48	.38
Social chat	1.52	.48	.34
Direct gaze	1.57	.43	.31
Imaginative play alone	1.66	.34	.49
Group play with peers	1.77	.23	.47
Imaginative play with peers	1.79	.21	.40
Scale2 (6 items):			
Idiosyncratic language	.44	1.56	.39
Unusual sensory interests	.70	1.30	.38
Stereotyped utterances	.77	1.23	.38
Hand and finger mannerisms	.85	1.15	.34
Compulsions/rituals	.86	1.14	.32
Repetitive use of objects	1.06	.94	.30
SCALE 1: coeff. of scalability H scale		.41	
SCALE 2: coeff. of scalability H scale		.35	

GROUP DIFFERENCES

To look for any differences in the two symptom dimensions found among the verbal subjects, we calculated sum scores per factor in order to obtain individual scale scores. The internal consistency for both factor scales related to the 4-5-age period was acceptable (Cronbach α = .88 and .66 for respectively factor 1 and factor 2). The group with AD showed higher mean scores on both factor scales compared to the PDD-NOS/AS group (the five subjects with AS were incorporated in the PDD-NOS group), however not reaching the level of significance (on factor scale1: mean AD 14.5 (1.0), mean PDD-NOS/AS 13.6 (.7); on factor scale 2: mean AD 3.2 (.5), mean PDD-NOS/AS 2.6 (.3)).

LATENT CLASS ANALYSIS

The latent class analysis revealed an optimal solution with two latent classes. The relative frequencies are shown in the figures, including the two scales found with PCA on items referring to child's behavior at the 4-5-age period. It can be seen from both figures that the first class (N= 49, figure 1) has relatively low scores on each scale (e.g. because of high frequencies in the first quartile), whereas the second class (N=38, figure 2) has relatively high scores on each scale (e.g. because of the high frequencies in the latter three quartiles). These findings suggest that the two latent classes differ only in symptom severity.

Figures 2.1-2.2

Probabilities for each derived scale with two latent classes. Each scale is divided into four categories (or quartiles). The categories (or quartiles) represent expected relative frequencies of scale scores and range from low to highly frequent.

Latent Class 1 (N=49) and Latent Class 2 (N=38) related to the 4-5 age period

Figure 2.1 Probabilities for class 1

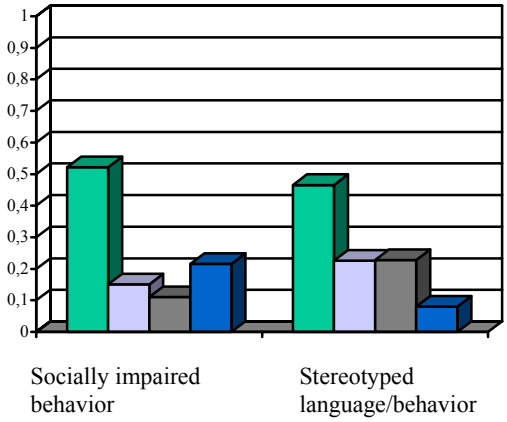
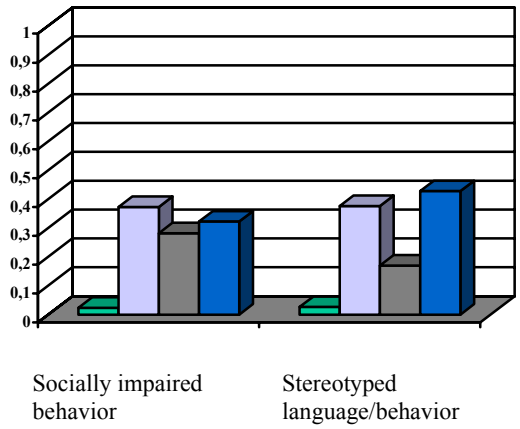


Figure 2.2 Probabilities for class 2



DISCUSSION

The present study could not confirm the DSM-IV-TR triad as the underlying symptom dimensions in a verbal ASD group. Moreover, two behavior domains appeared most relevant in representing the latent structure. We used an exploratory factor analysis to look for underlying symptom dimensions using the DSM-IV criteria for AD, however because the ratio number of items and sample size was not ideal, we examined the robustness of the factor structure found from PCA with Mokken scale analysis. A similar two-factor solution from the Mokken scale analysis emerged. With regard to this two-factor solution, the first factor referred to an inability to attend to other persons adequately, verbally and nonverbally. All behaviors were characterized by not being directed to others and resulted in social and communication impairments, manifested in daily living and in play situations (*impaired social communication*). The second factor referred to language skills, motor abnormalities and interests that appear unusually focused. For example, language characteristics like

idiosyncratic language and stereotyped utterances relate to unusual sensory interests, and motor mannerisms. This behavior domain seemed to encompass all behaviors related to unusually focused language and behavior skills (*stereotyped language/behavior*). Other studies revealed impaired social interaction and impaired language as two main features in autism (Fein *et al*., 1999; Wing & Gould, 1979; Berument, Rutter, Lord, Pickles, & Bailey, 1999). The present results suggested moreover, that impaired language skills were related to restricted interests and stereotyped mannerisms. With regard to classifications within ASD, our results indicated subjects with AD and subjects with PDD-NOS/AS to function along a continuum of autistic-like behaviors that vary in severity. This was confirmed by the latent class analysis that showed comparable profiles for both subtypes on the two extracted factors. The latent classes differed in severity rather than in profile, which implied a dimensional PDD construct.

In the DSM-IV-TR, the behaviors of autism are categorized into a triad and studies have shown that the behaviors in the triad are related to each other (Wing & Gould, 1979; Lord, Rutter, & Le Couteur, 1994; Spitzer & Siegel, 1990; Volkmar *et al*., 1994). However, regarding the underlying behavioral structure in the whole autism spectrum different dimensions emerged, which is comparable to other factor analytic studies. For example, three factors were shown in the ADI-R and ADOS-G on social communication skills (Robertson, Tanguay, L'Ecuyer, Sims, & Waltrip, 1999; Tanguay, Robertson, & Derrick, 1998), and two factors were shown in the domain scores of ADI-R and Vineland Adapative Behavior Scales (Sparrow, Balla, & Cicchetti, 1984) on autistic symptoms and level of functioning (Szatmari *et al*., 2002). In addition, Wadden, Bryson and Rodger (Wadden, Bryson, & Rodger, 1991) obtained a three factor solution on scores on the Autism Behavior Checklist (Krug, Arick, & Almond, 1980). Their three-factor model is similar to the two-factor solution of the present study: It included items about inappropriate responding to the environment in a factor about non-responsiveness, inattentive to social cues (factor 1 describing socially impaired behavior) and items about peculiar speech patterns, restricted interests and motor mannerisms as aloofness, being repetitive (factor 2 describing stereotyped language and behavior).

Limitations

This study has however some limitations that should be taken into account. First, four comments need to be made regarding the included group. (i.) The sample size is relatively small to examine a factor structure. Therefore, in addition, a nonparametric item response model (Mokken scale) was applied which confirmed the two-factor outcome. (ii.) The

symptom dimensions found are based solely on verbal subjects. Preliminary analyses (unpublished) of groups that include nonverbal subjects yield comparable dimensions, but they need further examination. (iii.) Subjects' etiology was not clarified in order to look for distinguishable symptom dimensions. It would be interesting to verify whether subjects with a known medical condition like fragile-X syndrome will show a different symptom structure. (iv.) The group with Asperger's Syndrome was clearly inadequately represented. Given the discussions about the validity of Asperger's Syndrome (Howlin & Asgharian, 1999) it will be intriguing to find out whether symptom dimensions in AD or PDD-NOS will differ from Asperger's Syndrome. In addition, it would be interesting to investigate whether the symptom dimensions differ between ASD subjects with mental retardation and ASD subjects functioning in the range of borderline to normal intelligence. Second, the symptom dimensions that are apparent in this study are based on one instrument, the ADI-R. However, this instrument is currently the most recent and extensive diagnostic measure that is available for autism and, additionally, is closely related to the DSM-IV criteria. In a future study it would be interesting to determine whether the same factor structure underlies the ADOS-G as well, because both instruments are considered complementary in research and in clinical settings (Lord, Leventhal, & Cook, 2001). Tanguay and co-authors carried out a factor analytic study of the ADI-R and of the ADOS-G. Although they found that a comparable factor structure underlies both instruments, their study omitted many items from the ADI-R, because it was concerned only with current scores on items about social communication (Robertson, Tanguay, L'Ecuyer, Sims, & Waltrip, 1999; Tanguay, Robertson, & Derrick, 1998). Third, the present study used a cross sectional design to look for behavioral dimensions on two time periods, as assessed by the ADI-R (past and current ratings). Eventually, it may be interesting to use the ADI-R in a longitudinal design to examine the stability of the extracted symptom dimensions. Finally, studies have indicated that distinguishing subjects with ASD is difficult at times (Allen *et al*., 2001) and that IQ plays a major role in prognosis (Wing, 1997; Mahoney *et al*., 1998). A follow-up study might reveal possible differences in the development of symptom dimensions among ASD subjects, functioning in different IQ ranges.

Clinical Implications

Examining phenotypic variation and underlying symptom dimensions in the autism spectrum is important for interpreting neurobiological mechanisms or developing effective treatments. The present study looked for the presence of the DSM triad underlying the behavioral criteria

of AD in a group of verbal ASD subjects, and showed that the symptom structure found did not confirm the triad of the DSM-IV-TR. Instead, the extracted dimensions gave empirical support for restructuring major DSM criteria. Moreover, two derived dimensions were shown to be the best representation of the latent structure in verbal ASD individuals. Within the construct of the autism spectrum, verbal individuals with AD or with PDD-NOS/AS appeared to function along a continuum of autistic-like behaviors in varying severity, implying a dimensional PDD construct. However more studies are needed to look for empirically derived symptom domains underlying the autism spectrum, given the restricted group of only verbal subjects included in this study.

3.

SYMPTOM STRUCTURE UNDERLYING THE ADOS-G AND ADI-R IN VERBAL CHILDREN AND ADOLESCENTS WITH AN AUTISM SPECTRUM DISORDER

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ABSTRACT

OBJECTIVE: The present study investigated the phenotypic variation in the autism spectrum, by examining the symptom structure underlying two international standardized classification instruments: the Autism Diagnostic Observation Schedule (ADOS-G) and the Autism Diagnostic Interview (ADI-R). METHOD: Data of verbal individuals with an autism spectrum disorder (n=78) and verbal individuals with only some autistic traits (n=78) were included for analysis. A nonparametric item response technique, the Mokken scale analysis, was applied to construct one-dimensional scales from the included ADOS-G and ADI-R items. Group differences on the derived symptom domains were examined with MANOVA and correlations between the derived domains and between the domains and the Autism Behavior Checklist were verified. RESULTS: Mokken scale analysis revealed seven unidimensional scales, covering three major symptom domains: 'inappropriate social communication' according to ADI-R and ADOS-G separately, 'impaired make-belief and social play' and 'stereotyped speech and behaviors'. Evidence for a continuum of symptom severity was found, with individuals with an Autistic Disorder showing more stereotyped features in speech and behaviors than individuals with milder variants of autism (like PDD-NOS) or with only some autistic traits. CONCLUSIONS: The symptom structure underlying the ADI-R and ADOS-G was found to comprise three major symptom dimensions on which subjects' behaviors fluctuated. The different scope of the instruments and the need for empirically derived symptom dimensions are discussed.

INTRODUCTION

Many studies found evidence that autism is a part of a spectrum of autistic-like disorders (Allen et al., 2001; Lord et al., 2000; Prior et al., 1998; Wing, 1997). Individuals with an autism spectrum disorder, such as Autistic Disorder, Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) or Asperger's Syndrome (American Psychiatric Association, 2000) are shown to differ from each other on a continuum of severity when their behaviors are controlled for language skills. However, PDD-NOS and Asperger's Syndrome are two classifications that still lack good psychometric qualities (Klin, Volkmar, Sparrow, Cicchetti, & Rourke, 1995; Mahoney et al., 1998; Sponheim, 1996). Studies therefore investigate the phenotypic variation in the autism spectrum, by establishing symptom domains empirically, in order to distinguish subtypes on the basis of the profiles on the derived symptom domains.

Currently, two international instruments are used to classify individuals with an autism spectrum disorder in a semi-standardized manner: the Autism Diagnostic Observation Schedule-Generic (ADOS-G), which is a play observation (Lord et al., 2000), and the Autism Diagnostic Interview-Revised (ADI-R), which is a standardized interview with the primary caregiver (Lord, Rutter, & Le Couteur, 1994). Both instruments explore many behaviors that concern autism and are used complementary. So far, two studies applied the ADOS and the ADI-R to identify symptom domains in autism (Robertson, Tanguay, L'Ecuyer, Sims, & Waltrip, 1999; Tanguay, Robertson, & Derrick, 1998). In both studies, 13 social communication items from the ADOS and 16 social communication items from the ADI-R were selected and factor analyzed. The results showed a comparable three-factor structure underlying both instruments: joint attention, affective reciprocity, and theory of mind. However, the factor that explained most variance in the two instruments differed. In the ADOS, the factor 'joint attention' explained most variance, representing items about sharing enjoyment in interaction, reciprocal communication and reporting experiences. In the ADI-R, the factor 'affective reciprocity' explained most variance. This factor corresponded to items about seeking comfort when hurt, offering to share, and being affectionate to others. The authors stated that apparently both instruments measured different manifestations of social communication skills, due to the different perspective on the child's functioning. Additionally, a weak correlation between the clinical diagnosis and the overall severity of deficits in social communication was found. This finding was interpreted as the presence of different symptomatology in the clinical classification groups; individuals with PDD-NOS or

Aspergers Syndrome may show good communication skills, but impaired scope of interests, use of objects or mannerisms instead. Because the authors focused on social communication deficits only, differences in stereotyped behaviors between groups could not have emerged.

The present study examined the symptom structure in verbal children and adolescents with a broad range in autistic symptomatology, i.e. with impairments in social communication, play skills and with stereotyped activities. With the symptom structure found, we aimed to gain insight into the phenotypic variation in the autism spectrum, by identifying major symptom domains and by examining how the classification groups functioned on the derived symptom domains. The current study extends on a previous study about symptom dimensions in verbal individuals with an autism spectrum disorder using the ADI-R (Van Lang *et al*., submitted; see chapter 2). In that study, parametric and nonparametric techniques indicated a two dimensional structure instead of the DSM triad underlying the autism criteria: socially impaired behavior and stereotyped language and behavior. This study examined whether the same structure will occur when the ADOS-G is added. In addition, the symptom structure is identified in a larger group of verbal individuals with autistic traits ranging from having a clinical classification (i.e. Autistic Disorder, PDD-NOS or Asperger's Syndrome) to individuals with only some minor autistic features not severe enough to warrant a clinical diagnosis.

MATERIALS AND METHODS

Participants

Two groups of verbal children and adolescents, all from three northern regions in the Netherlands, were recruited to this study: (a) from schools for children with mild to severe learning problems (N=120) and (b) from an Outpatient Clinic for patients with Autism Spectrum Disorders (N=36). The participants selected at the schools were all likely to be on the autism spectrum on the basis of screening with a questionnaire, completed by teachers (PDD-MRS, (Kraijer, 1997)). This questionnaire is specifically designed to detect PDD in this population. Subsequently, all participants from both groups were examined for their diagnostic classification and behavioral profiles with the ADI-R (Lord et al., 1994) and the ADOS-G (Lord et al., 2000). Based on the protocols of the ADI-R and videotapes of the ADOS-G, four experienced clinicians provided a clinical diagnosis of an Autistic Disorder (AD), PDD-NOS or Asperger's Syndrome (AS), or for any other disorder but PDD ('typically

developing') to each participant, based on the DSM-IV-TR criteria (American Psychiatric Association, 2000). For establishing the clinical diagnosis, the clinicians were blinded to the classifications according to both instruments, and a consensus diagnosis was reached when there was any doubt in classifying a participant (the inter-rater agreement with a weighted kappa was .68). With regard to the cognitive abilities of each participant, if a full-scale IQ (FIQ) had been determined within 2 years of the study, that figure was used. If not, one of the following Wechsler scales were used: Dutch versions of the WAIS-R (Uterwijk, 2000), WISC-R (Van der Steene et al., 1986), or WPPSI-R (Van der Steene & Bos, 1997). Exclusion criteria were: profound to severe mental retardation (FIQ<35), being untestable in a standard test situation, and being non-verbal. For the latter, we used the ADOS-G item about overall level of non-echoed language as criterion for verbalization. Only participants with functional use of at least three word phrases and comprehensible language were included. Of the 156 children and adolescents, the clinical raters classified 27 with AD, 48 with PDD-NOS, 3 with Asperger's Syndrome (AS) (combined into the category of 51 PDD-NOS/AS), and 78 as typically developing (TD). The TD group may have had some social communication problems, however their behaviors pointed more towards other behavioral disabilities than primarily impairments within the autism spectrum. The majority of the participants were male: 67 in the PDD group and 56 in TD group. The chronological ages varied between 5-20 years, with a mean of 12;02 years (SD 3;10) in the PDD group, and 10;10 years (SD 3;03) in the TD group. The FIQ ranges varied between 36-129, with a significant higher mean in the PDD group (mean FIQ of 69.0 (SD 22.1) in AD group, 68.8 (SD 22.7) in PDD-NOS/AS group, compared to 59.2 (SD 15.5) in TD group).

Measures

The ADOS-G (Lord et al., 2000) is a standardized play observation. The purpose is to elicit spontaneous behaviors through structured play materials and activities and through semistructured interactions pressed by the examiner. It provides the use of different modules 1 to 4, with each module being specified to participants' developmental and language level. The four modules are however capturing comparable items. The classification criteria of the ADOS-G algorithm are related to the DSM-IV triad of an Autistic Disorder or PDD-NOS, but the classification is based on social and communication domains only. Due to the small time limit of the assessment, the ADOS-G does not provide good opportunities to elicit restricted and repetitive behaviors (Lord et al., 2000). Reported scores on reliability and validity are substantial to excellent: good discrimination between having an autism spectrum disorder or

not, but less discrimination between PDD-NOS and Autistic Disorder (Lord et al., 2000). The previous version of the ADOS (Lord et al., 1989) showed a good differentiation between autism and language disorders (Noterdaeme, Sitter, Mildenberger, & Amorosa, 2000).
The ADI-R (Lord et al., 1994) is a semi-standardized interview with the principal caregiver, consisting of questions about the functioning of the child in the past and present. For all items, caregivers are asked to look back at the past corresponding to the 4-5-age period and then focus on the current status. With an established algorithm based on the DSM-IV triad of an Autistic Disorder, together with an age of onset before three (Lord et al., 1997), a classification of Autistic Disorder versus non-Autistic Disorder can be made. The ADI-R has reported scores on sensitivity and specificity of .86 and .91 respectively (Lord et al., 1994). For children with mental ages below 2 years and for higher-functioning individuals, specificity and sensitivity are lower (Lord et al., 1994). Interrater and retest reliability seem promising (Hill et al., 2001).
In the present study, we selected 12 ADOS-G items over modules 2 to 4, that measured same or comparable social and communicative behaviors (6 items about reciprocal social interaction, 5 items about language and communication, and 1 item about play and imagination skills). Of the 12 social communication items, 10 items are also included in the ADOS-G algorithm (with the exception of 'overall quality of rapport' in module 4, two items are not included in the algorithm: 'speech abnormalities associated with autism' and 'immediate echolalia'). We selected 37 ADI-R algorithm items for verbal individuals, representing social communication skills and repetitive and stereotyped behaviors. Only current ratings of ADI-R items are presented, because we wanted to compare the structure of ADI-R and ADOS-G relating to similar time periods. The Autism Behavior Checklist (ABC) (Krug, Arick, & Almond, 1980), a parent rating scale developed for the screening for autism, was used as a measure for the quantity of current autistic traits. The total score of the ABC is applied to look for a relationship with the symptom structure found.

Data Analysis

In the ADOS-G and in the ADI-R, all 3 scores were recoded as 2. Scores of 8 (not applicable) or 9 (not known) in the ADI-R were recoded as 0, and the score 7 (definite abnormality but unspecified) on the item about pronominal reversal as 1. For investigating the symptom structure, a non-parametric polytomous item response analysis was used, the Mokken scale analysis (Mokken, 1971). This analysis builds hierarchical, unidimensional scales and is based on the assumption of the presence of an underlying latent attribute represented by a pool of

items related to this attribute (De Jong & Molenaar, 1987). The stochastic distribution of the response categories for each combination of participant and item is examined, and as a result, the observed response patterns for the latent attribute is explained, and participants' responses to each item separately on the latent attribute is predicted. In the present study, the program MPS5, Mokken Scale analysis for Polytomous items-Revised (Molenaar & Sijtsma, 2000) was used to construct unidimensional scales from the 49 included items (12 ADOS-G and 37 ADI-R items). The derived scales are constructed in a stepwise search procedure, based on the frequency of participants' responses per item, running from no response (difficult items with a score of 0) to full response (easy items with a score of 2). Each scale is build on a highly correlated item pair and results in a hierarchy of items ordered by its difficulty. The deviation of the observed data structure from the perfect scalogram structure of Guttman (deterministic model) is tested by Loevinger's scalability coefficient H. A minimal value of .30 is recommended, and H values varying between .30-.40 are supposed to reflect a weak scale, varying between .40-.50 a medium scale, and exceeding .50 a strong scale (De Jong et al., 1987). Group differences on the symptom structure found are computed with MANOVA. Due to the variety in chronological age (CA) and FIQ of the participants, mean scores are adjusted for CA and FIQ. Posthoc pairwise comparison applying Least Significant Difference (LSD) was used to compare the mean scores per group. To look for a relationship between the derived Mokken scales and between the ABC total score and the derived scales, pearson's correlation (bivariate) was applied.

RESULTS

SYMPTOM STRUCTURE

Mokken scale analysis revealed 7 unidimensional scales, of which six scales consisted of ADI-R items and one scale of ADOS-G items. Scales IV to VII represented stereotyped features in speech and behavior (relating to the ADI-R), of which three scales consisted of either one item pair or three items. We therefore decided to present scale IV only, consisting of five items. Tables 3.1 to 3.4 shows how the item response per scale is constructed.

Table 3.1 - 3.4

Seven scales resulting from the Mokken scale analysis on 37 ADI-R and 12 ADOS-G items over N=156 (Mean = mean group score; Difficulty = max.score of 2 – mean score; H-i = goodness of fit for each item separately to the scale)

3.1 SCALE I: 'Social communication ADI-R'

14 items:	Mean	Difficulty	H-i
Range of facial expressions to communicate	.43	1.57	.37
Seeking to share own enjoyment with others	.46	1.54	.44
Showing and directing attention	.47	1.53	.38
Nodding	.52	1.48	.33
Headshaking	.54	1.46	.30
Quality of social overtures	.55	1.45	.36
Pointing to express interests	.56	1.44	.34
Appropriateness of social responses	.56	1.44	.35
Social chat	.63	1.37	.35
Convential instrumental gestures	.65	1.35	.34
Social smiling	.65	1.35	.39
Offers comfort	.72	1.28	.42
Reciprocal conversation	.98	1.02	.34
Having friends	1.35	.65	.29
Coeff. of scalability H		.36	

Note: ADI-R items with current ratings

3.2 SCALE II: 'Make-belief and social play skills ADI-R'

8 items:	Mean	Difficulty	H-i
Response to other children's approaches	.23	1.77	.66
Interest in children	.30	1.70	.66
Imaginative play	.33	1.67	.59
Spontaneous imitation of actions	.33	1.67	.56
Imitative social play	.34	1.66	.65
Imaginative play with peers	.42	1.58	.69
Group play with peers	.49	1.51	.69
Offering to share	.86	1.14	.32
Coeff. of scalability H		.60	

Note: ADI-R items with current ratings

3.3 SCALE III: 'Social communication ADOS-G'

10 items:	Mean	Difficulty	H-i
Stereotyped/idiosyncratic words or phrases	.22	1.78	.30
Overall quality of rapport	.45	1.55	.44
Speech abnormalities associated with autism	.51	1.49	.33
Quality of social response	.56	1.44	.49
Conversation	.58	1.42	.46
Descriptive, convential, instrumental gestures	.65	1.35	.33
Facial expressions directed to others	.66	1.34	.47
Amount of reciprocal social communication	.74	1.26	.56
Quality of social overtures	.76	1.24	.46
Unusual eye contact	.79	1.21	.43
Coeff. of scalability H		.43	

3.4 SCALE IV: 'Stereotyped speech and behavior in ADI-R'

5 items:	Mean	Difficulty	H-i
Neologisms/idiosyncratic language	.14	1.86	.34
Verbal rituals	.32	1.68	.41
Stereotyped utterances	.37	1.63	.38
Circumscribed interests	.72	1.28	.34
Inappropriate questions	.74	1.26	.41
Coeff. of scalability H		.38	

Note: ADI-R items with current ratings

The first scale (weak scale coefficient H of .36) consisted of 14 ADI-R items about inappropriate social communication. The three most difficult items, on which the participants responded least, were impaired use of facial expressions to communicate and less sharing and directing enjoyment and attention with others. Most participants responded frequently to having problems with offering comfort, reciprocal conversation and with establishing friendships. Scale II consisted of 8 ADI-R items encompassing impaired make-belief and social play (strong scale coefficient H of .60). Difficulties in responding to and having interest in other children were least occurring, followed by impaired make-belief, like imitation and imagination skills. The items about group play with peers and offering to share occurred more often. Scale III was constructed with ADOS-G items only (medium scale coefficient H of .43). Ten items about inappropriate social communication were interrelated, of which items about stereotyped words and phrases were scored rarely and unusual eye contact most frequently. Scale IV consisted of five ADI-R items about stereotyped characteristics in speech

and behavior (weak scale coefficient H of .38). Idiosyncratic language was scored rarely, as were verbal rituals and stereotyped utterances. Participants responded more frequently in having circumscribed interests and putting inappropriate questions. When the ADI-R ratings from the 4-5-age period were used, four scales emerged (data not shown). The first scale consisted of 26 ADI-R items about impairments in social communication and play skills, and included 4 items about stereotyped characteristics in speech. The second scale was composed of 10 ADOS-G items and the third and fourth scale with stereotyped speech and behaviors from the ADI-R.

GROUP DIFFERENCES

The three groups are compared on their mean scores per derived Mokken scale. A summary scale of scale IV to VII is computed, in order to have a complete measure of stereotyped speech and behaviors. The scores are adjusted for CA and FIQ, because both were of significant influence on the scale ratings (respectively $F(4,148)= 45,648$, $F(4,148)= 5,657$, $p<.01$).

Table 3.5

Mean scores (SD) per clinical classification group, adjusted for CA and FIQ, on the derived Mokken scales I, II, III, and a summary scale IV-VII

	AD N=27	PDD-NOS/AS N=51	TD N=78	Posthoc pairwise comparison
Scale ratings:				
Scale I (range 0-26)	12.8 (1.0)	11.9 (.8)	5.9 (.6)	AD, NOS > TD[1]
Scale II (range 0-15)	4.7 (.7)	4.1 (.5)	2.3 (.4)	AD, NOS > TD[1]
Scale III (range 0-16)	10.0 (.7)	6.8 (.5)	4.0 (.4)	AD, NOS > TD[1] AD > NOS[1]
Sum. Scale IV-VII (range 0-16)	9.8 (.7)	5.9 (.5)	3.2 (.4)	AD, NOS > TD[1] AD > NOS[1]

Note: AD: Autistic Disorder, AS: Asperger's syndrome, TD: Typically developing, NOS = PDD-NOS/AS; [1] $p<.01$

A significant main effect of group on the scale ratings emerged ($F(8,269)= 14,175$, $p<.01$). Pairwise comparison (LSD) revealed that the AD group and the PDD-NOS/AS group had higher scores on each derived Mokken scale compared to the TD group ($p<.01$). The AD group showed significant higher scores than the PDD-NOS/AS group ($p<.01$) on scale III and summary scale IV. When the AD group is compared to the PDD-NOS/AS group on the separate items in both scales, univariate analysis with pairwise comparison showed a score of 1 (slightly shown) or 2 (definitely shown) more frequently in the AD group ($p<.05$) on the following items of scale III and summary scale IV-VII: ADOS-G and ADI-R items about stereotyped speech and inappropriate facial expressions, ADOS-G items about less reciprocal communication with undirected eye-contact, and ADI-R items about behavioral mannerisms and circumscribed interests.

CORRELATIONS

Significant lineair correlation's were observed between scale I and scale III ($r =.38$, $p<.01$), and between scale I and summary scale IV ($r =.48$, $p<.01$). A significant lineair correlation between the total score on the ABC and scale I ($r =.51$, $p<.01$) and summary scale IV ($r =.55$, $p<.01$) was found.

DISCUSSION

The symptom structure that underlied the ADI-R and ADOS-G in a verbal group of individuals with a broad range of current autistic symptomatology resulted in seven unidimensional scales: six from the ADI-R and one from the ADOS-G. The symptom structure shifted slightly when ADI-R ratings from the 4-5-age period were applied. The six scales derived from the ADI-R presented information about three symptom domains, 'inappropriate social communication', 'impaired make-belief and social play' and 'stereotyped speech and behaviors'. From the ADOS-G, only one scale about 'inappropriate social communication' was found. In the studies of Tanguay (Tanguay et al., 1998) and Robertson (Robertson et al., 1999), current ratings on social communication in the ADI-R and (a previous version of) the ADOS-G showed a structure of three domains: joint attention, affective reciprocity and theory of mind. Their domains of 'joint attention' and 'affective reciprocity' could not be replicated in the present study. Instead, the items of both domains clustered into one ADI-R and one ADOS-G scale about inappropriate social communication.

A reason for why we could not have replicated this distinction, could result from different inclusion criteria used. In our study many participants with FIQ's in the mild to moderate range were incorporated. Since age and IQ were shown to have an effect on the derived scales, it may be that due to participants' relatively fewer competencies, less differentiation in social communication skills have emerged. Their domain 'theory of mind' however was analogous to our ADI-R scale about impaired make-belief and social play. In addition, we found a separate scale of items about stereotyped features in speech and behaviors, that were not incorporated in the studies of Tanguay and Robertson.

Regarding the phenotypic variation on the derived scales, we found evidence for a continuum of symptom severity, comparable to other studies (Allen et al., 2001; Lord et al., 2000; Prior et al., 1998; Wing, 1997). Significant differences in symptom severity occurred between AD and PDD-NOS/AS on inappropriate social communication (ADOS-G scale III) and on stereotyped speech and behaviors (ADI-R summary scale IV). When these differences were looked upon per item, the AD group revealed more verbal and behavioral stereotyped features than the PDD-NOS/AS group, such as idiosyncratic words, stereotyped utterances and verbal rituals (in both instruments), reciprocal communication (in ADOS-G), and behavioral mannerisms and circumscribed interests (in ADI-R). This severity continuum on the derived symptom domains implied that the children and adolescents varied along dimensions of symptoms. In addition to the group differences, we aimed to see which major symptom dimensions could be identified. The established positive lineair correlation between scale I and III and between scale I and IV suggested a relationship between inappropriate social communication and stereotyped features in speech and behavior. In addition, this relationship was confirmed by the established correlation between the quantity of autistic traits, measured by the ABC, and increasing symptomatology on scale I and IV. In a previous study where we have investigated the symptom structure of the ADI-R in a verbal group of individuals with an autism spectrum disorder only, two dimensions showed to have best face validity: socially impaired behavior and stereotyped language and behavior (Van Lang *et al*., submitted; see chapter 2). Our present results corresponded largely to this structure, when now the ADOS-G was included, and a larger sample of individuals with a broad range of autistic symptoms and current ratings were applied.

Nonetheless, a separate scale about impaired make-belief and social play was found. Apparently, above the age of 4-5 years, difficulties with play skills (i.e. make-belief) and playing with other children become more differentiated so that they result in a distinct scale. In addition, the current ratings also revealed a significant differentiation in behaviors between

AD and PDD-NOS/AS, that was not present in our previous study. As indicated by Tanguay and Robertson, the ADI-R and ADOS may measure different manifestations of social communication skills, due to the different perspective on the child's' functioning. Our results gave support to this notion that the ADI-R has a broader scope of measuring symptom dimensions on different levels (i.e. social communications, play skills and stereotyped features), whereas the ADOS-G measures a cross-section of several specific autistic symptoms on one dimension (i.e. social communication). In addition, our results gave evidence of a fluctuation of autistic behaviors along the symptom dimensions of social communication, play skills and stereotyped features, instead of fluctuations along the DSM triad of behaviors.

The present study has three limitations that need further attention. First, only verbal children and adolescents were included, with very few participants with Asperger's Syndrome. Moreover, many of the participants functioned in the lower FIQ ranges. Second, most items that were incorporated about stereotyped features were based on the ADI-R. Due to less reliability of the ADOS-G items about stereotyped behaviors, the derived symptom dimension of stereotyped features is solely based on one instrument. However, as was shown, the AD group had more frequently stereotyped characteristics than the PDD-NOS/AS group, and accordingly than the TD group, this was also confirmed by the number of occurrences of stereotyped features on the ADOS-G items (22% in AD, 13% in PDD- NOS/AS, and 11% in TD). Third, we used a nonparametric item response analysis, instead of factor analysis, to identify the symptom structure. An advantage of this technique is the hierarchy in item difficulty given per scale. Focusing on this hierarchy, our results of the ADI-R scales could roughly be interpreted as a tendency from most to least difficulties in joint attention, understanding others and their feelings to establishing reciprocal relationships (scale I); in attention for others, make belief skills to more reciprocal play with others (scale II); and in stereotyped characteristics in speech, behaviors to having circumscribed interests (summary scale IV). The hierarchy in the ADOS-G scale could not easily be explained. However, interpreting the hierarchy in item responses in all the derived scales, over a group with a large variability in chronological age, is a little inconclusive. Therefore, normative data about developmental processes are important to determine, in order to aim at clinical subthresholds for separate developmental areas (Klin, Jones, Schultz, Volkmar, & Cohen, 2002).

CONCLUSION

To conclude, the derived symptom dimensions of ‘inappropriate social communication’, ‘impaired play skills’ and ‘stereotyped features in speech and behavior’ were based on two internationally standardized diagnostic intruments. The results gave support for a continuum of autistic symptomatology, in which individuals with AD could be distinguished from individuals with PDD-NOS/AS by having a more severe condition and by more verbal and behavioral stereotyped features. Investigating symptom dimensions in a group of individuals with a continuum of autistic symptomatology is very useful for diagnostic purposes. In addition, effects of behavioral or pharmacological interventions or inheritable vulnerabilities can be better monitored, when dimensions of symptoms are empirically established.

4.

STRUCTURAL EQUATION ANALYSIS OF A HYPOTHESIZED SYMPTOM MODEL IN THE AUTISM SPECTRUM

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ABSTRACT

OBJECTIVE: Several studies showed a different symptom structure underlying the spectrum of autistic-like disorders from the behavior triad as mentioned in the DSM-IV. In the present study, a hypothesized symptom model for autism was constructed, based on earlier explorative findings, and was tested with confirmatory analysis. METHOD: Items from the Autism Diagnostic Interview (ADI-R) were used to examine the goodness-of-fit of the hypothesized symptom model, compared to the goodness-of-fit of two DSM-IV models: (a) with ratings reflecting child's behaviors at age 4-5 years, and (b) with ratings reflecting subjects' current functioning. The three models were tested in a group of 255 verbal and nonverbal subjects with minor to severe autistic symptomatology. RESULTS: The DSM-IV models were shown to have estimation problems. Conversely, the hypothesized symptom model encountered no such problems and revealed to have an adequate fit on the sample data. However, some of the observed variables were weak indicators for the three latent factors in the model. CONCLUSIONS: The hypothesized symptom model appeared to be a plausible model in a group of subjects with a broad range of autistic behaviors and levels of functioning. Nevertheless, the stability of the model needs further examination in a larger group of subjects with disorders in the autism spectrum, taking into account subject's intellectual disability.

INTRODUCTION

Many studies revealed that autism is a genetically determined disorder (Rutter, Silberg, O'Connor, & Simonoff, 1999), and recent studies showed this genetic vulnerability also for the broader autism phenotype (Constantino & Todd, 2000; Silverman et al., 2002; Spiker, Lotspeich, Dimiceli, Myers, & Risch, 2002). Although the disorder has a neurodevelopmental origin, it is yet defined by its behavioral properties. In the DSM-IV-TR (American Psychiatric Association, 2000), autism is described by impairments in three behavior domains (the DSM triad): qualitative impairments in reciprocal behavior, qualitative impairments in communication, and the occurrence of stereotyped behaviors or restricted interests. In order to examine candidate genes that contribute to the genetic susceptibility in autism, and the relationship with autistic behaviors, it is important to establish symptom domains that are empirically derived. Although several studies have shown that the behavior domains of the DSM triad are highly interrelated (Spitzer & Siegel, 1990; Volkmar et al., 1994; Wing & Gould, 1979), recent studies provide evidence that the structure of the autistic symptomatology differs from the DSM triad. Factor analytic studies on autistic core features, for example, showed a symptom structure that differed from the DSM domains, suggesting symptom domains of 'joint attention', 'affective reciprocity' and 'theory of mind' (Robertson, Tanguay, L'Ecuyer, Sims, & Waltrip, 1999; Szatmari et al., 2002; Tanguay, Robertson, & Derrick, 1998) or 'autistic symptomatology' and 'level of functioning' (Szatmari et al., 2002).

In accordance with this research, two earlier studies of the present authors also gave evidence of a different symptom structure in autism, for N=87 verbal subjects with a disorder on the autism spectrum, and N=156 verbal subjects with mild to severe autistic symptomatology respectively (Van Lang *et al*., submitted; see chapters 2 and 3). In both studies, the Autism Diagnostic Interview-Revised (ADI-R) (Lord, Rutter, & Le Couteur, 1994) was used as a framework to establish symptom domains in a group of verbal individuals with an autism spectrum disorder. The ADI-R is a standardized diagnostic interview for primary caregivers, and yields a comprehensive description of child's behaviors over two time periods: the 4-5 age period, and the current status of functioning. A classification of an Autistic Disorder is made with an ADI-R algorithm that consists of 37 extracted items. These items correspond to the DSM-IV criteria of an Autistic Disorder. The items that are specifically related to so-called verbal subjects (i.e. subjects who had functional and comprehensible use of at least three word phrases) were used accordingly in both studies. Depending on the applied age period, three candidate symptom domains appeared to have best

face validity: impaired social communication, stereotyped features in speech and behavior, and impaired play skills.

Impaired social communication was composed mostly of items from the DSM domain 'impaired reciprocal behavior', but also extended to items about inadequate use of gestures and failure to initiate or sustain conversational interchange from the DSM domain 'impaired communication'. *Stereotyped features in speech and behavior* was reflected by items of the DSM domain 'stereotyped behaviors and restricted interests', but also included items about stereotyped, repetitive or idiosyncratic speech characteristics from the DSM domain 'impaired communication'. *Impaired play skills* emerged as a separate factor when current ratings were applied, combining items from the DSM domains 'impaired social interchange' and 'impaired communication', i.e. failure to develop peer relationships and lack of varied spontaneous make-belief or social imitative play. However, because these derived symptom domains were extracted from two explorative techniques, applying only to verbal subjects, it is necessary to investigate whether the hypothesized symptom model also holds in a larger sample of verbal and nonverbal subjects, using confirmatory test procedures.

Structural Equation Modeling (SEM) was chosen as the statistical technique to test this hypothesized symptom model in a sample of N=255 verbal and nonverbal subjects with minor to severe autistic symptomatology. In general, a structural equation model is a combination of a measurement model and a (structural) latent variable model (Bollen, 1989). The models considered in the present study are confirmatory models, i.e. measurement models with correlated latent variables (the symptom domains). First, the DSM triad model (Model A1) was estimated and tested. For this model, the ADI-R items from the algorithm were applied, using ratings from the 4-5 age period, because these ratings correspond directly to the DSM criteria for Autistic Disorder. Second, the DSM triad model (Model A2) was estimated and tested, using the ADI-R algorithm items with ratings from the current status instead. It is argued that current ratings give a more reliable picture of child's behavior, especially when the subjects are amply aged above 4-5 years. As such, current ratings are supposed to be less subjected to information bias by child's primary caregivers. Finally, the hypothesized symptom model (Model B2) was estimated and tested on the same sample data of model A2, i.e. with current ratings, in order to substantiate the three symptom domains that were derived from the two earlier explorative analyses, as mentioned above.

METHOD

Investigation of the models

By means of the labels per behavior domain as presented in the ADI-R algorithm, the symptom domains of the broader autism phenotype are examined. The ADI-R labels consist of three to four items and are directly related to the DSM criteria of an Autistic Disorder, reflecting the DSM triad of qualitative impairments in reciprocal social interaction (*S*), qualitative impairments in communication (*C*), and having repetitive behaviors and stereotyped patterns (*R*). In order to encompass information about the DSM triad for verbal and nonverbal subjects and to restrict the number of items, sum scores per label were calculated. As a result, 12 ADI-R variables were determined: Failure to use nonverbal behaviors to regulate social interaction (*S1*); Failure to develop peer relationships (*S2*); Lack of shared enjoyment (*S3*); Lack of socio-emotional reciprocity (*S4*); Lack of, or delay in, spoken language and failure to compensate through gesture (*C1*); Lack of varied spontaneous make-belief or social imitative play (*C2*); Relative failure to initiate or sustain conversational interchange (*C3*); Stereotyped, repetitive or idiosyncratic speech (*C4*); Encompassing preoccupation or circumscribed pattern of interest (*R1*); Apparently, compulsive adherences to non-functional routines or rituals (*R2*); Stereotyped and repetitive motor mannerisms (*R3*); Preoccupations with part-objects or non-functional elements of materials (*R4*). These 12 variables were used in the analyses as the ADI-R indicators (or observed measurements) for the symptom domains (or latent factors) in the three models being tested. Figure 4.1 shows which indicators are used for which symptom domains in Models A and B.

The first factor model being tested (Model A1) was the DSM-IV triad with ratings applying to the 4-5 age period. The following measurement model was examined ($x = \Lambda\xi + \delta$), where the observed variables $x_¡$ ($¡=1,2,..12$) are a linear function of a latent factor ξ and a measurement error $\delta_¡$. In this three-factor model, the latent variables or factors are the three DSM symptom domains: 'impaired social interaction' ($\xi1$) with four indicators (*S1* to *S4*), 'impaired communication' ($\xi2$) with four indicators (*C1* to *C4*), and 'stereotyped behaviors' ($\xi3$) with four indicators (*R1* to *R4*). The second factor model being tested (Model A2) was the DSM-IV triad, examining the same measurement model as in model A1, but with ratings applying to the current status instead. The third factor model being tested (Model B2) was the hypothesized symptom model based on earlier exploratory findings, with ratings of subject's current status. The following measurement model was being tested with the three

hypothesized symptom domains: 'impaired social communication' (ξ1) with five indicators (*S1*, *S3*, *S4*, *C1* and *C3*), 'stereotyped language and behaviors' (ξ2) with five indicators (*C4*, *R1*, *R2*, *R3* and *R4*), and 'impaired make-belief and play skills' (ξ3) with two indicators (*S2* and *C2*)[1]. For all three models, non-zero covariances between the three factors were assumed.

[1] It should be noticed that although the last factor has only two indicators, these indicators are total scores of eight ADI-R items about impaired play skills.

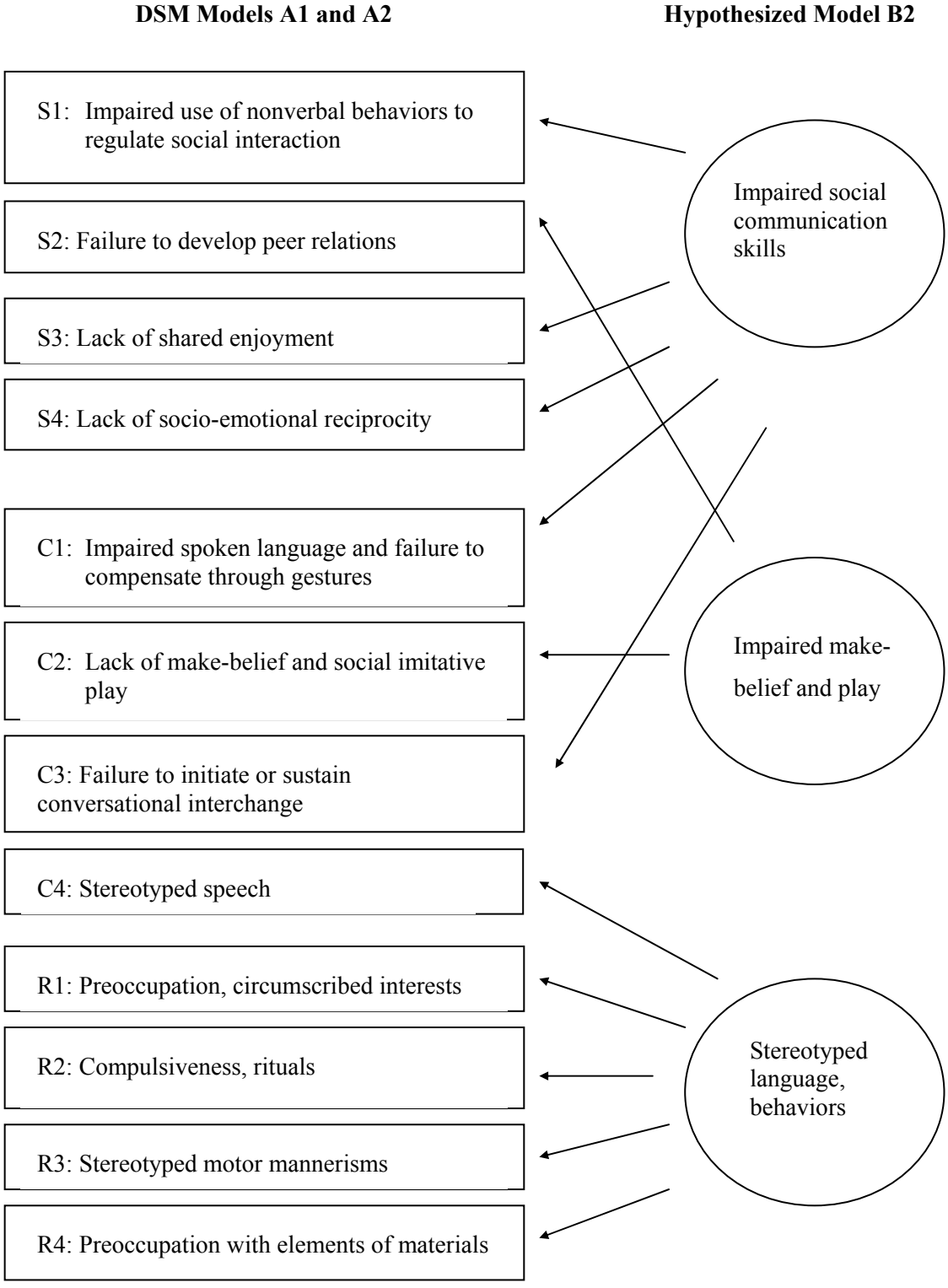

Figure 4.1
The indicators of the three factors in model B, as contrasted to the DSM models A1 and A2: S1 to S4 relate to the DSM domain 'qualitative impairments in reciprocal social interaction'; C1 to C4 relate to the DSM domain 'qualitative impairments in communication'; R1 to R4 relate to the DSM domain 'repetitive behaviors and stereotyped patterns'.

Sample

Of the 308 participants with autistic symptomatology and with ADI-R data available, 255 children and adolescents with a full-scale IQ > 20 were selected. They were recruited by two different designs. First, 209 participants were recruited by a population-based screening for Pervasive Developmental Disorders (PDD) at schools for children with mild to severe learning problems. These subjects were likely to have a disorder on the autism spectrum according to the PDD-MRS, a scale completed by teachers and specifically designed to detect PDD in this population (Kraijer, 1997). Second, 46 participants were recruited by a clinical study in an Outpatient Clinic for patients with Autism Spectrum Disorders. All participants (N=255) were examined in detail on their autistic behaviors with the Autism Diagnostic Interview Revised (Lord et al., 1994) and the Autism Diagnostic Observation Schedule (Lord et al., 2000) and were classified accordingly. In addition, based on the ADI-R protocols and ADOS-G videotapes, each participant received a clinical judgement of having an autism spectrum disorder or not, made by four experienced clinicians (for a detailed description of the procedure, see De Bildt *et al.,* 2003b). The cognitive abilities of each participant were determined either by an established FIQ if it had been determined within 2 years of the study, or by an reassessed FIQ with Dutch versions of the WAIS-R (Uterwijk, 2000), WISC-R (Van der Steene et al., 1986), WPPSI-R (Van der Steene & Bos, 1997) or the Dutch non-verbal intelligence scale SON-R (Snijders & Snijders-Oomen, 1975). Participants with profound mental retardation (FIQ < 20) and participants who were untestable in a standard test situation were excluded.

In this group of 255 participants, 130 received a clinical judgement of a disorder on the autism spectrum (ASD) according to the DSM-IV-TR criteria. The other 125 were judged to have social or communication problems, but their behaviors were not severe enough to warrant a clinical diagnosis of an autism spectrum disorder, and were defined as “typically developing subjects”. The ASD group was composed of 54 subjects with an Autistic Disorder (AD), 3 with Asperger’s Syndrome (AS), and 73 with a Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS). The majority of the subjects were male: 196 boys and 59 girls. The chronological ages varied between 4-20 years, with a mean of 11;03 (in years and months), and a standard deviation of 3;11. The FIQ ranges varied between 20-129, with most participants falling in the severe (N=66), moderate (N=52), and mild (N=88) FIQ range, and relatively less in the borderline (N=28), normal (N=15), or above normal (N=6) FIQ range.

Data Analysis

A Maximum Likelihood (ML) estimation procedure was used to examine the goodness of fit of the models. The assumptions of the ML procedure are: (1) the sample observations are independently distributed, (2) the indicators have a multivariate normal distribution, (3) the hypothesized model is approximately correct, (4) a sample covariance matrix S is being analyzed, and (5) a large sample size N is used, in order to approximate asymptotic properties of parameter, standard error and model-fit estimators (Jöreskog & Sörbom, 1989). With respect to the requirements of multivariate normal distribution, the 12 ADI-R indicators were not normally distributed (a median interquartile range of 2.00, and a median skeweness of .95 , with minimum .14 and maximum 1.40, and a median kurtosis of .01, with minimum-1.08 and maximum 1.14). Although the skewness and kurtosis values were not extreme (Boomsma & Hoogland, 2001), it was decided to use a robust ML estimation procedure to improve on the estimates of standard errors and model fit while analyzing a sample covariance matrix S. The global model fit was evaluated using the scaled χ^2-statistics of Satorra and Bentler (1994), which is a mean-adjusted chi-square statistic. The robust estimation procedure can be summarized as follows. First, the sample covariance matrix S and corresponding (estimates of) asymptotic covariance matrices of these sample covariances, ACôv (S), were calculated using the PRELIS program 2.54. Second, the estimated covariance matrix S and ACôv (S) were used as input for the LISREL program 8.54 to estimate the postulated models using robust ML estimation. The PRELIS 2.54 program is part of the LISREL program 8.54 (Jöreskog & Sörbom, 1996).

RESULTS

Can the models be estimated?

Both DSM models (Model A1 and Model A2) encountered an estimation problem that could be labeled as an empirical identification problem. It appeared that the covariance matrix of the latent factors in both models was not positive definite, showing a correlation larger than one between the factors *S* (DSM domain of reciprocal social interaction) and *C* (DSM domain of communication). These findings suggest a high multicollinearity between the factors *S* and *C* when ADI-R ratings of child's age of 4-5 years and ADI-R ratings of subject's current functioning were applied. The nature of the estimation problem required further investigation. Apparently, there is a discrepancy between the sample data and the postulated model, and the

cause of the problem could be the random sample data, or the postulated model, or both. To investigate whether the problem might be due to the sample covariance matrix S, two random subsamples of size N=205 and N=155 were taken from the total sample size of N=255. For each of these two subsamples, models A1 and A2 were estimated, and in all cases the problems of an inproper covariance matrix of the latent variables remained. In addition, different starting values were used, and a different estimation program (EQS 5.4; Bentler, 1995) was applied as an additional check on the results. In both cases, however, the problem remained. Furthermore, models A1 and A2 were also tested with the restriction of zero covariances between the factors (i.e. factors were assumed to be uncorrelated), and resulted in inadequate fit measures with modification indices pointing to a high correlation between *S* and *C*. It was therefore concluded that the irregularities encountered were (primarily) due to the postulated model; the Models A1 and A2 cannot be properly estimated and are therefore implausible. Subsequently, it would make no sense to discuss estimates of fit of both models, let alone the size of parameter estimates and corresponding standard errors (for a detailed presentation of the LISREL output on the Models A and B, see the internet site: www.ppsw.rug.nl\~boomsma.htm).

In contrast to Models A1 and A2, no estimation problems were encountered with Model B2 (see Table 4.1). The estimated covariance matrix of the latent factors appeared to be a proper matrix. The parameter estimates could be identified and revealed that the correlations between the three latent factors were substantively different from zero. In addition, low standard errors are found, indicating a good stability (reliability) of the parameter estimates, and the test statistic t-values, for the null hypothesis of population parameters having a value of zero, were all larger than five.

Table 4.1

Estimated correlation matrix of the latent factors for Model B2 (N=255). Presented are the estimated correlations, the corresponding estimated standard errors (in parentheses), and the test statistics (t-values).

	1. Impaired social communication	2. Impaired play skills	3. Stereotyped language/behavior
1.			
2.	0.48		
	(0.06)		
	8.09		
3.	0.48	0.37	
	(0.07)	(0.07)	
	6.98	5.27	

Goodness-of-fit indices

A number of goodness-of-fit measures of Model B2 are presented in Table 4.2.

Table 4.2

Goodness-of-fit indices for Model B2 (N=255). The cut-off criteria mentioned in the notes are partly based on the findings of Hu & Bentler (1999)

	Global Fit measures[1]					RMSEA[2]	SRMR[3]	NNFI[4]
	df	χ^2-NWLS	p	χ^2- SB	p			
Model B2	51	74.20	0.02	65.59	0.08	0.03 C.I. (0.0-0.06)	0.05	0.98

NOTE:

1 The Global Fit measures are a Normal Theory Weighted Least Squares chi-square (χ^2-NWLS) and a mean-adjusted chi-square of Satorra-Bentler (χ^2- SB), taking the non-normality of the data into account. Models with a scaled χ^2-value with $p > 0.05$ are judged to have a reasonable model fit to the observed data.

2 Root Mean Square Error of Approximation (RMSEA) is the value of the model test-statistic for close fit. Values ≤ 0.06 indicate a reasonable fit. C.I. is the 95% confidence interval.

3 Standardized Root Mean Square Residual (SRMR) is a standardized measure of the average of fitted residuals. Values ≤ 0.08 indicate a reasonable fit.

4 Nonnormed Fit Index (NNFI) is a measure of the improved fit of the postulated model relative to the independence model. Values ≥ 0.95 indicate a reasonable fit.

The overall fit of model B2 was found to be adequate, applying ML cut-off criteria from Hu and Bentler (1999) on the estimated values of the RMSEA, SRMR and NNFI.

In Figure 4.2, the completely standardized estimates of the factor loadings of model B2 are presented.

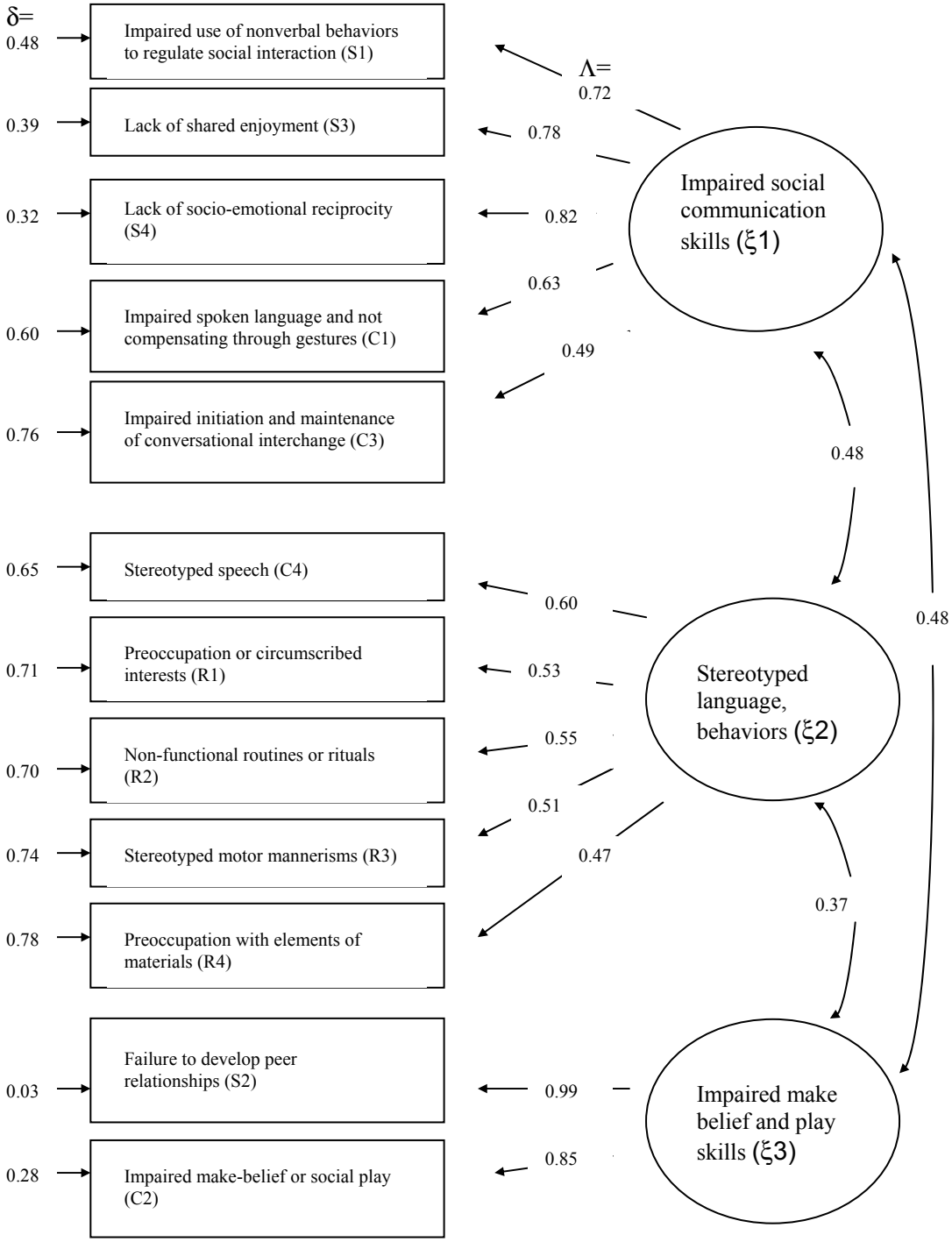

Figure 4.2
Confirmative analysis on the hypothesised model B (N=255). Presented are the completely standardised estimates of factor loadings between symptom domains (ξ) and indicators (Λ), and estimated correlations between the symptom domains and variances of the measurement errors (δ).

The completely standardized estimates of the factor loadings vary between .47 and .99, and the squared multipele correlation for the indicators (R^2) varies between .22 and .97 (estimates not shown in this paper). These findings point out that the indicators are substantially reflected by the factors, but that some indicators have a relatively weak association with their corresponding factor. This may partly be explained on the basis of the frequency distribution of subject's responses on some of the items. It appeared that the majority of subjects did not have a positive score on the items about stereotyped features in speech and behaviors (*R1 to R4*), or on the item about 'impaired initiation and maintenance of conversational interchange' (*C3*). In general, these items represent behaviors that are most prominent in individuals with a severe condition on the autism spectrum, i.e. for individuals with AD. In the sample size of N=255, only 54 subjects (about 20%) had a clinical classification of AD, and it could be argued that this proportion is too restricted to get a good distribution of features that reflect current stereotypies in speech and behavior.

DISCUSSION

The hypothesized symptom model (Model B2) with three latent constructs or symptom domains fitted the sample data reasonably well. Both DSM models (with ratings applying to the 4-5 age period and to the current age status of the child respectively) revealed estimation problems, indicating a high correlation between the DSM domains 'impaired reciprocal social interaction' and 'impaired communication'. Model B2 was based upon a combined construct of impairments in reciprocal social interaction and communicating skills, and did not encounter such estimation problems. Moreover, Model B2 showed no substantive discrepancy between the sample and model-implied covariances in a group of individuals with a broad range of autistic-like behaviors and levels of functioning. Therefore, Model B2 might provide a useful measurement structure for future studies, aimed to examine the relationship between empirically derived symptom domains and, for instance, autistic susceptibility genes.

The three latent constructs in Model B2 are based on the symptomatology of autism, and have a different item structure than that of the DSM triad. In Model B2, *Impaired social communication* contained information about poor verbal and nonverbal social communicative interchange. *Impaired make-belief and play* was comprised of a lack of play skills in individual activities and in relationship with peers. *Stereotyped language and behavior* consisted of stereotyped characteristics in speech and behavior. These latent constructs were

identified in two earlier studies in which explorative techniques were used (Van Lang *et al*., submitted; see chapters 2 and 3). They emerged as underlying constructs in verbal individuals with an established disorder on the autism spectrum (N=87), and in verbal individuals with a broader autism phenotype (N=156). In the present study, the inclusion criteria were broadened to verbal and nonverbal individuals with a broad scope of various autistic behaviors (N=255), and to individuals with a full-scale IQ larger than 20 (instead of a full-scale IQ larger than 35). The results showed that the validity of the latent variable structure from the explorative studies was not falsified in this confirmatory study.

Evidence for a different symptom structure than the DSM triad emerged from other studies as well (Robertson et al., 1999; Szatmari et al., 2002; Tanguay et al., 1998). These authors also used the ADI-R as the framework for investigating the behavior structure in autism. Conditional upon the included sample and the applied ADI-R indicators (item scores or domain scores), the autism symptomatology was specified into two or three separate symptom domains or it was combined with a distinct domain of adaptive functioning. Comparing the factors of Model B2 with the results of the group of Robertson and Tanguay (Robertson et al., 1999; Tanguay et al., 1998), shows that the factor 'impaired play skills' of Model B2 has similarities with their factor 'theory of mind'. In addition, the factor 'impaired social communication' of Model B2 may be a combination of their factors 'joint attention' and 'affective reciprocity'. However, the factor 'stereotyped language/behaviors' of Model B2 cannot be compared, because stereotypies in behavior were not included in the analyses by the group of Robertson and Tanguay. As is concluded in a review study by Beglinger and Smith (2001), no system is yet available that accounts for the symptom heterogeneity in autism. However, based on this review, the authors proposed a dimensional conceptualization for autism, in which four subtypes can be identified: variations in developmental delays, in social impairments, in restricted behavioral features, and in FIQ. The factors from Model B2 give a partial support for this proposed conceptualization of autism, but also shows an additional domain of impairments in play skills.

Although empirical support for Model B2 was not falsified, it is nevertheless essential to investigate the validity of the model in a new sample of autistic individuals. It was argued that due to the skewness and kurtosis of items about stereotyped characteristics in language and behavior, and problems in conversational interchange (i.e., showing many scores of 0, suggesting that the behaviors were not present), low standard estimates of factor loadings and low squared multiple correlations for indicators were found. These items refer to behaviors

that are largely indicative for individuals with an Autistic Disorder, and in our sample only 54 subjects with an Autistic Disorder could be distinguished. Therefore, to further substantiate our model, it needs subsequently to be tested in a larger group of individuals with autism spectrum disorders.

In addition, it should be noticed that a large part of the sample were individuals with an intellectual disability (about 80%), and it could be argued that due to the relatively lower cognitive abilities of this group, the latent construct of stereotyped language and behavior turned up (Beglinger et al., 2001). As was shown by Szatmari and colleagues (2002), symptom severity and level of functioning might be two separate dimensions underlying the phenotypic variation in autism. Replication studies or cross-validation are therefore needed to establish the predictive quality of Model B2 in a preferably larger group of individuals with varying degrees of autistic symptomatology, and with varying degrees of intellectual functioning.

5.

A COMPARISON OF CENTRAL COHERENCE SKILLS BETWEEN ADOLESCENTS WITH AN INTELLECTUAL DISABILITY WITH AND WITHOUT A COMORBID DISORDER IN THE AUTISM SPECTRUM

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ABSTRACT

BACKGROUND: Studies have shown a high comorbidity between intellectual disability and autism. The central coherence theory hypothesizes that individuals with autism process information in a more detail-focused fashion (have a weak central coherence). METHOD: The central coherence skills of adolescents having an intellectual disability with and without a comorbid disorder in the autism spectrum are compared. Forty-three adolescents from schools for severe learning problems are examined. RESULTS: The group with an autism spectrum disorder, and more specifically with an Autistic Disorder, performed better on the tasks in which detail-focused processing was beneficial to global processing. CONCLUSIONS: The results indicated that adolescents with a comorbid disorder in the autism spectrum have a weaker central coherence than the control group. In addition, partial support is given for variability in weak central coherence within the autism spectrum. Theoretical implications for the central coherence concept are being discussed.

INTRODUCTION

It has been shown that about 75% of individuals with autism is intellectually disabled (Bailey *et al.*, 1996), and that about 20-30% of individuals with an intellectual disability may have autism or an autism spectrum disorder (Dykens, 2000; Kraijer, 1997). Considering this high comorbidity, questions are raised about the relationship and specific characteristics between autism and intellectual disability. Recently, the information processing in intellectually disabled individuals is being investigated (Garner *et al.*, 1999). For autism, the central coherence theory (Frith, 1989) gives hypotheses about a characteristic style of information processing. This theory, which is based on the frequently observed dissociate cognitive abilities in autism like the uneven cognitive profile (Happé, 1994a) and islets of ability (Shah & Frith, 1993; Pring *et al.*, 1995), assumes that autistic individuals process information in a qualitatively different manner than other individuals. In contrast to the global processing style of healthy control individuals, people with autism are supposed to process information locally, that is, in a detail-focused way. Because of this local processing style, autistic individuals take less account of the context in which the information is put in, and they consequently experience difficulties in social communication and display restricted or rigid behaviors. The autistic core features and possible co-occurrence of islets of ability are thus explained to result from the local processing style.

In the last decade, this theory has been a topic in many studies in which the central coherence skills of autistic individuals are compared to those of control samples [for a review, see Happé (1999)]. Results in which these skills are measured with visuospatial tasks confirm the theory to a large extent. Autistic individuals performed tasks where a design or a figure had to be divided into their constituent parts faster than control individuals. For example, autistic individuals perceived the constituent blocks in an unsegmented condition of a Block Design Task more easily (Happé, 1999; Ehlers *et al.*, 1997; Shah & Frith, 1993). In addition, they performed Embedded Figures Tasks in which hidden shapes in drawings have to be found as quickly as possible, better than control individuals (Happé, 1994b; Jolliffe & Baron-Cohen, 1997; Shah & Frith, 1983). Results in which central coherence skills are measured with perceptual or verbal-semantic tasks revealed that autistic individuals have a tendency for fragmented perception (Jarrold & Russell, 1997; Happé, 1996), and that they benefit less from the context of meaning in sentences, narratives and memory tests (Happé, 1994b; Jolliffe & Baron-Cohen, 1999). However, some studies failed to replicate these findings (Brian & Bryson, 1996; Ozonoff *et al.*, 1991; Ropar & Mitchell, 1999). This inconsistency may be

explained on the basis of how weak central coherence was measured in terms of an inability to process globally versus the preference for processing locally. Recent studies suggest that people with autism are able to process globally when they are instructed to do so, however they process information locally when no such instructions are offered (Mottron *et al.*, 1999; Plaisted *et al.*, 1999; Rinehart *et al.*, 2000).

Many current studies that examine the theory limit their focus on central coherence skills in higher functioning groups of individuals with autism (Jolliffe & Baron-Cohen, 1997; Jolliffe & Baron-Cohen, 1999; Rinehart *et al.*, 2000; Ropar & Mitchell, 1999). Based on the assumption that autistic individuals have a weak central coherence, regardless of age and of cognitive ability, a confirmation of a weak central coherence in an intellectually disabled group with autism make the theory more robust. The present study investigates the central coherence skills in a group of adolescents having an intellectual disability with and without a comorbid disorder in the autism spectrum (like subjects with an 'Autistic Disorder'; and subjects with a milder variant of autism, Pervasive Developmental Disorder Not Otherwise Specified; 'PDD-NOS'). Central coherence skills are measured with two visual spatial tasks, generally accepted as measures for central coherence: Child Embedded Figures Test (CEFT) and Block Design Task. Both tasks revealed to be applicable to adolescents functioning in the moderate to mild IQ ranges (Shah & Frith, 1983; Shah & Frith, 1993). In view of the continuum of autistic like disorders, we were interested if a weak central coherence is apparent in adolescents with an Autistic Disorder and in adolescents with PDD-NOS, irrespective of intellectual functioning. A suggested variability in central coherence skills within the autism spectrum has been reported (Happé, 1999; Ropar & Mitchell, 2001). We hypothesized that subjects at the upper end of the spectrum, supposedly related to a more severe condition (Autistic Disorder), show a weaker central coherence than subjects at the lower end of the spectrum disorder (PDD-NOS). In addition, we were interested in the relationship between weak central coherence and number of autistic traits, as measured with the Autism Behavior Checklist. We hypothesized a weak central coherence to be positively correlated to the number of autistic traits, because a difficulty of integrating information into a comprehensive and meaningful whole (i.e. weak central coherence) will be reflected in impaired social insight, communication and play skills (i.e. autistic traits). Although Teunisse and co-authors did not find a correlation between social impairments and a weak central coherence (Teunisse *et al.*, 2001), earlier results suggested a relationship between a low sensitivity for social cues and good disembedding skills (Jolliffe & Baron-Cohen, 1997; Witkin *et al.*, 1971).

MATERIALS AND METHODS

Participants

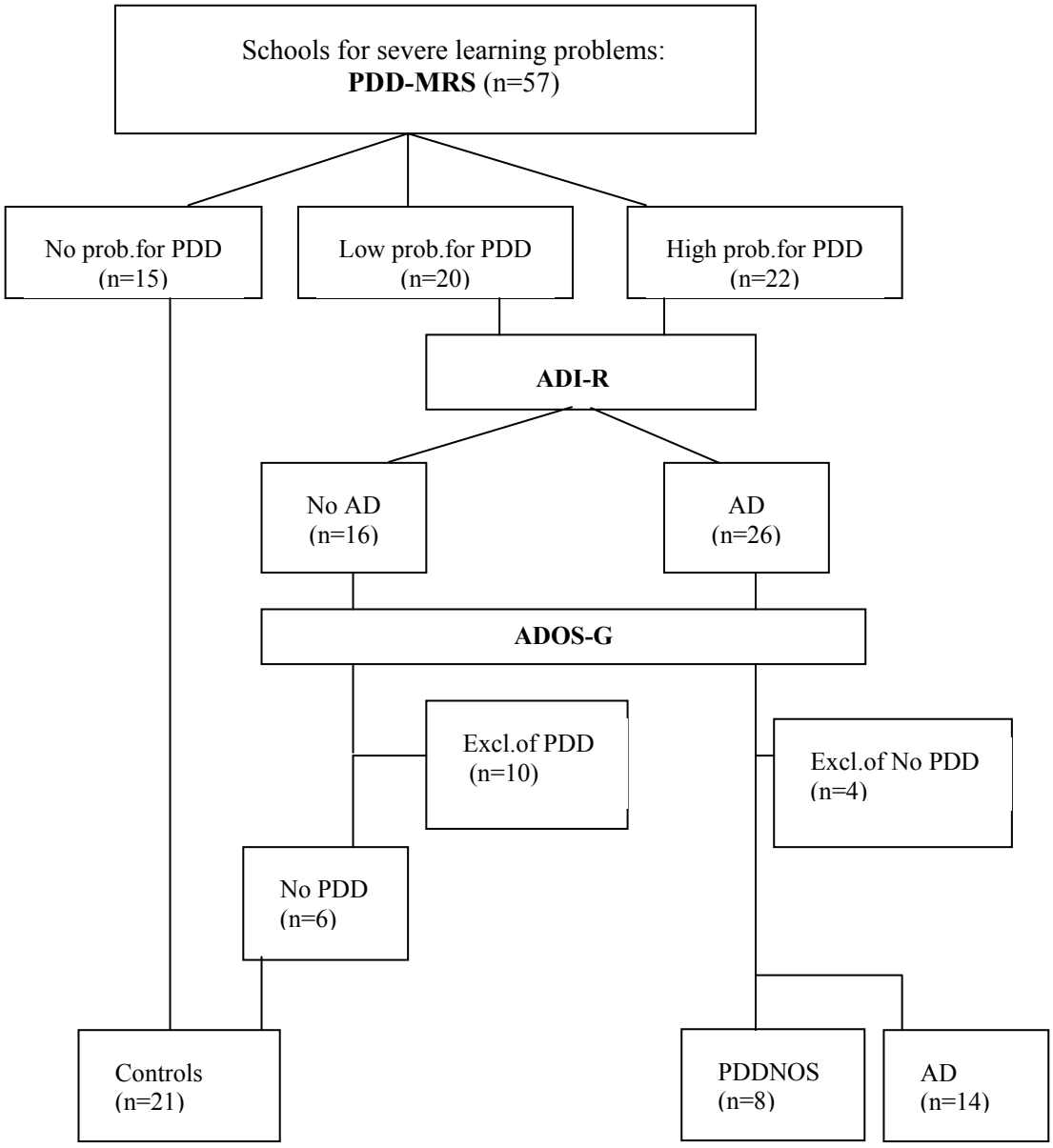
Initially, 57 participants with chronological ages between 10-20 years were included in this study. They were all attending schools for children with severe learning problems in three northern regions in The Netherlands. Participants with an Autism Spectrum Disorder or Pervasive Developmental Disorder (PDD) were defined by three instruments: (1) the Scale of Pervasive Developmental Disorder in Mentally Retarded Persons (PDD-MRS) (Kraijer, 1997), (2) the Autism Diagnostic Interview Revised (ADI-R) (Lord *et al.*, 1994), and (3) the Autism Diagnostic Observation Schedule (ADOS-G) (Lord *et al.*, 2000). Regarding the intellectual capacities of the participants, full-scale IQ's (FIQ) were used if recently established (within the range of 2 years).

If recent FIQ's were not available, participants were examined with Dutch versions of the Wechsler scales WISC-R (Van der Steene *et al.*, 1986) or WPPSI-R (Van der Steene & Bos, 1997), or with a Dutch non-verbal intelligence scale SON-R (Snijders & Snijders-Oomen, 1975). Participants with a profound to severe mental retardation (a total FIQ below 30) were excluded.

First, all participants were categorized according to their scores on the PDD-MRS. Participants falling into the low- and high-probability categories for an autism spectrum disorder or PDD (n=42) were examined in more detail with the ADI-R and ADOS-G, in order to establish a diagnostic classification. Criteria used to define a disorder on the autism spectrum were (a) an Autistic Disorder (AD) at age 4-5 years according to the algorithm criteria of the ADI-R, and (b) a PDD classification at the present age of the participant according to the algorithm criteria of the ADOS-G. The differentiation between AD and PDD-NOS resulted from the algorithm criteria of the ADOS-G, in which the AD cut-off scores are 3-5 points higher than the PDD-NOS cut-off scores, dependent on the ADOS-G module being applied. Criteria used to define the control group were (a) falling within the no-probability category or (b) falling within the low-probability category of the PDD-MRS, and (c) additionally *not* into any PDD category according to the ADI-R and ADOS-G. For the purpose of establishing a control group with no apparent autistic traits, 10 participants who did not had AD according to the ADI-R but fell into the PDD category of the ADOS-G were excluded. Considering the PDD group, 4 participants who met the criteria for AD on the ADI-R but not for PDD according to the ADOS-G were also excluded (see Figure 5.1).

Figure 5.1

Selection diagram of the 43 included participants



Ultimately forty-three participants were included in this study, of which 22 were classified with PDD and 21 as control individuals. Of the 22 PDD participants, 14 had AD and 8 PDD-NOS. A t-test for equality of means revealed no group effects on chronological age and FIQ.

Table 5.1

Group characteristics, with mean scores and SD (in parentheses) for age and IQ scores (FIQ: full-scale IQ score, VIQ: verbal IQ score, PIQ: performal IQ score)

Group	N	Mean age year;months (10;0-19;2)	Mean FIQ (31-82)	Mean VIQ[a] (28-79)	Mean PIQ[a] (33-104)	Sex boy:girl
Control	21	14;5 *(2;7)*	52.1 *(12.0)*	52.6 *(11.4)*	57.2 *(18.0)*	13 : 8
PDD	22	14;9 *(2;2)*	53.4 *(11.5)*	54.9 *(13.0)*	57.0 *(12.7)*	17 : 5
PDD in:						
AD	14	14;6 *(2;3)*	51.4 *(12.6)*	51.6 *(12.4)*	56.4 *(13.8)*	9 : 5
PDD-NOS	8	15;5 *(2;0)*	57.0 *(8.8)*	59.9 *(13.1)*	57.9 (*11.7)*	8 : 0

Note: [a] for VIQ and PIQ, the N is smaller due to 4 nonverbal participants (19 controls, 20 PDD with 12 Autistic Disorder and 8 PDD-NOS)

Measures

The central coherence abilities were examined by two tasks: Block Design Task and Child Embedded Figures Test. Both tasks were specifically chosen for the participants in our sample, because both are generally accepted to measure central coherence abilities and both tasks measure these abilities relatively independent of subjects' verbal and memory capacities. Each participant was being tested individually in a separate room at school.

The *Block Design task* is an adaptation of the task developed by Shah and Frith (1993). It consists of two conditions, an unsegmented and a segmented condition in which participants are asked to copy each presented design as quickly as possible with four wooden blocks. First, in the unsegmented condition (UC), a total of eight whole compositions of designs are separately presented and participants are required to copy the exact designs. In the segmented condition (SC), eight different designs are presented, but are already presegmented. As can be expected, participants will be aided by this presegmentation of the constituent blocks of the designs. Each participant starts with UC and ends with SC. In this way it was possible to measure how much each participant profits from the presegmentation in SC. The eight designs in both conditions are matched for pass rates (accuracy) and difficulty in composition (response time for correct copying) (Happé *et al.*, 2001). A time limit of two minutes per design was applied. In all, the mean accuracy and the mean response time per correct design (RT) were measured for UC and SC. With regard to the profit from the presegmentation, two

formulas were used: a mean absolute profit in response time (*APRT = RT.UC – RT.SC*) and a mean relative profit in response time (*RPRT = APRT / RT.UC*). The latter was measured, in order to relate the APRT per individual to their response times in UC, i.e. relative to their own group.

The *Child Embedded Figure Test* (CEFT*)* (Witkin *et al.*, 1971) is a task consisting of a total of 25 concrete drawings in which a hidden target figure had to be found. Two different target figures are presented; a triangle figure is hidden in the first eleven drawings followed by a house figure in the subsequent fourteen drawings. The present administration of the CEFT was a modified version used by Shah and Frith (1983). Participants were asked to locate the hidden figures as quickly as possible. When they indicated that they found the target figure, they had to draw the line with their finger, as a check for accuracy for the observer. In contrast to the original CEFT, we wanted to exclude the confounding of memory skills. Therefore, additionally, we used a transparent sheet with each target figure, in order to aid the participants in remembering the figure during their search. A time limit per drawing of two minutes was added together with a breaking rule of failing five consecutive figures. Because of the variability in presented drawings per participant due to the breaking rule, we examined the mean of the total score, and in addition, the mean in score per target figure separately (triangle and house targets). No significant group differences occurred in the mean number of attempts to locate a target figure ($F(2,33)=1,262$, $p=.296$).

The *Autism Behavior Checklist* (ABC) (Krug *et al.*, 1980) is a (parent) rating scale, developed for the screening of autism. Parents were asked to complete the scale, consisting of 57 dichotomous items about the occurrence of participants' behaviors that are related to autism. For the purpose of the present study, the total ABC score was used as an index for the quantity of current autism symptomatology. For all participants, the total weighted score ranged from 1 to 77, with a significantly higher mean in the PDD group ($t(-3,852)$, $p<.001$).

Data-analyses

General Linear Model (GLM) approach with multivariate design was used to establish group differences in accuracy and response time in the Block Design Task (UC) and in accuracy of the CEFT target figures (due to the variability of response times per CEFT item, mean response times per group were not calculated). Chronological age (CA) and FIQ were taken as covariates, because both variables had significant main effects on the task performances in both groups. No sex effects were observed. Posthoc pairwise comparison with Least Significant Difference (LSD) was used to look for differences in task performances between

the three classification groups: AD, PDD-NOS and control. Pearson's correlation was applied to examine the relationship between autistic features and task performances.

RESULTS

Block Design performances

Table 5.2

Unsegmented Block Designs; mean accuracy and mean response time per correct design (95% confidence interval; CI), adjusted for age and FIQ

	N	Mean accuracy (maximum of 8)		Mean response time per correct design (in seconds)	
Group		Mean	95% CI	Mean	95% CI
Control	17	5.1	(4.2 - 6.0)	33.9	(28.0 – 39.8)
PDD	20	5.4	(4.6 – 6.2)	25.0 [1]	(19.6 – 30.4)
PDD in:					
AD	12	5.6	(4.6 - 6.7)	20.9 [2],[3]	(14.2 - 27.6)
PDD-NOS	8	5.0	(3.7 - 6.4)	31.3	(23.0 - 39.7)

Note:
[1] : significantly lower than control group (p<.05)
[2] : significantly lower than control group (p<.01)
[3] : AD different from PDD-NOS at p=.057

Six from the 43 participants were excluded, because they were not able to make any correct design in the unsegmented condition (UC) (4 controls and 2 with AD). Of the remaining 37 participants, GLM with multivariate design revealed no significant main effect of group ($F(2,32)= 2,583$, p=.091). However, in the response time, posthoc pairwise comparison showed that the PDD participants were significantly faster in copying a correct design than the control participants (p=.031). No group differences showed up in mean accuracy. When looking at differences in mean accuracy and response time in UC between the three classification groups, posthoc pairwise comparison revealed that the AD group performed significantly faster than the control group (p=.005), and faster than the PDD-NOS group, although not significantly at the α<.05 level (p=.057). In the profit from response time, no significant group differences emerged (control versus PDD group, respectively *APRT* 13.7 (C.I. 8.5-18.8):10.2 (C.I. 5.4-15.1); and *RPRT* 3.5 (C.I. 2.7-4.2):3.7 (C.I. 3.0-4.5)).

CEFT performances

Table 5.3

CEFT: Mean accuracy (95% confidence interval; CI) for the total score and the scores on the two target figures separately, adjusted for age and FIQ

Group:	N	**Total score** range 0-25		**Triangle targets** range 0-11		**House targets** range 0-14	
		Mean	95% CI	Mean	95% CI	Mean	95% CI
Control	21	10.9	(8.5-13.3)	7.5	(6.4-8.5)	3.5	(1.9-5.0)
PDD	22	12.9	(10.5-15.2)	7.3	(6.3-8.4)	5.6[1]	(4.0-7.1)
PDD in:							
AD	14	13.5	(10.5-16.4)	7.6	(6.3-8.9)	5.9[2]	(3.9-7.8)
PDD-NOS	8	11.8	(7.8-15.8)	6.8	(5.1-8.6)	5.0	(2.3-7.6)

Note:
[1] : PDD higher than control group at p=.063
[2] : AD higher than control group at p=.060

A significant main effect of group was found ($F(2,38)= 3,258$, $p=.049$). Table 5.3 shows that the PDD participants found more house targets than the control participants, however not reaching the significant level of $\alpha<.05$ level ($p=.063$). Posthoc pairwise comparison revealed that the AD group found more house targets than the control group ($p=.06$). No significant group differences occurred in CEFT total score or on the triangle targets.

Correlation to autistic features

A significant negative correlation was observed between the ABC total score and response time on the Block Design Task UC ($r =-.42$, $p=.012$). No correlation between the ABC total score and accuracy on the tasks emerged.

Table 5.4

Pearson correlation's (two tailed) between task performances and the total score of the ABC over N=43

Task measures:	Block Designs UC: Response time	CEFT: Total accuracy	CEFT: Triangle accuracy	CEFT: House accuracy
ABC total score	-.420*	.025	-.172	.134

*p<.05

DISCUSSION

Our results gave partial evidence that in adolescents with an intellectual disability, individuals can be distinguished on the basis of how they process information. The group with an intellectual disability and with a comorbid disorder in the autism spectrum showed a weaker central coherence than the age and IQ matched control group with an intellectual disability. This finding is consistent with the results of Shah and Frith with individuals functioning in the mild IQ ranges (Shah & Frith, 1983; Shah & Frith, 1993), and with results of studies that included higher functioning subjects (Happé, 1996; Jarrold & Russell, 1997; Jolliffe & Baron-Cohen, 1999; Ropar & Mitchell, 2001). Regarding differences in central coherence abilities within the autism spectrum, a tendency towards a weaker central coherence in the group with AD compared to the group with PDD-NOS was shown on the Block Design Task. In the unsegmented condition of this task, the adolescents with AD performed faster than the adolescents with PDD-NOS, and the performances of the PDD-NOS were similar to the performances of the control subjects. This was confirmed by an established correlation between the number of autistic traits and fast performances on this task. However, no group differences were shown on how much they profited from the segmented condition, suggesting that both groups profited from the given presegmentation. In addition, no differences within the autism spectrum were observed on the CEFT. Contrary to the results of Ropar and Mitchell, revealing variability in weak central coherence between normal developing subjects with AD and Asperger's Syndrome (Ropar & Mitchell, 2001), our results could only partially support variability in weak central coherence between intellectually disabled adolescents with AD and PDD-NOS.

The difference in information processing in intellectually disabled adolescents with and without a comorbid disorder in the autism spectrum was of specific interest in the present study. It was shown that intellectually disabled adolescents with the comorbid disorder in the autism spectrum, and more specifically with AD, performed better on tasks where detail-focused processing is beneficial to global processing. The results therefore provide support for a weak central coherence in autism, irrespective of intellectual functioning. However, two limitations of the design need to be addressed. First, weak central coherence was measured with two visuospatial tasks only. Although both tasks are generally accepted to measure central coherence and are to a reasonable account applicable to adolescents with an intellectual disability, our data confirmed the better visuospatial skills in intellectual disabled individuals with an autism spectrum disorder only. The findings do not measure disembedding skills on the perceptual or verbal-semantic level. Secondly, the results of this study supported the view of a more local, or piece-meal processing style in adolescents with many autistic traits (AD), however the analyses were based on relatively small sample sizes. The results are therefore best seen as to generate hypotheses about variability in central coherence skills between individuals with a disorder in the autism spectrum. Finally, a remark about the construct validity of the central coherence concept is needed. If individuals with a comorbid disorder in the autism spectrum process information in a detail-focused manner, and do not voluntarily attend to the context in which the information is embedded, one would expect difficulties in (reciprocal) social communication. In addition, one would expect a positive correlation with the occurrence of restricted interests and stereotyped and rigid behaviors. Interestingly therefore, the relationship between weak central coherence and the three behavior domains of autism separately needs to be examined. Rigid behaviors are also explained on the basis of executive functioning problems (Garner *et al.*, 1999; Ozonoff *et al.*, 1991), however the behavioral phenotype of the autism spectrum disorder in general may be better explained within the paradigm of a weak central coherence. A major advantage of this theory is that hypotheses can be postulated about disturbances in the mechanisms of the information processing. Recent studies suggest that during the input of the information processing, autistic individuals perceive or store information in a more fragmented way, that is also supported by activation of different brain regions that are found during task performances (Milne *et al.*, 2002; Ring *et al.*, 1999; Schultz *et al.*, 2000). Nevertheless, more research is required to clarify the concept of central coherence and additionally to investigate whether different styles of information processing might help in further disentangling the relationship between autism and intellectual disability.

CONCLUSION

Between the intellectually disabled adolescents that attend schools for children with severe learning problems, our results point towards a weak central coherence in adolescents with comorbid autism. Furthermore, the results provide an indication for a weaker central coherence in individuals at the upper end of the autism spectrum, supported by the correlation between the number of autistic traits and faster performances in the unsegmented block designs. If these results can be replicated on larger sample sizes and further validated with more tasks, the different styles in information processing of individuals with an intellectual disability could have clinical implications. For the intellectually disabled individuals with comorbid autistic traits, for example, extra attention to the explicit meaning of information would be beneficial for their understanding of what people expect from them. In addition to research questions, it would be captivating to look at the relationship between weak central coherence and the three behavior domains of autism separately: impaired social interaction, impaired communication and stereotyped behavior. The association between cognitive performances (like weak central coherence) and clear types of behaviors may result in a better understanding of individual differences in the population of intellectual disabled persons.

6.

ARE SUBJECTS FUNCTIONING IN THE MILD-TO-NORMAL IQ RANGE WITH AUTISM SPECTRUM DISORDERS CHARACTERIZED BY A WEAK CENTRAL COHERENCE?

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ABSTRACT

BACKGROUND: No systematic studies have been conducted that investigated the effect of age on the use of a weak central coherence, and no evidence is clearly provided yet for a weaker central coherence in autistic subjects. The present study examined the influence of age on weak central coherence in a group of normally developing children, and compared weak central coherence between autistic individuals with a mild-to-normal IQ range and normally developing children. METHOD: Weak central coherence was measured with two visual-spatial tasks. The effect of age on weak central coherence was examined in 76 normally developing children attending elementary schools. The question whether autistic subjects show a weaker central coherence than normally developing children, two groups of subjects, matched on mental age, were selected (N=2x21). RESULTS: Significant age effects were seen on the task performances in the normally developing children. Mental age also showed to be of influence on the task performances in the autism group and control group. No effect of group membership occurred and no correlation between the task performances and autistic behaviors was observed. CONCLUSIONS: Weak central coherence is a function of age in normally developing children and in autistic individuals. No evidence for a weaker central coherence in the autism group was found, and no relationship between autistic behaviors and weak central coherence was shown, suggesting that autistic individuals do not display a weaker central coherence than control children in the performances of two visual-spatial tasks.

INTRODUCTION

Theories that make hypothesizes about the use of a particular cognitive processing style in autism, aim to try to understand why people with autism exhibit impairments in social and communicative abilities, and why they display stereotyped mannerisms or have restricted interests. The theory of a weak central coherence in autism is an influential theory in characterizing the way in which autistic individuals process information. It hypothesizes that people with autism employ a qualitatively different processing style from normal developing individuals. They are supposed to process information in a local style, being more focused on details, and as a consequence they make less allowance for the context in which the information is put in (Frith, 1989). Due to this cognitive processing style, autistic individuals experience difficulties in reciprocal social communication, especially because these situations require the ability to account for the given context. The theory puts the core features of autism thus as a consequence of utilizing such a particular cognitive processing style.

In the last two decades, the theory received empirical support from several studies, (Shah & Frith, 1983; Shah & Frith, 1993) (Jolliffe & Baron-Cohen, 1997; Ropar & Mitchell, 2001; Happé, 1999), showing that people with autism performed better than control subjects on tasks where detail-focused processing was beneficial to global processing. For instance, in embedded figures tests where simple shapes hidden in complex drawings have to be found, autistic individuals benefit from their local processing style in having good disembedding skills. However, a number of studies failed to replicate these findings (Brian & Bryson, 1996; Ropar & Mitchell, 1999; Ozonoff, Pennington, & Rogers, 1991). The studies of Ozonoff, Pennington and Rogers (1991) and Brian and Bryson (1996) showed no group differences on disembedding tasks, suggesting that individuals with autism were similarly distracted by the presented stimuli as the matched control peers. In addition, the results of Ropar and Mitchell (1999) showed that individuals with autism or Asperger's Syndrome were as much susceptible to visual illusion lines as control individuals, suggesting that they were similarly misled by the provoking illusory context of the lines. This inconsistency in findings may be explained on the basis of how weak central coherence was measured in terms of an inability to process globally versus the preference for processing locally. Several studies revealed that higher-functioning people with autism were able to process globally when they were instructed to do so, however they processed information locally when no such instructions were offered (Mottron, Belleville, & Menard, 1999; Plaisted, Swettenham, & Rees, 1999; Rinehart, Bradshaw, Moss, Brereton, & Tonge, 2000).

In a previous study of the present authors (Van Lang *et al*., submitted; see chapter 5), task performances of two groups of adolescents attending schools for severe learning problems were compared; a group with a comorbid disorder on the autism spectrum and an age and IQ matched control group. Subjects' disembedding skills were assessed with two visuospatial tasks, generally accepted to measure weak central coherence in individuals with intellectual disabilities. In order to capture subjects' preference for weak central coherence, a time limit of two minutes was applied, that was considered to be large enough to elicit subjects' choice of responding. The results showed that the task performances were influenced by age and IQ. The group comparisons were therefore adjusted for these effects and revealed a partial evidence of a weaker central coherence in the group with a comorbid disorder in the autism spectrum.

Because age was shown to be of influence on weak central coherence, the present study started with a systematic investigation of weak central coherence in a group of normally developing children. Although other studies have suggested an age effect in weak central coherence (Brian et al., 1996; Jarrold, Butler, Cottington, & Jimenez, 2000), or in a similar concept like field dependency and field independency (Hall, Gregory, Billinger, & Fisher, 1988; Shade, 1984; Witkin, Oltman, Raskin, & Karp, 1971), no systematic study on age effects in weak central coherence has been conducted yet. In addition, because only partial evidence for a weaker central coherence in the group with an autism spectrum disorder and a comorbid intellectual disability was found, the present study examined the tendency for weak central coherence in individuals with autism spectrum disorders, who did not have such severe intellectual disabilities. The present study also examined whether weak central coherence was associated with characteristic autistic behaviors. Because the theory formulates that autistic core features emerge as a result of the cognitive processing style, we expected to find an association between the task performances and the number of autistic core features, as measured by two standardized classification instruments.

SUBJECTS

Control subjects

Seventy-six normally developing control subjects from two elementary schools in the Netherlands were assessed with central coherence tasks. Of the 76 children, 50 were girls and 26 were boys, with chronological ages varying between 6;04 – 12;11 (years and months).

ASD subjects

From the total of 54 subjects who were able to perform the central coherence tasks and who fell into the autism spectrum according to the PDD-MRS (Kraijer, 1997), 32 received a clinical classification of an autism spectrum disorder (ASD) and 36 fulfilled the criteria for AD according to the Autism Diagnostic Interview –Revised (ADI-R) algorithm criteria (Lord, Rutter, & Le Couteur, 1994). In order to select a relatively homogeneous group with a clearly established disorder on the autism spectrum, the following inclusion criteria were applied: (1) a clinical classification of an Autistic Disorder (AD) or Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) established by four experienced clinicians (for information about the classification procedures, see De Bildt *et al.,* 2003b); (2) fulfilling the criteria for AD according to the ADI-R algorithm domain scores about impaired socialization and communication and age of onset before 36 months (2 subjects did not fulfil the domain scores of stereotyped behaviors); and (3) a full-scale IQ (FIQ) ≥ 50. Twenty-one ASD subjects were selected, of which 15 received a clinical judgement of PDD-NOS and six of AD. Of the 21 ASD subjects, 17 were boys and 4 girls, with chronological ages varying between 6;10-17;09 (in years;months).

Cognitive abilities and matching procedures

Twenty-one control subjects were selected, which were matched on the mental age of the ASD group. To measure mental age, Dutch versions of the WISC-R (Van der Steene et al., 1986) or WPPSI-R (Van der Steene & Bos, 1997) were applied to the ASD subjects [1], or Full-scale IQ's (FIQ) were used if they had been determined within 2 years of the study.

[1] For ASD subjects who could not perform the measure required for their chronological age (CA) due to their mental handicap, a lower version was used (i.e. the WPPSI-R instead of WISC-R), and an estimated FIQ was calculated (by means of the median of age equivalent scores per subtask/CA x 100).

An indication of mental age was then given by applying the formula FIQ/100 x chronological age (CA). For the control subjects, a normal intelligence rate was assumed, because according to their teachers, none were having major difficulties at school and none were known to receive any psychiatric or psychological care. Therefore, their mental ages were supposed to be reflected by their chronological ages. The ASD group had a mean FIQ of 71.7 (SD:15.0; range 50-110). In addition, the ASD group had a significantly higher CA ($F(1,40)=22,522$, $p<.01$; mean 143.3 months, SD:36.3) than the control group (mean 99.5 months, SD:21.7). The mean mental age (MA) in the ASD group was 7;08 (SD: 2;01; in years; months) and in the control group 7;09 (SD: 1;09; in years; months).

Measures

The central coherence abilities were examined by two visuospatial tasks, generally accepted to measure weak central coherence in subjects functioning in the range of elementary school age. In both tasks, subjects' disembedding skills are measured. These skills are beneficial to perform the tasks relatively accurately and fast.

The *Child Embedded Figure Test* (CEFT*)* (Witkin et al., 1971) is a task consisting of a total of 25 concrete drawings in which a hidden target figure have to be found. Two different target figures are presented; a triangle figure is hidden in the first eleven drawings followed by a house figure in the subsequent fourteen drawings. The present administration of the CEFT was slightly modified from Shah and Frith' administration of the task (1983). After teaching the participants the tasks' instructions by means of the CEFT examples, all participants were asked to locate the hidden target figures as quickly and accurately as possible. When participants indicated that they found the target figure, they had to draw the line with their finger as a check for accuracy for the observer. To exclude the confounding of memory skills, a transparent sheet with each target figure was used to aid the participants in remembering the figure during their search. Per test item, a time limit of two minutes was added. The dependent variables of interest were the mean number of correctly found target figures (accuracy) and the mean response time used to detect each correctly found target figure (RT).

The *Block Design task* is an adaptation of the task developed by Shah and Frith (1993). It consists of two conditions, an unsegmented and a segmented condition with eight different designs each. In the unsegmented condition, eight designs with whole compositions are presented and in the segmented condition, eight different designs with already presegmented compositions are presented. The eight designs in both conditions are matched for pass rates (accuracy) and difficulty in composition (response time for correct copying) (Happé, Booth,

Charlton, & Hughes, 2001). All participants started with examples and were instructed to copy the presented design as quickly and accurately as possible with four wooden blocks. After the examples, each participant started with the eight test items of the unsegmented condition (UC) and ended with the eight test items of the segmented condition (SC). With this procedure it was possible to measure how much each participant profited from the given presegmentation. Per design, a time limit of two minutes was applied. The dependent variables of interest were the mean accuracy and mean response time per correctly copied design (RT) of the UC condition, and how much each group profited in RT from the presegmentation.

The *Autism Diagnostic Interview* (ADI-R) and the *Autism Diagnostic Observation Schedule* (ADOS-G) were used as continuous measures of autistic core features (Lord et al., 1994; Lord et al., 2000). Both instruments are internationally standardized diagnostic assessments and have accompanying algorithms that are used to make classifications of an Autistic Disorder (ADI-R and ADOS-G) or PDD-NOS (ADOS-G) according to DSM-IV criteria. The total scores of the algorithms, with ratings applying to subjects' current status, were used as indications for the number of autistic core features.

Data-analyses

In the *CEFT performances,* only subjects who performed the whole task were included. Therefore, 3 control subjects (mean MA 7;01 years; months), and 2 ASD subjects (mean MA 6;00 years; months) were excluded from the CEFT analyses. In the *Block Design Task*, all control subjects and all ASD subjects performed the task entirely. In the ASD group, however, 2 subjects showed an extreme response time on the Block Design Task UC (respectively 91.7 and 98.3 sec.). They were therefore treated as outliers (a drop in mean RT from 31.2 ± 3.7 to 24.9 ± 2.5 was observed when the outliers were excluded from the analyses). A multivariate analysis of variance was executed to examine the role of age on the task performances in the control group; accuracy and RT per task were taken as dependent variables and three age categories as independent variables (6;00-7;11 (in years;months), n=21; 8;00-9;11, n=22; and 10;00-12;11, n=33). Second, we compared the group performances of the ASD group and the control group, by selecting 21 control subjects matched to the mental ages of the 21 ASD subjects. No sex effects on the task performances were observed. However, age was shown to be of influence on the task performances, therefore multivariate analyses of variances with mental age as covariate were applied. Third, pearson's correlation was used to explore the association between the task performances and

the number of autistic core features as measured by the ADI-R and ADOS-G (a significant positive correlation was shown between the total scores of the ADI-R and ADOS-G, r = .598, p=.011).

RESULTS

Are the cognitive task performances associated with chronological age?

In Figures 6.1 to 6.6, the mean accuracy and mean response time on the CEFT and on the Block Design Tasks are presented over three age groups of normally developing children.

Figures 6.1-6.6

Descriptive statistics, mean and 95% confidence intervals [CI], of the accuracy and RT on the CEFT and Block Design Task of normal control subjects over three age-categories

Figure 1: CEFT accuracy (with a total score of 25) over N=73;
age categories of 6-7 years (n=19); 8-9 years (n=21); and 10-12 years (n=33).

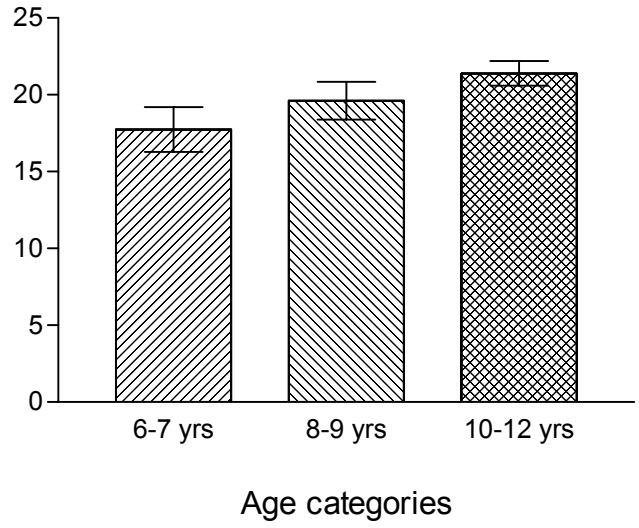

Figure 2: CEFT response time in seconds (RT) over N=73;
age categories of 6-7 years (n=19); 8-9 years (n=21); and 10-12 years (n=33).

Figure 3: Block Design Task UC accuracy (with a total score of 8) over N=76;
age categories of 6-7 years (n=21); 8-9 years (n=22); and 10-12 years (n=33).

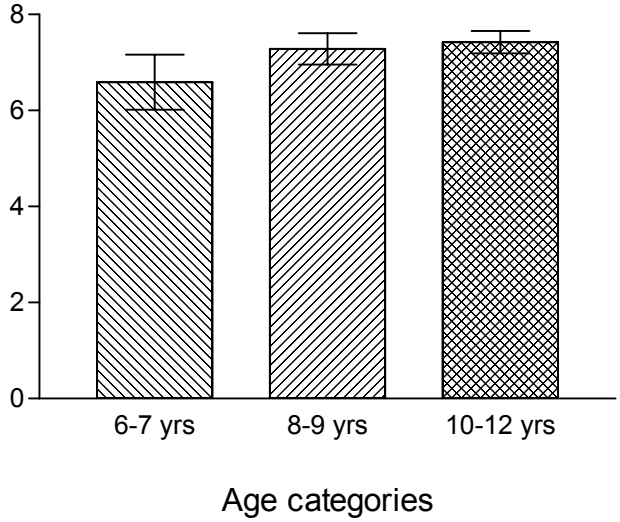

Figure 4: Block Design Task UC Response time in seconds (RT) over N=76;
age categories of 6-7 years (n=21); 8-9 years (n=22); and 10-12 years (n=33).

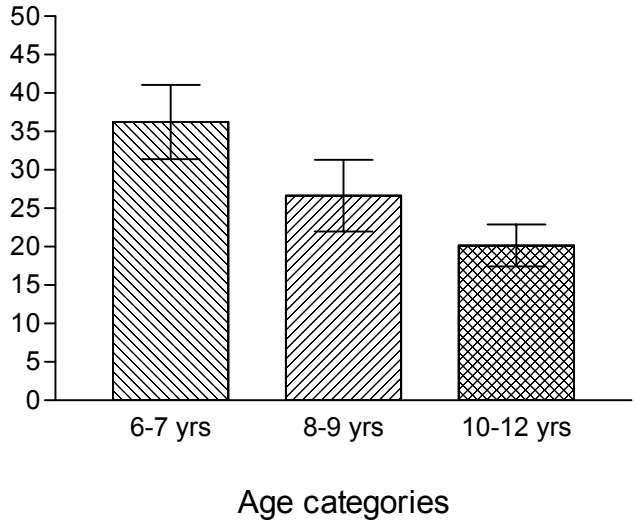

Figure 5: Block Design Task SC accuracy (with a total score of 8) over N=76;
age categories of 6-7 years (n=21); 8-9 years (n=22); and 10-12 years (n=33).

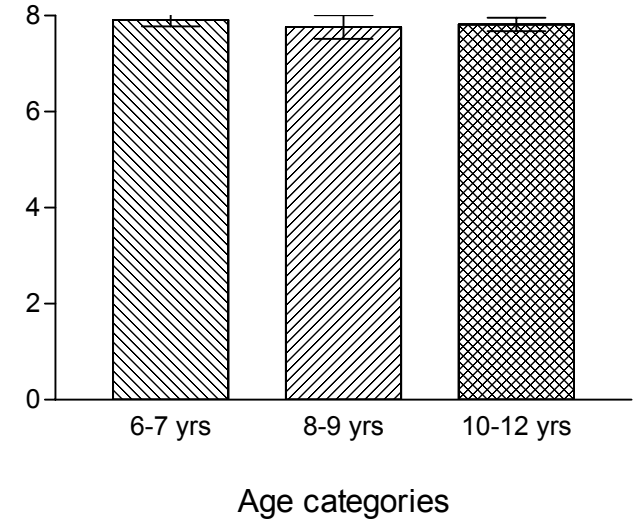

Figure 6: Block Design Task SC Response time in seconds (RT) over N=76;
age categories of 6-7 years (n=21); 8-9 years (n=22); and 10-12 years (n=33).

As can be seen from the Figures 6.1 - 6.6, the accuracy and the RT on both tasks are a function of chronological age in the normally developing control subjects. Although the data are cross-sectional, subjects become more accurate on the CEFT ($F(2,70)=12.056$, $p<.01$) and on the Block Design Task UC ($F(2,73)=5.115$, $p<.01$) when they grow older. On the Block Design Task SC however, a ceiling- effect in accuracy was reached ($F(2,73)=.563$, $p=.572$). With respect to the response time in which the tasks were performed correctly, a significant decrease over the three age categories emerged (on CEFT ($F(2,70)=10.706$, $p<.01$); on the Block Design Task UC ($F(2,73)=15.429$, $p<.01$) and SC ($F(2,73)=33.433$, $p<.01$)), implying that with increasing age children become faster in disembedding skills.

Is there evidence for a weak central coherence in the ASD group?

Table 6.1 shows the task performances of the ASD group and the control group.

Table 6.1

CEFT and Block Design task: mean performances (± SD) adjusted for mental age, for the ASD group and normal control group

Task performances:		ASD group	Control group	P-value
CEFT:	N	19	20	
Accuracy		17.8 (± 0.7)	19.3 (± 0.6)	N.S.
RT		14.1 (± 1.1)	16.3 (± 1.1)	N.S.
Block Designs UC	N	19	21	
Accuracy		6.2 (± 0.3)	7.0 (± 0.3)	N.S.
RT		24.9 (± 2.5)	29.5 (± 2.4)	N.S.
Block Designs SC				
Accuracy		7.8 (± 0.1)	7.9 (± 0.1)	N.S.
RT		14.6 (± 0.7)	16.3 (± 0.7)	N.S.
Profit in RT		10.3 (± 2.1)	13.3 (± 2.0)	N.S.

A significant main effect of mental age was seen on the task performances (CEFT ($F(2,35)=21.719$, $p<.01$); Block Design Task UC ($F(2,36)=7.094$, $p<.01$), Block Design Task SC ($F(2,36)=15.838$, $p<.01$), and Block Design Task profit in RT ($F(2,36)=3.489$, $p<.05$)). No significant main effect of group membership was observed, though on the Block Design Task UC, group membership showed a marginal main effect ($F(2,36)=2.857$, $p=.071$). As can be seen from Table 6.1, the ASD group did not show a better accuracy on either task, however they performed slightly faster than the control group (not reaching any significance level).

Table 6.2

Pearson's correlation between the two cognitive task performances over n=17 ASD subjects who completed both tasks entirely.

	CEFT		Block Designs UC		Block Designs SC	
Autistic behaviors according to:	Accuracy	RT	Accuracy	RT	Accuracy	RT
ADI-R: total score[1]	.103	.045	.305	-.054	.322	-.123
ADOS-G: total score[2]	-.135	.024	.019	.166	.272	.092

Note:

[1]: The total ADI-R score is derived from the sum of the ADI-R algorithm items of impaired social and communication skills and stereotyped behaviors, ranging from 31-56

[2]: The total ADOS-G score is derived from the sum of the ADOS-G algorithm items of impaired social and communication skills, play skills and stereotyped behaviors, ranging from 2-21

As Table 6.2 shows, no significant correlations were found between the cognitive task performances and number of autistic core features over the 17 subjects with an autism spectrum disorder that completed both tasks entirely. Table 6.3 shows the intercorrelations between the task performances.

Table 6.3

Pearson's correlation between the two cognitive task performances over n=37 subjects who completed both tasks entirely.

	CEFT Accuracy	Block Designs UC: RT
CEFT: RT	-.253	.524**
Block Designs UC: accuracy	.569**	-.305[1]

[1] p=.067, ** p<.01

Table 6.3 shows significant positive correlations between the accuracy of both tasks and between the RT of both tasks. Within the CEFT, accuracy was associated with response speed, though not reaching a significance level. In the Block Design task UC, accuracy and response speed tended to be linked (p= .067).

DISCUSSION

Comparable to what other studies have been suggested (Brian et al., 1996; Witkin et al., 1971; Jarrold et al., 2000), we found disembedding skills to be a systematic function of age in normally developing children of elementary school-age. Subjects who fell into the age category of 6-12 years performed the disembedding tasks faster and more accurately as they grow older. In the CEFT, a systematic increase in the accuracy and response time was observed, and in the Block Design Task, a systematic increase in the response time emerged. In the accuracy of the Block Design Task however, a ceiling-effect in the eight designs was noticed. Apparently, weak central coherence is a cognitive style that develops in normal developing children between 6-12 years, and it may also be that this development will continue after age 12.

In addition to these age effects in normally developing children, the specificity of weak central coherence was examined in individuals with autism spectrum disorders. We selected 21 individuals with an autism spectrum disorder, functioning in the mild-to-normal IQ range, and compared their disembedding skills with 21 mentally age-matched control children. We did not find evidence of a weaker central coherence in the group with an autism spectrum disorder however. In both groups, disembedding skills were found to be related to mental age and no group effect emerged on the task performances. These results support the findings of Ozonoff, Pennington and Rogers (1991) and those of Brian and Bryson (1996), showing that individuals with autism are similarly distracted by the presented stimuli as the matched control subjects. The ASD individuals showed less accuracy on the disembedding performances but executed the tasks slightly faster than the control individuals. However, the group differences did not reach any significance level, therefore indicating that autistic individuals do not employ a stronger preference for detail-focused processing than normal developing control subjects on the two visual-spatial tasks.

Besides the group comparison, the correlational analyses could also give no support for an association between the disembedding skills and amount of autistic core features, as indicated by total scores on two classification instruments (the ADI-R and ADOS-G). We hypothesized that due to the local processing style, people with autism experience difficulties in comprehending social information, because they pay relatively more attention to pieces of information and they therefore communicate in a different fashion. However, similar to the results of Teunisse and colleagues (2001), we were not able to find a significant correlation between the cognitive task performances and autistic behaviors.

However, some limitations of the present study need to be taken into account. First the inclusion criteria of the group require some attention. About half of the ASD subjects functioned in the mild IQ range (11 of 21 subjects had a FIQ between 50-70), and consequently a large variety of age and IQ existed amongst the included ASD subjects. Because weak central coherence revealed to be a function of age to a large extent, the ASD group and control group were matched on mental age. However, interpreting the results is difficult when a discrepancy between the groups in age and IQ exists, and measuring mental age directly would have justified the cognitive strengths and weaknesses per individual more. Second, weak central coherence was measured with two visuospatial tasks, and the response times on these tasks were assessed with a stopwatch. Although the two tasks were shown to be highly correlated, new computerized tasks in which the response time can be measured in a more reliable fashion are recommendable. Third, the concept of a weak central coherence requires more refinement. The question of where autistic individuals differ from others in the process of information use, needs to be solved. The present study employed weak central coherence as an outcome measure without examining this process. However, several studies revealed that feature processing (detail preference) in autism is more likely than impaired global processing (Mottron, Burack, Stauder, & Robaey, 1999; Plaisted et al., 1999, Rinehart et al., 2000)). In addition, different neural or brain mechanisms are found to be active during central coherence performances in autistic individuals, pointing to brain functions that are more associated with feature processing (Plaisted et al., 1999; Ring et al., 1999; Schultz et al., 2000; Milne et al., 2002). Nevertheless, questions about the validity of the concept remain, such as whether weak central coherence is part of the executive functioning paradigm (Teunisse, Cools, van Spaendonck, Aerts, & Berger, 2001; Ropar et al., 2001), implying that weak central coherence is in fact a disability in the shifting between local and global processing styles.

To conclude, weak central coherence was not found to be a specific cognitive marker in the autism group functioning in the mild-to-normal IQ range. The tendency for weak central coherence was positively linked with age or mental age in both normal developing children and in children and adolescents with autism spectrum disorders. It would be interesting in future studies to investigate weak central coherence longitudinally, in order to unravel the role of age on disembedding skills in both lower functioning individuals and individuals with normal intelligence rates. If weak central coherence reflects a cognitive style that develops systematically in normally developing children, the question arises whether autistic children follow the same development in weak central coherence. In addition, the

relationship with executive functioning may be important in this respect as well, as the question arises whether autistic children learn to shift between global and local processing styles as easily as normally developing peers do.

7.
GENERAL DISCUSSION

The studies described in this thesis are concerned with the identification of symptom domains that may underlie the autistic symptomatology, and with the characterization of a weak central coherence in individuals with autism spectrum disorders. First, possible symptom domains were identified in the first three studies. The underlying structure of the symptomatology was explored and a hypothesized symptom model was constructed and tested with confirmatory analysis. In addition, differences in symptom profile between individuals with autistic disorder symptoms were examined (see chapters 2-4). Second, the theory of a weak central coherence in autism was investigated in the last two studies. By means of the hypothesized detail-focused processing style in autism, as suggested by the theory of a weak central coherence, individuals with and without a disorder on the autism spectrum were compared in their utilization of such a processing style. The association between weak central coherence and number of autistic features was examined (see chapters 5-6). In this chapter, the findings of the studies are discussed, followed by some limitations of the studies. Suggestions for further research and clinical implications are presented at the end of this chapter.

IDENTIFICATION OF SYMPTOM DOMAINS

Towards a hypothesized symptom model

Autism is categorized into the Pervasive Developmental Disorders in the DSM-IV-TR (American Psychiatric Association, 2000), and is described by impairments on three behavior domains: impaired social interaction, impaired communication and the occurrence of repetitive and stereotyped behaviors. These three behavior domains (i.e. the DSM triad) consist of several symptoms that were suggested to be sensitive and specific for autism by international field trial clinicians (Volkmar *et al.*, 1994). However, factor analytic studies showed a different symptom structure than the DSM triad underlying the spectrum of autistic disorders (Robertson *et al.*, 1999; Szatmari *et al.*, 2002; Tanguay *et al.*, 1998). These findings are important, because studies that investigate for instance the etiology of autism require empirically derived symptom domains in order to relate distinct clusters of autistic behaviors

to possible candidate genes. Moreover, symptom domains that are empirically derived are also useful to examine the effects of therapies on specific clusters of behaviors.

In this thesis, chapters 2, 3 and 4 described a hypothesized model of a symptom structure that may underlie the autism spectrum. The symptom structure was explored first in verbal individuals with autistic symptomatology, by means of a parametric factor analysis and a nonparametric item response analysis on the core features of autism, the DSM-IV criteria for Autistic Disorder. These core features were assessed with two well-standardized classification instruments, the Autism Diagnostic Interview Revised (ADI-R) (Lord *et al.*, 1994), and the Autism Diagnostic Observation Schedule (ADOS-G) (Lord *et al.*, 2000). Both instruments yield extensive descriptions of subject's behavioral functioning; the ADI-R focuses on child's age of 4-5 years and subjects' current functioning, and the ADOS-G focuses on subjects' current functioning only. Because many of the autistic core features as measured with the ADI-R and ADOS-G are specified to subjects' verbal abilities, the symptom structure was explored first in verbal subjects. The derived symptom structure that was found to have best face validity in verbal subjects, differed from the DSM triad and consisted of three candidate factors: (factor 1) *impaired social communication* contained information about poor verbal and nonverbal social communicative interchange, (factor 2) *stereotyped features in language and behavior* consisted of stereotyped characteristics in language and behavior, and (factor 3) *impaired play skills* was comprised of information about a lack of play skills in individual activities and in relationship with peers (see chapters 2 and 3).

In chapter 4, a hypothesized symptom model was constructed, based on the three factors derived from the explorative analyses, and consisted of ratings reflecting subjects' current functioning. Summary scores of related autistic core features from the ADI-R were used, because these item scores were applicable to verbal and nonverbal subjects. The hypothesized symptom model was tested with confirmatory analysis in a large group of verbal and nonverbal individuals with minor to severe autistic symptomatology. The goodness-of-fit measures of the DSM triad model were compared to the goodness-of-fit measures of the hypothesized symptom model. The results showed that the DSM model encountered estimation problems, due to a high correlation between the DSM domains 'impaired socialization' and 'impaired communication'. As a consequence, no goodness-of-fit measures for the DSM model could be estimated. The hypothesized symptom model on the other hand did not encounter estimation problems, and turned out to be a plausible model in the sample of verbal and nonverbal individuals with minor to severe autistic symptomatology.

Still, the stability of the hypothesized symptom model needs further examination in a new and larger group of subjects with autism spectrum disorders. The influence of intellectual functioning on the derived symptom domains needs also more examination, because many participants in the cohorts that were used functioned below the range of normal intelligence. As was shown by Szatmari and colleagues (Szatmari *et al.*, 2002), symptom severity and level of functioning may be two separate factors that underlie the autism phenotype. It can be argued that the derived symptom domain of 'stereotyped language and behavior' is for example an artifact of the lower intelligence levels of most of the included participants. However, stereotyped features in language, like putting inappropriate questions, pronominal reversal and idiosyncratic language are also known to occur in higher functioning individuals with autism spectrum disorders (Bishop, 1989). Therefore, the hypothesized symptom model may be considered a useful framework for future studies, to examine for instance the heredity of distinct symptom domains in individuals with autism spectrum disorders.

Dimensions in symptomatology

With respect to the phenotypic variation within the autism spectrum, our studies contributed to the finding that individuals with an Autistic Disorder (AD), Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), and Asperger's Syndrome (although scarcely represented in the sample) are functioning on the same spectrum of autistic-like disorders, when controlled for language skills (Allen *et al.*, 2001; Lord *et al.*, 2000; Prior *et al.*, 1998) (see chapters 2 to 4). The symptom profiles of different groups of individuals with autistic symptom disorders were investigated and compared, showing that they differed in amount and severity of the displayed behaviors, rather than in behavioral profile.

Given this continuity of autistic symptoms ranging from typically developing individuals to clinical autistic individuals, the symptom domains reflect dimensions in symptomatology. An interesting question would be how the derived dimensions in the hypothesized symptom model are related to each other? As is shown by several studies, people with autistic disorders are characterized by impairments in social and communication skills (Berument *et al.*, 1999; Fein *et al.*, 1999; Wing & Gould, 1979; Beglinger & Smith, 2001), and many authors have argued that these impairments are the core deficits in autism (Klin *et al.*, 2002; Tanguay *et al.*, 1998). Although the hypothesized symptom model confirmed the dimension of impaired social communication as a combined factor, it also showed two other factors that contributed to the symptomatology of autism. Impaired play skills emerged as a distinct factor, resembling the factor 'theory of mind' that was found by

the group of Tanguay and Robertson (Robertson *et al.*, 1999; Tanguay *et al.*, 1998). This might indicate that besides impaired social communication, people with autism show additional impairments in theory-of-mind skills, reflecting a social-cognitive deficit in the understanding and use of pretence and putting motives and beliefs to other people in play situations and in daily living. Furthermore, whereas other studies did not include stereotyped behaviors in their analyses, the hypothesized symptom model showed a factor of stereotyped features in language and behavior. These features may reflect cognitive deficits in the planning, shifting and inhibition (e.g. executive functions) of behaviors, resulting from the impaired control function of social knowledge. However, the relationships between these symptom dimensions are merely hypotheses that would be interesting to investigate in further research.

WEAK CENTRAL COHERENCE

Comparing groups in the use of a weak central coherence

With respect to the theory of a weak central coherence in autistic individuals, our studies could not provide clear evidence for this theory (see chapters 5-6). It is hypothesized that autistic individuals make use of a qualitatively different cognitive processing style than age-matched control subjects, and that due to this processing style, people with autism process information in a local or detail focused manner, at the expense of the context in which the information is put in (Frith, 1989).

In this thesis, chapter 5 described a study in which the tendency for a weak central coherence was examined in adolescents attending schools for severe learning problems. Two groups of adolescents were distinguished and compared in the utilization of such a cognitive processing style: a group of adolescents with a comorbid disorder on the autism spectrum, and a group of adolescents without this comorbid disorder. The results showed a tendency for a weak central coherence in the group with a comorbid autism spectrum disorder, however this was observed on one task only. In another study, in which the tendency for a weak central coherence was compared between individuals with autism spectrum disorders functioning in the mild-to-normal IQ range, and a normal control group matched on mental age (see chapter 6), no evidence was found of a weak central coherence in the autism group. The results revealed that weak central coherence was influenced by (mental) age and not by group

membership, implying that children become better at detecting details from whole configurations with increasing age.

Although no clear evidence was found for a weaker central coherence in the autism groups than in the matched control groups, the concept of a weak central coherence is relatively new and deserves further refinement. The question of where autistic individuals differ from others in the process of information use is not clearly described yet. The present studies employed weak central coherence as an outcome measure, and did not examine the component processes in the task performances. Other studies, for example, that contrasted the ability of global processing to local processing, indicated that autistic individuals can process information globally but have a preference for processing locally (Mottron *et al.*, 1999a; Plaisted *et al.*, 1999; Rinehart *et al.*, 2000). These findings may be confirmed by a different neural or brain activation that was seen during the task performances of autistic individuals (Ring *et al.*, 1999; Schultz *et al.*, 2000), pointing to a higher activation of the ventral occipitotemporal area in the autism group (associated with local processing of visual information), and a higher activation of the prefrontal cortical areas in the control group (associated with integrative functioning of the working memory). In addition, the relationship between weak central coherence and a deficit in the executive functioning deserves more attention, since it has been hypothesized that weak central coherence may be explained by a deficit in the shifting between global and local processing styles (Ropar & Mitchell, 2001; Teunisse *et al.*, 2001). This may suggest that both theories share a part in the explanation of why autistic subjects display autistic behaviors. Given the findings of the two studies of chapters 5 and 6, it may be that the intellectually disabled adolescents experienced difficulties in finding the most efficient strategy to solve the visual-spatial tasks, in favor of the local processing bias of the autism group. However, compared to normally developing children, no local processing bias of the autism group emerged. This may be explained by the good shifting abilities of the normally developing children between global and local processing styles, in favor of the local strategy to solve the two visual-spatial tasks accurately and fast. In sum, many discussions about the concept validity of weak central coherence remain, raising important and interesting questions for further research about whether all or a subset of autistic individuals use a local processing style, and whether weak central coherence reflects a deficit in the shifting between global and local processing strategies, dependent on the most efficient style for a given context.

Weak central coherence in association with autistic behaviors

Because the theory of a weak central coherence in autism hypothesizes that the autistic behaviors emerge as a result of the detail-focused processing style, the association between weak central coherence and the number of autistic core features was explored. In the study on schools for children with severe learning problems (see chapter 5), a significant negative correlation between the unsegmented condition of the Block Design Task and autistic symptomatology was observed, applying the Autism Behavior Checklist (Krug *et al.*, 1980). This finding indicates a possible variation of weak central coherence within the group with an autism spectrum disorder, pointing to a weaker central coherence in individuals with the more severe condition on this spectrum (i.e. with an Autistic Disorder) than individuals with a less severe condition (i.e. with PDD-NOS). However, no correlation between the task performances and autistic symptomatology in the autism group that functioned in the mild-to-normal IQ range was observed (see chapter 6). The number of autistic core features was assessed with summary ratings from the ADI-R and ADOS-G, and no evidence for an empirical association between the cognitive task achievements and behavioral characteristics was observed.

LIMITATIONS OF THE PRESENT STUDIES

Sample composition

Our sample consisted of N=299 individuals from 4-20 years with data available about subject's behavioral functioning according to the ADI-R, with intelligence rates known, and a clinical classification made by the clinical raters. As a result, a heterogeneous group of subjects with a broad range of minor to severe autistic disorder symptoms were included. In the general population, a (conservative) estimate for the prevalence of people with an Autistic Disorder would be about 1 per 2.000, and for the spectrum of autistic disorders (including PDD-NOS and Asperger's Disorder) 1 per 1.000 (Tanguay, 2000). In the three northern provinces of the Netherlands where this study was conducted, 74 were clinically classified with an Autistic Disorder, 84 with PDD-NOS, and 3 with Asperger's Syndrome. This sample distribution of 161 subjects with an autism spectrum disorder does not reflect the population distribution of autism spectrum disorders. However, the primary goal of the present studies was to investigate the behavioral phenotype of autism, and therefore to encompass as many

subjects with autism spectrum disorders as possible, with substantial attention being paid to individuals with additional an intellectual disability.

Yet, to identify symptom domains that underlie the spectrum of autistic disorders, the number of subjects with a clinical classification of an autism spectrum disorder was considered to be small (see chapter 4). In addition, the number of subjects that were able to perform the cognitive tasks measuring central coherence skills, was also considered to be restricted (see chapter 5). Especially in the light of the huge variability in behavior expression and in cognitive functioning that is seen in autism, larger sample sizes are needed. In addition, the presented studies about symptom domains and weak central coherence showed to be influenced by variations in age and IQ. Therefore, when phenotypic variation in the autism spectrum is verified, multicenter studies are recommendable, because these designs generate more possibilities to include larger groups of individuals with autism spectrum disorders, and provide opportunities to divide the sample into more homogeneous subgroups. As a result, possible confounders such as age, IQ and verbal abilities can be more easily controlled.

Examining symptom domains with explorative techniques

In chapters 2 and 3, the symptom domains that may underlie the autistic core features (e.g. the DSM-IV criteria for Autistic Disorder) were examined with a parametric technique, Principal Component Analysis (PCA), and with a nonparametric item response technique, Mokken scale analysis. Two remarks regarding these two explorative techniques, and the items that were used in the analyses, deserve further attention. First, regarding the statistical technique PCA, the ratio of the number of items that were used in the analysis and the sample size of N=87 (see chapter 2) was not ideal. In addition, the items were not normally distributed. Therefore, the derived factor structure from PCA was examined again with a nonparamteric technique, the Mokken scale analysis, because this technique takes account of item's nonnormality, and is not negatively influenced by a large number of item variables. Still, because PCA is a well-known technique to study factors underlying a range of items, it was decided to present the results from PCA, but to focus on the (less known) Mokken scale analysis in the further analyses (see chapters 2 and 3).

Second, regarding the items that were used in PCA and Mokken scale analysis, two different age condition were applied: items containing information about subject's 4-5 age period, and about subject's current age status. In chapter 2, the primary aim was to investigate whether the derived factor structure was similar to the structure of the DSM triad. As such, the age condition of the 4-5-age period was used, and a different structure from the DSM triad

emerged. It was decided that a two-factor solution had the best face validity, which was confirmed with the item ratings of subject's current age status. However, in chapter 3, the primary aim was to examine the factor structure exploratively in a larger group of subjects, and with ratings of subject's current functioning on two diagnostic instruments. It was decided that a three-factor solution had best face validity, showing a new (third) factor about impaired play skills. It was concluded that when information about subject's current age status was applied, revealing information about 156 subjects with ages between 4-20 years, play skills are more differentiated than in the 4-5 age period, and therefore become a separate factor. In chapter 4, this three-factor solution was taken as the hypothesized symptom model for confirmatory analysis, because it was argued that the three-factor solution with item ratings of subject's current functioning gives a more reliable and differentiated picture of subject's symptomatology.

Cognitive tasks and matching procedures in the assessment of weak central coherence

Some considerations relating to the tasks that are applied for measuring weak central coherence deserve attention, and the matching procedures that were used to compare groups in the use of a weak central coherence. First, both tasks, the CEFT and Block Design Task, were selected for the purpose of the present thesis, because they are known to measure weak central coherence in individuals with severe learning problems. Nevertheless, both tasks were also applied in individuals with autism spectrum disorders without any severe learning problems, having full-scale IQ's in the normal or above normal IQ range (see chapter 6). These tasks were relatively easy for this (small) group of autistic individuals, and preferably more advanced tasks that measure detail processing also more accurately are highly recommendable. For instance, tasks that are currently used in higher functioning subjects with autism spectrum disorders, measure weak central coherence not only on the visuospatial level, but also focus on the verbal-semantic level (i.e. the ambiguous words task of (Jolliffe & Baron-Cohen, 1999), or perceptual level (i.e. Navon task (Mottron *et al.*, 1999b; Plaisted *et al.*, 1999), and visual illusion lines of (Happé, 1996). Interestingly, a battery of several tasks that tap local and global processing styles simultaneously would make it possible to further refine the concept of weak central coherence. Furthermore, such a battery of tasks would help to develop similar but distinguishable tasks that can measure weak central coherence in autistic individuals at appropriate age (or cognitve) levels.

Secondly, it is known that people with autism are characterized by uneven intellectual abilities, usually pointing to a higher performal than verbal ability (PIQ > VIQ), in favor of

visuospatial and constructional skills (Joseph *et al.*, 2002). In the present studies, the subjects were matched on their full scale IQ (FIQ) and age, or on mental age as a combined construct of FIQ and age, and it could be argued that due to the high discrepancy between PIQ - VIQ, matching should be done on these measures rather than FIQ. However, as was shown by Joseph and colleagues (2002), the discrepancy between PIQ and VIQ lessens when children become older. In addition, they found that there was a high degree of individual variation in cognitive profiles and that the PIQ - VIQ discrepancy was related to higher social impairments, as indicated by summary ratings of the ADOS-G. These findings indicate the importance of taking into account subjects' differential cognitive abilities and the influence of age, when cognitive functions are being examined.

SUGGESTIONS FOR FURTHER RESEARCH

Developmental perspective

Because age and IQ were shown to be of influence on the derived symptom domains and on the tendency for a weak central coherence, normative data will be most useful in interpreting the results on the basis of its quantitative deviation from normality. First, the derived symptom domains may be partly explained by the characteristics of the sample, i.e. by many included participants with intelligence levels below the normal range. It would be interesting to determine which specific behaviors reflect developmental delay, rather than 'pure' autistic symptoms. For instance, the behaviors of repetitive features like hand and finger mannerisms, unusual sensory interests and repetitive use of objects, are also known to occur frequently in individuals with developmental delays, i.e. with an intellectual disability (Dykens, 2000; Turner, 1999). In addition, behaviors like the use of other's body to communicate, not putting arms up to be lifted, or stereotyped play skills may be deviant manifestations of certain developmental age-periods, whereas other behaviors like no or indirect gaze, one-sided conversation or restricted interests may be more generally deviant manifestations over the whole age-span. Normative data of behaviors that occur in certain developmental stages, and data of how these behaviors might switch into similar but more mature behaviors for boys and girls, provide an indispensable scheme for interpreting subjects' functioning on the basis of its developmental delay or deviance. The ADI-R tries to take account of behaviors that result from developmental delay (like imaginative play skills) or from deviance (like *qualitative* abnormalities in reciprocal interaction) in its coding of autistic-like behaviors, however,

normative data with accompanying interval ratings would make the coding more reliable. Second, the studies in this thesis about the tendency for a weak central coherence in individuals with an autism spectrum disorder, showed that the disembedding task performances in both the autistic individuals and in normal controls were largely explained by variations in (mental) age. Normative data of disembedding skills in normal developing subjects as well as in intellectually disabled subjects would therefore be interesting to build on. With such normative data of subjects' accuracy and response speed on well-standardized tasks, cognitive performances of autistic subjects can be more easily and reliably interpreted, and would serve as a useful framework for identifying the specificity of such a cognitive style, relative to subjects with other clinical diagnoses.

Dimensional versus categorical approach

This urge for normative data of behavioral and cognitive functioning in normal and intellectually disabled children and adolescents arise from the debate about the advantage of a dimensional approach over a categorical approach. Clearly, the dimensional approach is based on the assumption of continuously distributed behaviors that vary between normality and abnormality, whereas the categorical approach is based on the assumption of a dichotomous distribution of abnormal behaviors (they either exist or not). Because of the huge variability in clinical patterns seen in autism, the dimensional approach capitalizes on the useful insights into strengths and weaknesses per individual with an autism spectrum disorder. However, normative data are difficult to obtain, need regular updates and are influenced by cultural differences. The categorical approach on the other hand has the advantage of being internationally standardized and takes account of the important (negative) consequence that autism has on individuals' daily functioning. Nevertheless, both approaches may be used complementary to each other. Normative data about developmental processes are important for determining the quantitative deviation from normality, whereas clinical subthreshold levels per developmental area might serve as an additional outline to evaluate subject's qualitatively abnormal or deviant functioning. For instance in adaptive functioning, it is known that autistic individuals show apparent gaps in the developmental sequences of behaviors (VanMeter *et al.*, 1997), reflecting not only a delay in the development of adaptive behaviors, but also a difference in the sequence in how these behaviors are developed.

Longitudinal research

A way to gain more insight into the role of age and IQ on the development of autistic-like behaviors and on weak central coherence, is longitudinal research. Evidence from follow-up studies showed that a low IQ, low levels of adaptive functioning and the absence of communicative speech at age 5-6 years are indicative of a poorer long-term outcome (Kraijer, 1997; Nordin & Gillberg, 1998; Stevens *et al.*, 2000). However, there is a need for more prospective longitudinal studies to establish the influence of cognitive and verbal abilities in differing groups of individuals with an autism spectrum disorder (Joseph *et al.*, 2002). In addition, longitudinal designs are also interesting to obtain more knowledge into the development of behaviors and cognitive symptoms. Klin and colleagues suggest that impairments in socialization are primary in autism, resulting in impaired language and communication skills, learning problems and the occurrence of unusual behavior patterns (Klin *et al.*, 2002). However, as is shown by studies in autism (Howlin *et al.*, 2000) and in language disordered children (Bishop, 1989; Toppelberg & Shapiro, 2000), language functions reflecting the content (semantics) and use (pragmatics) of language are highly correlated to social functioning, and it remains unclear which functions are disturbed first, affecting other functions in early life (Klin *et al.*, 2002). The investigation of a reduced joint attention, no or indirect eye contact and restricted exploration of the environment in young autistic children is promising, because it may detect effects of these early social-emotional deficits on the development of other neural or cognitive brain functions. As such, the tendency for a weak central coherence may be seen in the light of an inborn style to process information locally, that results in a focus on isolated aspects of the environment without the normal drive to explore the surroundings. However, it may also be the other way round; weak central coherence as a consequence of not being able to attend to social interchange, resulting from less stimulation of brain functions in early life, and a diminished maturation of specific cognitive functions. Nevertheless, the ADI-R, as a measure for subjects' behavioral functioning, and the theory of a weak central coherence, as an explanation of why autistic subjects exhibit behavioral impairments, yield both important frameworks, that can be used to examine developmental trajectories of specific behaviors and cognitive functions in people with autism spectrum disorders. Furthermore, they provide the opportunity for further research to integrate behavioral and cognitive studies with neuroanatomic, neurochemical or neurofunctional studies, or with genetic studies, and test hypotheses about how behaviors are linked to information processes, together with these biological correlates, simultaneously.

CONCLUSION

The three derived symptom dimensions, as described in the hypothesized symptom model, gave support for another symptom structure that underlie the autism spectrum than the DSM triad. They confirmed the finding of a continuum in the autistic symptomatology, ranging from typically developing individuals with minor autistic disorder symptoms to clinical autistic individuals. However, age and intelligence were both of influence on the derived symptom dimensions, and further research on the hypothesized symptom model is therefore needed, to investigate the validity of the model in a preferably larger and more homogeneous group with autism spectrum disorders with and without intellectual disabilities. In addition, age and intelligence also showed to have a main effect in explaining differences in weak central coherence. No clear evidence of a weaker central coherence in the autism group was provided, yet weak central coherence may still serve as an external validity to identify subgroups within the autism spectrum. It may be that individuals with autism spectrum disorders experience difficulties in choosing the most efficient strategy to solve a task with global or local processing styles. In addition, this difficulty may be more prominent in individuals with an Autistic Disorder than in individuals with less severe autistic symptomatology, especially when compared to healthy control children. However, this needs to be further investigated in more homogeneous groups with respect to clinical diagnosis and intellectual functioning. Interesting questions for further research are how behavior dimensions interact with specific cognitive processing styles such as a weak central coherence, and how they might be associated with neurochemical or brain mechanisms or candidate genes. In addition, the development of behavior dimensions and cognitive processing styles are a promising area for future (longitudinal) research, in order to unravel the influence of age on the phenotype of autism.

CLINICAL IMPLICATIONS

The extracted symptom dimensions underlying the autistic behaviors are important for future etiological or effect studies. For instance, genetic studies can use these symptom dimensions to examine the heredity of specific clusters of symptoms separately. In addition, these symptom dimensions may also serve as reliable and valid outcome measures when investigating the effect of certain therapies on specific clusters of behaviors. With regard to

the theory of a weak central coherence in autism, adolescents with severe learning problems and a comorbid disorder on the autism spectrum showed to have a weaker central coherence than the matched control group. This finding suggests that autistic adolescents with an intellectual disability experience more difficulties integrating information into a comprehensive whole. An important educational implication may be that these adolescents will therefore benefit from specific help, that enables them to understand clearly what is being said or done. Furthermore, this finding may have implications for future brain studies in autism, suggesting that further research should focus on a different activation of brain regions that are associated with global versus local processing strategies in normal control children and in clinical children (Ring *et al.*, 1999; Schultz *et al.*, 2000).

SUMMARY

The aim of the studies in this thesis was to gain more insight into the phenotype of autism. Three studies focused on the behavioral phenotype of autism, and examined symptom domains that underlie the spectrum of autistic disorders. Since evidence increasingly suggests that the symptom structure in autism may differ from the symptom structure as described in the DSM-IV edition, chapters 2 to 4 in this thesis report studies of the symptom structure of autism in a group of children and adolescents between 4 and 20 years of age, with minor to severe autistic symptoms. Two other studies focused on the theory of a weak central coherence in autism, and examined whether autistic individuals use of a particular cognitive processing style as predicted by the theory. Autistic people are hypothesized to process information in a local style, being more detail-focused, and making less allowance for the context in which the information is put in. Because evidence for this theory is still conflicting, and recent studies restrict their focus on higher functioning individuals with autism spectrum disorders, the chapters 5 and 6 in this thesis studied the tendency for a weak central coherence in low functioning individuals with autism spectrum disorders, and in individuals with autism spectrum disorders functioning in the mild-to-normal IQ range.

Chapter 2 explored the symptom structure of autism in a verbal group of individuals with a clinical diagnosis of an autism spectrum disorder with a full-scale IQ > 35 (N=87). The behavioral descriptions reflecting subject's functioning at age 4-5, and subject's current status, were obtained from the classification items of the Autism Diagnostic Interview (ADI-R), and used to examine the underlying structure in symptomatology. These classification items (or Algorithm items) of the ADI-R are based on the DSM-IV criteria for Autistic Disorder, and were considered to provide a good framework for investigating the symptom structure of autism. With these items, the derived symptom structure could be compared to the symptom structure as described by the DSM triad. By means of a *parametric factor analysis* (Principal Component Analysis) and a *nonparametric item response analysis* (Mokken Scale Analysis), two factors were found to have best face validity: 'socially impaired behavior' and 'stereotyped language and behavior'. The first factor explained 25% of the variance and contained information about subjects' behaviors that are characterized by not being directed to others, resulting in social and communication impairments manifested in daily living and play

situations. The second factor explained 13% of the variance, and comprised information about behaviors featuring stereotyped linguistic utterances, motor abnormalities and interest patterns that appear unusually focused. This two-factor solution differs from the DSM structure for autism, especially as regards the DSM domain ‘impaired communication’. The derived symptom structure revealed that the DSM domains ‘impaired socialization’ and ‘impaired communication’ correlate strongly, as do the behaviors that reflect stereotyped features in language production, motor mannerisms and interest patterns. Moreover, differences in severity rather than symptom profile were found to distinguish best between subjects with different disorders on the autism spectrum.

In chapter 3, the symptom structure of autism was again explored, but in a larger group of verbal individuals with autistic symptoms ranging from minor to severe pathology with a full-scale IQ > 35 (N=156), and applying classification items of the Autism Diagnostic Observation Schedule (ADOS-G) in addition to the classification items of the ADI-R. These classification items reflected subject’s current functioning instead of subject’s functioning in the period between their fourth and fifth year. Thirty-seven ADI-R items, and twelve ADOS-G items, measuring comparable social and communicative behaviors across ADOS-G modules 2-4, were used in the *nonparametric item response analysis* (Mokken Scale Analysis). From the derived seven unidimensional scales, four were found to have best face validity. Two scales were related to ‘inappropriate social communication’, one according to the ADI-R and one according to the ADOS-G. The two other scales were based on the ADI-R and were related to 'impaired make-belief and social play’, and ‘stereotyped characteristics in language and behavior’. This structure in symptomatology revealed to be comparable to the structure that was found in chapter 2, although a separate scale about ‘impaired make-belief and social play’ emerged. Apparently, above the age of 4-5 years, difficulties with play skills (i.e. make-belief) and playing with other children become more differentiated, so that they result in a distinct scale. In addition, subjects with minor autistic symptomatology and subjects with different disorders on the autism spectrum differed in symptom severity, with subjects with an Autistic Disorder showing significantly more impairments on ‘inappropriate social communication’ according to the ADOS-G, and on ‘stereotyped language and behavior’ according to the ADI-R, than the other classification groups.

In chapter 4 a hypothesized symptom model was constructed, based on the explorative studies described in chapters 2 and 3. The hypothesized symptom model contained three factors that reflected subject's current functioning according to the ADI-R: 'impaired social communication', 'stereotyped features in language and behavior', and 'impaired play skills'. This hypothesized symptom model was tested with *confirmatory analysis* in a large group of verbal and nonverbal individuals with autistic disorder symptoms, with a full-scale IQ > 20 (N=255). Summary scores of the ADI-R classification items per behavior domain (i.e. the 12 subheadings or labels of the ADI-R Algorithm) were used as the ADI-R indicators, and the goodness-of-fit measures of the hypothesized symptom model were compared to the goodness-of-fit measures of the DSM triad model. A robust Maximum Likelihood (ML) procedure was applied to improve the estimates of standard errors and model fit, because the ADI-R indicators were found to be not normally distributed and the sample size was found to be restricted. The confirmatory analysis showed that the DSM triad model encountered severe estimation problems. The DSM domains of 'impaired socialization' and 'impaired communication' showed to be (too) highly correlated, and therefore no goodness-of-fit measures for the DSM model could be estimated. Conversely, the hypothesized symptom model did not encounter such estimation problems and showed to have adequate goodness-of-fit measures. In addition, although the hypothesized symptom model fitted the sample data, some estimated squared multipele correlations for indicators were found to be low. This finding suggests that some behaviors were rarely scored, such as behaviors that reflected stereotyped mannerisms. These behaviors are indicative for subjects with an Autistic Disorder, and these subjects were represented by about 20% of the included sample. Nevertheless, the hypothesized symptom model was considered to be a useful framework for future research, although it needs subsequent examination in a larger group of individuals with varying degrees of autistic symptomatology with and without intellectual impairments.

Chapter 5 described a study, in which the tendency for a weak central coherence was compared between adolescents with an intellectual disability, with and without a comorbid disorder in the autism spectrum (N=43). All adolescents were selected from schools for children with severe learning problems and both groups were matched on chronological age and on IQ. The tendency for a weak central coherence was assessed with two cognitive tasks that are known to measure weak central coherence in lower functioning subjects: (adapted versions of) the Block Design Task and the Child Embedded Figures Test (CEFT). The results

revealed that age and IQ had significant main effects on the task performances. Therefore, the task performances of both groups were adjusted for age and IQ (both taken as covariates in the *multivariate analyses of variance*). The autism group performed significantly faster on the Unsegmented condition of the Block Design Task, and additionally found more house targets in the CEFT. These findings appeared to be specifically related to subjects with an Autistic Disorder, and this was confirmed by a significant association between the number of autistic behaviors as measured by the Autism Behavior Checklist and fast performances on the Unsegmented condition of the Block Design Task. It was concluded that the findings give partial evidence for a weaker central coherence in adolescents with an intellectual disability and with a comorbid disorder in the autism spectrum. In addition, hypotheses are generated about a variability in central coherence skills between individuals with a disorder on the autism spectrum, suggesting a stronger tendency for a weak central coherence in individuals with an Autistic Disorder than in individuals with a milder variant of autism (i.e. with PDD-NOS).

In chapter 6 the effect of age on weak central coherence was examined first in a group of healthy control children from elementary schools (n=76). The cognitive style of a weak central coherence was then compared between subjects with an autism spectrum disorder functioning in the mild-to-normal IQ range, and a selection of control subjects matched on mental age (N=2x21). The same two cognitive tasks measuring weak central coherence, as presented in chapter 5, were used. The results from the 76 healthy control subjects showed that the tendency for a weak central coherence was largely influenced by age. With increasing age, subjects become faster and more accurate on the Block Design Task (with the exception of a ceiling-effect in the accuracy on the Segmented condition of the Block Design Task) and on the CEFT. In the comparison of group performances, a significant main effect of mental age was seen on all task performances, suggesting a significant influence of mental age on the tasks for both the autistic and control subjects. Therefore, task performances were adjusted for mental age in the *multivariate analyses of variance*. No effect of group membership occurred and no association between the task performances and number of autistic behaviors, as measured with summary ratings of the ADI-R and ADOS-G, was found. It was concluded that weak central coherence is a function of age and that it is not specifically related to individuals with autism spectrum disorders. Nevertheless, because the included group of subjects with an autism spectrum disorder was rather heterogeneous in the composition of age and IQ, further

research should focus on larger and more homogeneous samples of subjects with disorders in the autism spectrum, taking into account age and IQ as possible confounders. In addition, longitudinal studies might shed light on the development of weak central coherence in normal developing children and in children with autism spectrum disorders.

In chapter 7 the findings from the five studies are discussed, and limitations of the studies and suggestions for further research are presented. With regard to the identification of symptom domains in autism, the symptom structure that may underlie autistic behaviors showed to be different from the symptom structure as described in the DSM triad. The three derived symptom domains that reflected subject's current functioning, were considered to be useful for further etiological research or for studies that investigate the effectiveness of therapy on specific clusters of autistic behaviors. With regard to the theory of a weak central coherence in autism, partial evidence for a weaker central coherence in intellectually disabled individuals with autism spectrum disorders was provided, but not for the subjects with autism spectrum disorders who functioned in the mild-to-normal IQ range. An explanation for these inconsistent findings may be, that the local bias in autistic subjects disappear when their performances are compared to normal control subjects, because normal control subjects have learnt to shift between most efficient strategies to solve tasks with local or global processing styles. It was shown that weak central coherence was largely influenced by (mental) age. Further research of the relationship between cognitive processing styles and behavioral characteristics should therefore account for differences in age and IQ levels of subjects with autism spectrum disorders. Furthermore, because age and IQ were shown to play an important role in the symptom domains and in weak central coherence, larger (multicenter) studies are highly recommendable. A promising research field arises when questions can be addressed about how behavior dimensions may interact with cognitive processing styles, and how they may be associated with neurochemical or brain mechanisms or candidate genes. In addition, longitudinal studies that investigate the development of behavior dimensions and cognitive processing styles are also important, to clarify the influence of (mental) age on the phenotype of the autism spectrum.

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SAMENVATTING

Het doel van dit proefschrift is om meer inzicht te krijgen in de fenotypering van het autisme spectrum (zie hoofdstuk 1 voor introductie en overzicht). In drie studies (hoofdstuk 2-4) is de symptoomstructuur van autisme in kaart gebracht. Hierbij wordt de vraag gesteld of er binnen de autistische gedragingen verschillende symptoomdomeinen onderscheiden kunnen worden en of deze symptoomdomeinen overeenkomen met de drie gedragsdomeinen zoals die in de DSM-IV staan beschreven. In de studies is de symptoomstructuur van autisme onderzocht bij een groep kinderen en adolescenten van 4-20 jaar, met autistisch gedrag variërend van mild tot ernstig. Twee andere studies (hoofdstuk 5-6) richten zich op de zwakke centrale coherentie theorie, die veronderstelt dat kinderen en adolescenten met een autisme spectrum stoornis informatie meer gefragmenteerd verwerken dan andere kinderen en adolescenten. Tot nu toe is deze theorie vooral getest bij autistische adolescenten of volwassenen met een relatief hoog IQ. In dit onderzoek echter wordt deze theorie onderzocht bij een groep adolescenten met ernstige leerproblemen, een groep kinderen en adolescenten met een laag tot gemiddeld IQ en een groep gezonde controle kinderen van de basisschool.

In *hoofdstuk 2* is de symptoomstructuur van autisme onderzocht bij een groep kinderen en adolescenten met een stoornis binnen het autisme spectrum. Er is hierbij gekozen voor een groep kinderen en adolescenten die zich verbaal kunnen uiten en die een IQ > 35 hebben (N=87). Het autistische gedrag is gemeten door middel van de ADI-R, een gestandaardiseerd interview dat wordt afgenomen bij ouders of verzorgers van het kind (Autism Diagnostic Interview). Met de ADI-R wordt het huidige autistisch gedrag van het kind in kaart gebracht en het autistische gedrag van het kind tussen de leeftijd van 4 en 5 jaar. De ADI-R items die nodig zijn om een classificatie van een Autistische Stoornis vast te stellen volgens de criteria van de DSM-IV (de ADI-R algoritme items) zijn in de statistische analyses gebruikt. Deze items hebben betrekking op de leeftijdsperiode van 4 tot 5 jaar. Hierdoor wordt het mogelijk om de gevonden symptoomstructuur te vergelijken met de structuur zoals die in de DSM-IV staat weergegeven. Met behulp van een *parametrische factor analyse* (Principal Component Analysis) en een *nonparametrische item respons analyse* (Mokken Scale Analysis) zijn er twee factoren gevonden, te weten een ‘stoornis in de sociale communicatie’ en ‘stereotyp taal en gedrag’. De eerste factor verklaart 25% van de variantie en wordt gekenmerkt door

autistische gedragingen die betrekking hebben op ‘het niet gericht zijn op de ander’, waardoor sociale wederkerigheid en communicatie moeilijk tot stand kunnen komen en problemen met ‘alleen spelen’ of ‘samen spelen’ zich voordoen. De tweede factor verklaart 13% van de variantie en wordt gekenmerkt door autistische gedragingen die betrekking hebben op stereotypieën in taal en gedrag en het hebben van beperkte interessegebieden. De twee gevonden factoren wijken af van de drie symptoomdomeinen uit de DSM-IV en suggereren dat de DSM symptoomdomeinen de structuur van autisme niet adequaat weergeven. Naast de twee gevonden symptoomdomeinen laat het onderzoek zien dat personen met verschillende DSM-IV geclassificeerde diagnoses op de twee gevonden symptoomdomeinen van elkaar verschillen in ernst van symptomatologie.

In *hoofdstuk 3* is de symptoomstructuur opnieuw onderzocht in een grotere groep kinderen en adolescenten, waarbij de autistische symptomatologie variëerde van mild tot ernstig. In dit onderzoek is gekozen voor kinderen en adolescenten die zich verbaal kunnen uiten, en die een IQ > 35 hebben (N=156). De classificatie-items van de ADI-R zijn in dit onderzoek uitgebreid met de classificatie items van de ADOS-G, een gestandaardiseerde spelobservatie dat bij de persoon zelf wordt afgenomen (Autism Diagnostic Observation Schedule). De beschrijvingen van het huidige autistisch gedrag volgens de ADI-R en de ADOS-G zijn geanalyseerd met behulp van een *nonparametrische item response analyse* (Mokken Scale Analyse), wat resulteerde in zeven unidimensionele schalen. Twee schalen worden gekenmerkt door ‘niet adequate sociale communicatie’ (één volgens de ADI-R en één volgens de ADOS-G). De vijf andere schalen konden worden teruggebracht tot twee schalen, die beiden gebaseerd zijn op de ADI-R en gekenmerkt worden door 'stoornis in spelvaardigheden’ en ‘stereotypieën in taal en gedrag’. De gevonden symptoomstructuur komt overeen met de gevonden symptoomstructuur zoals beschreven in hoofdstuk 2, alleen in dit onderzoek is er ook een derde factor naar voren gekomen die stoornissen in spelvaardigheden representeert. Door actuele gedragsbeschrijvingen van de personen te gebruiken, in plaats van retrospectieve beschrijvingen van het gedrag zoals het was tussen de leeftijd van 4 en 5 jaar, worden de spelvaardigheden gedifferentieerder en resulteren zij in een aparte schaal. Naast de gevonden structuur in symptomatologie, blijken de kinderen en adolescenten met een Autistische Stoornis significant meer problemen te vertonen op de symptoomdimensie ‘stoornis in sociale communicatie’ van de ADOS-G en op de symptoomdimensie ‘stereotypieën in taal en gedrag’ van de ADI-R, dan de kinderen en adolescenten met de andere classificatie diagnoses.

In *hoofdstuk 4* is een hypothetisch symptomen model opgezet, dat direct voortvloeit uit de resultaten van de studies uit hoofdstuk 2 en 3. Het hypothetisch symptomen model bestaat uit drie factoren, die gebaseerd zijn op het huidige gedrag van de persoon volgens de ADI-R: 'stoornis in de sociale communicatie', 'stereotypieën in taal en gedrag' en 'stoornis in spelvaardigheden'. Het hypothetische symptomen model is getoetst met behulp van een *confirmatoire analyse* (Structural Equation Modeling) bij een grote groep kinderen en adolescenten die zich verbaal, of alleen nonverbaal kunnen uiten (N=255). Er is hierbij gekozen voor een groep kinderen en adolescenten met een IQ > 20. De autistische symptomatologie van deze kinderen en adolescenten variëerde van mild tot ernstig. In de statistische analyses zijn 12 somscores van de ADI-R classificatie-items gebruikt. De passingsmaten van het hypothetische symptomen model en die van het DSM model zijn getoetst, waarbij in de analyse procedure rekening is gehouden met de niet-normale verdeling van de gegevens en de relatief beperkte steekproefomvang voor confirmatoire analyses ($\chi 2$ toets van Satorra en Bentler). De resultaten laten zien dat het DSM model niet herkend kan worden, omdat de factoren 'stoornis in socialisatie' en 'stoornis in communicatie' te sterk met elkaar samenhangen. Hierdoor konden voor het DSM model geen parameterschattingen berekend worden. Het hypothetische symptomen model wordt in de analyse wel ondersteund en laat ook goede passingsmaten zien. Ondanks deze goede passingsmaten, zijn enkele factorladingen uit het hypothetische symptomen model laag. Dit zou verklaard kunnen worden doordat deze factorladingen betrekking hebben op stereotyp gedrag dat over het algemeen gescoord wordt door proefpersonen met een Autistische Stoornis. Van de in totaal 255 proefpersonen, had slechts 20% een Autistische Stoornis. Niettemin biedt het hypothetische symptomen model een goede basis om de eigenlijke symptoomstructuur van autisme te bestuderen, bij voorkeur in een grotere groep kinderen en adolescenten met een autisme spectrum stoornis, die functioneren op verschillende intelligentie niveaus.

In *hoofdstuk 5* is een studie beschreven, waarin twee groepen adolescenten met ernstige leerproblemen zijn vergeleken op het gebruik van zwakke centrale coherentie als cognitieve stijl om informatie te verwerken: een groep met en een groep zonder comorbide stoornis op het autisme spectrum (respectievelijk N=22 en N=21). De adolescenten volgden allemaal speciaal onderwijs op scholen voor Zeer Moeilijk Lerende kinderen (ZML-scholen). De twee groepen zijn gematcht op leeftijd en IQ. Om de theorie van een zwakke centrale coherentie bij

adolescenten met leerproblemen nader te onderzoeken, is gebruik gemaakt van twee visueel-ruimtelijke taken, te weten een voor deze groep aangepaste versie van de CEFT (Child Embedded Figures Test) en van de Block Design Taak. Uit de *multivariate variantie analyses* komen significante hoofdeffecten van leeftijd en IQ op de taakuitkomsten naar voren. Om die redenen zijn de taakuitkomsten van de twee groepen adolescenten gecorrigeerd voor leeftijd en IQ (beiden zijn als covariaat gebruikt). De resultaten op de Block Design Taak laten zien dat de groep met een comorbide stoornis op het autisme spectrum significant sneller presteert op de ongesegmenteerde versie van de Block Design Taak dan de controle groep. Tevens is gevonden dat op deze versie van de Block Design Taak het aantal autisme gedragingen volgens de ABC (Autism Behavior Checklist) significant correleert met de snelheid van reageren. Dit suggereert dat adolescenten met een Autistische Stoornis een zwakkere centrale coherentie hebben dan adolescenten met PDD-NOS. De resultaten van de CEFT laten zien dat de groep met een comorbide stoornis op het autisme spectrum meer 'huis-'figuren ontdekt dan de controlegroep. Geconcludeerd wordt dat de resultaten van beide taken de theorie van een zwakke centrale coherentie ten dele ondersteunen bij adolescenten die gekenmerkt worden door een autisme spectrum stoornis en ernstige leerproblemen. Ook lijken de resultaten erop te wijzen dat binnen de groep adolescenten met een autisme spectrum stoornis, personen met een Autistische Stoornis een zwakkere centrale coherentie hebben dan personen met PDD-NOS.

In *hoofdstuk 6* is ten eerste de invloed van leeftijd op zwakke centrale coherentie onderzocht bij een groep gezonde controle kinderen van de basisschool (N=76). Ten tweede is de zwakke centrale coherentie als cognitieve stijl onderzocht bij twee groepen kinderen en adolescenten: in een groep met een autisme spectrum stoornis en een IQ > 50 (N=21) en in een selectie van de gezonde controle kinderen, gematcht op mentale leeftijd van de groep met een autisme spectrum stoornis (N=21). De twee visueel-ruimtelijke taken beschreven in hoofdstuk 5 zijn ook hier gebruikt om de zwakke centrale coherentie te onderzoeken. De resultaten laten zien dat het niveau van functioneren op zwakke centrale coherentie sterk leeftijdsafhankelijk is. Naarmate de kinderen ouder zijn, presteren ze nauwkeuriger en sneller op beide taken (met uitzondering van het gevonden plafondeffect in de gesegmenteerde versie van de Block Design Taak). Aangezien er in de analyses een significant hoofdeffect van mentale leeftijd op de taakprestaties is gevonden, is mentale leeftijd in de *multivariate variantie analyses* als covariaat meegenomen bij het vergelijken van zwakke centrale coherentie tussen beide

groepen kinderen en adolescenten. De resultaten laten zien dat het hoofdeffect van groep niet significant is. Ook wordt er geen significant verband gevonden tussen autistisch gedrag zoals gemeten met de ADI-R of ADOS-G en de taakprestaties. Geconcludeerd wordt dat zwakke centrale coherentie positief gerelateerd is aan (mentale) leeftijd, maar dat de zwakke centrale coherentie theorie niet bevestigd wordt bij de groep met een autisme spectrum stoornis en een IQ > 50. Opgemerkt moet worden dat de groep met een autisme spectrum stoornis sterk variëerde qua leeftijd en IQ. In toekomstig onderzoek is het derhalve belangrijk rekening te houden met het effect van (mentale) leeftijd op de zwakke centrale coherentie als cognitieve verwerkingsstijl. Hopelijk zullen designs met grotere cohortgrootten en homogenere groepssamenstellingen meer mogelijkheden opleveren om de theorie verder te onderzoeken.

In *hoofdstuk 7* worden de resultaten van de hierboven beschreven studies kritisch besproken en worden suggesties gedaan voor toekomstig onderzoek. Een belangrijk resultaat uit de hoofdstukken 2-4 is dat de symptoomstructuur van autisme verschilt van de symptoomstructuur zoals die in de DSM-IV(-TR) staat beschreven. De drie gevonden symptoomdomeinen van het hypothetische symptomen model bieden goede mogelijkheden voor toekomstig onderzoek naar de etiologie van autisme en/of de effectiviteit van therapieën. Met behulp van de gevonden symptoomdomeinen kan gericht worden nagegaan of specifieke genvariaties gerelateerd zijn aan specifieke symptoomdomeinen en of (nieuwe) therapieën vooral hun effect hebben op bepaalde symptoomdomeinen. Het gegeven dat de zwakke centrale coherentie theorie uit hoofdstuk 5-6 ten dele bevestigd wordt in de groep met een autisme spectrum stoornis en met ernstige leerproblemen, maar niet in de groep met een autisme spectrum stoornis en een IQ >50, roepen nog vragen op. Een mogelijke verklaring is dat het voordeel van een zwakke centrale coherentie bij kinderen met een autisme spectrum stoornis vooral opvalt bij kinderen met ernstige leerproblemen. Kinderen met ernstige leerproblemen hebben in het algemeen moeite met het kiezen van de meest efficiënte strategie om een taak te maken (zoals de keuze voor een globale of locale strategie). Het voordeel van een zwakke centrale coherentie bij kinderen met een autisme spectrum stoornis is dan duidelijk te zien. In vergelijking met gezonde controle kinderen daarentegen, lijkt dit voordeel van een zwakke centrale coherentie bij kinderen met een autisme spectrum stoornis tenietgedaan te worden. De resultaten van de gezonde controle kinderen laten zien dat het niveau van functioneren op zwakke centrale coherentie sterk leeftijdsafhankelijk is en dit zou suggereren dat de gezonde controle kinderen al vroeg in de ontwikkeling leren welke strategie

het meest efficiënt is om taken succesvol te volbrengen. Toekomstig onderzoek dient daarom rekening te houden met leeftijdseffecten op de zwakke centrale coherentie als strategie om informatie te verwerken. Met behulp van grotere steekproefomvangen kunnen bijvoorbeeld gemakkelijker dan in de hier gerapporteerde studies mogelijk was, homogenere subgroepen met betrekking tot leeftijd en IQ geselecteerd worden en kan de invloed van leeftijd en IQ op symptoomdomeinen en cognitieve verwerkingsstijlen onderzocht worden. Daarbij zou het interessant zijn om na te gaan hoe de symptoomdomeinen verband houden met de cognitieve verwerkingsstijlen van autistische individuen en hoe deze zich vervolgens verhouden tot genetische overerving, neuroanatomische of neurochemische kenmerken of hersenfuncties. Daarnaast is het belangrijk om niet alleen cross-sectioneel onderzoek te doen, maar ook na te gaan hoe symptoomdomeinen zich ontwikkelen en hoe de ontwikkeling van cognitieve verwerkingsstijlen van kinderen met autisme zich verhoudt tot die van gezonde controle kinderen.

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CURRICULUM VITAE

Natasja van Lang werd geboren op 15 december 1969 in Zoetermeer. In 1988 behaalde zij haar VWO-diploma in Purmerend en verhuisde zij naar Maastricht om daar Gezondheidswetenschappen te studeren. Na in 1993 te zijn afgestudeerd in Gezondheidswetenschappen, richting Geestelijke Gezondheidskunde, heeft zij de studie (ontwikkelings-) Psychologie in Leiden gevolgd en deze in 1994 afgerond. Haar interesse in de kinder- en jeugdpsychiatrie en in het onderwerp autisme is ontstaan gedurende haar stage en scriptie in beide studies.

In haar eerste baan als onderzoeker, kwam zij terecht bij de Open Universiteit in Heerlen. Daar richtte ze zich op een onderzoek naar de tevredenheid van studenten met een lichamelijke en/of geestelijke handicap over het studeren aan de Open Universiteit. Hierna werkte ze op de onderzoeksafdeling van de Volwassenenpsychiatrie aan het Academisch Medisch Centrum te Amsterdam en werkte ze mee aan het aanvragen van subsidies voor onderzoek naar de zorgbehoeften en zorgaanbod voor mensen met schizofrenie. In 1998 was zij werkzaam op de onderzoeksafdeling Neuropsychologie en Psychiatrie aan de Universiteit Maastricht en werkte zij mee aan een europees onderzoek naar (neuropsychologische) tests voor ouderen met dementie en aan de Nederlandse vertaling van een neuropsychologische testbatterij voor kinderen.

In 1999 is zij weer ‘teruggekeerd’ naar de kinder- en jeugdpsychiatrie en naar het onderwerp autisme en is zij met begonnen met haar promotie-onderzoek naar symptoom dimensies en centrale coherentie in autisme op de afdeling Kinder- en Jeugdpsychiatrie (Accare) aan de Rijksuniversiteit Groningen. Op dit moment is zij werkzaam als post-doc onderzoeker op de afdeling Kinder- en Jeugdpsychiatrie van het Erasmus- Medisch Centrum in Rotterdam, waar zij zich met name richt op (longitudinaal) onderzoek naar kinderen met internaliserende gedragsproblemen.