THE CHAOTIC MIND

A study of children with thought disorders and social contact problems

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The Chaotic Mind: A study of children with thought disorders and social contact problems

Chaos in mijn hoofd: Een studie onder kinderen met denkstoornissen en sociale contactproblemen

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1 Introduction

Introduction

This thesis contains the results of three different lines of investigation. The first aim of this thesis is to provide more information about children with Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), from a behavioral, as well as from a cognitive perspective. The second aim is to get a better understanding of what is considered as formal thought disorder (FTD) and how this plays a role in children with social contact problems. The final aim of this thesis comes from a biological point of view. We investigated the role of finger length ratios in children with Pervasive Developmental Disorders (PDDs) and other psychiatric disorders. Although there is some overlap among the different study samples, the aims and methods will be described for each of the three topics separately.

PDD-NOS

DSM-IV (APA, 1994) provides 12 explicit criteria for autistic disorder, divided over the domains of social interaction, communication, and stereotyped interests and repetitive behaviors. A child must display at least six criteria for a diagnosis of autistic disorder to be assigned. For a DSM-IV diagnosis of PDD-NOS, criteria are not explicit and are somewhat ambiguous. No specific items or scoring algorithms are provided. As a consequence, children with PDD-NOS may have different combinations of symptoms (Walker et al., 2004) and therefore constitute of a very heterogeneous group. Buitelaar and colleagues (1999) developed standardized research criteria for PDD-NOS that differentiated reliably between PDD-NOS and non-PDD children. These explicit research criteria are used in the first two studies included in this thesis in which the study sample consists of children with PDD-NOS. The research criteria are listed in Table 1.1.

Studies that provide information on the prevalence rates of PDD-NOS often fall short of strict diagnostic criteria, and assessment procedures differ per study and change over time, which makes prevalence rates difficult to compare (Fombonne, 1999). As Wing and Potter (2002) pointed out, prevalence rates of all types of PDDs in recent studies seem considerably higher than in older studies. Recently, Chakrabarti and Fombonne (2001) suggested that PDD-NOS is at least twice as common as autistic disorder in the general population and that this substantial group may have similar treatment needs as the autistic group (Fombonne, 1999). The paradox is that, although PDD-NOS may be much more common, the disorder is much less frequently studied than autistic disorder (Volkmar & Lord, 1998).

Although it is known that children with autism suffer from co-morbid medical and psychiatric problems, the prevalence of co-morbid psychiatric disorders is not known in children with PDD-NOS. Additional symptoms may cause considerable distress in daily

Table 1.1. PDD-NOS research criteria (Buitelaar & Van der Gaag, 1998).

A.	A total of three (or more) items from (1), (2), and (3), with at least one item from (1):
	(1) Qualitative impairment in social interaction:
	(a) Marked impairment in the use of multiple non-verbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
	(b) Failure to develop peer relationships appropriate to developmental level
	(c) A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g. by a lack of showing, bringing, or pointing out objects of interest)
	(d) A lack of social or emotional reciprocity
	(2) Qualitative impairment in communication:
	(a) In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
	(b) Stereotyped and repetitive use of language or idiosyncratic language
	(3) Restricted, repetitive, and stereotyped patterns of behavior, interests, and activities:
	(a) Stereotyped and repetitive motor mannerisms (e.g. hand or finger flapping or twisting, or complex whole-body movements)
B.	Does not meet criteria for autistic disorder or for another specific pervasive developmental disorder

Note. PDD-NOS = Pervasive Developmental Disorder Not Otherwise Specified.

life, and may respond favorably to treatment, whereas for the core deficits in communication and social interaction there may be no cure available (Tanguay, 2000). Knowledge of co-morbidity patterns in PDD-NOS may also enhance further research regarding subtypes of PDD-NOS.

Further, previous studies have assessed the intelligence profiles of children with autism and Asperger syndrome repeatedly, but nothing is known about these profiles in children with PDD-NOS. Clinicians often presume the same Intelligence Quotient (IQ) scores and patterns as found in children with autism will be present in children with PDD-NOS.

Therefore, the aims of this first part of the study were twofold: (1) to assess the rate of co-morbid psychiatric disorders in children with PDD-NOS, and (2) to investigate intelligence profiles in children with PDD-NOS.

Sample

The study with respect to co-morbid disorders in children with PDD-NOS, included a clinical sample from the university outpatient department of child and adolescent psychiatry, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, the Netherlands. Children visited the department between July 2002 and September 2004. All consecutively referred children between 6.5 and 12 years of age (n = 503) were screened for the presence of a PDD-NOS research diagnosis, and 108 of them met sufficient research criteria. Eighteen children or their parent(s)/caretaker(s) were not eligible to participate, thus this study sample consisted of 94 children with PDD-NOS.

With respect to the intelligence profiles study, the selection procedure was identical, only the time period differed slightly (July 2002 until April 2004). Of the 396 consecutively referred children, 85 received a diagnosis of PDD-NOS. For 9 children scores from intelligence tests were not available or reliable, which yielded a study sample of 76 children with PDD-NOS.

Formal thought disorder

FTD has been considered a central characteristic of schizophrenia since the first descriptions of this disorder by Bleuler (1911) and refers to a disturbance in thought processes (APA, 1994). More specifically, FTD is described as the presence of illogical thinking, loose associations, incoherence, and poverty of content of speech (APA, 1980).

FTD in children has been demonstrated to be a possible precursor of future psychotic episodes and even schizophrenia (Ott et al., 2001; Parnas et al., 1982). FTD can be reliably assessed in childhood (Caplan et al., 1989), for instance by using extensive research instruments. It is unknown however, how sensitive the practicing clinician is in detection of FTD during a child psychiatric interview.

Further, there is a possible subgroup of children with PDD-NOS, labeled under Multiple Complex Developmental Disorder (MCDD), and these children seem to be characterized by the presence of FTD. MCDD is currently no DSM-IV disorder and these children are classified as PDD-NOS. It is unknown however, if and how children with PDD-NOS differ from those with MCDD. Therefore, the aims of this second part of the study were

Table 1.2. MCDD research criteria (Buitelaar & Van der Gaag, 1998).

A total of five (or more) items from (1), (2) and (3), with at least one item from (1), one item from (2), and one item from (3):
(1) Impaired regulation of affective state and anxieties:
(a) Unusual or peculiar fears and phobias, or frequent idiosyncratic or bizarre anxiety reactions
(b) Recurrent panic episodes or flooding with anxiety
(c) Episodes of behavioral disorganization punctuated by markedly immature, primitive, or violent behaviors
(2) Impaired social behavior:
(a) Social disinterest, detachment, avoidance, or withdrawal
(b) Markedly disturbed and/or ambivalent attachments
(3) The presence of thought disorder:
(a) Irrationality, magical thinking, sudden intrusions on normal thought process, bizarre ideas, neologism, or repetition of nonsense words
(b) Perplexity and easy confusability
(c) Overvalued ideas, including fantasies of omnipotence, paranoid preoccupations, over engagement with fantasy figures, referential ideation

Note. MCDD = Multiple Complex Developmental Disorder.

twofold: (1) to assess the association between a research based measurement and the clinician's judgment of FTD, and (2) to investigate whether children with PDD-NOS can be delineated from those with MCDD. Research criteria for MCDD are listed in Table 1.2.

Sample

In the study of FTD, 172 children, aged between 6 and 12 years were included. They all visited the university outpatient department of child and adolescent psychiatry, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, the Netherlands, between July 2002 and July 2004. All children participated in a larger study regarding the identification of children at risk for the development of psychotic episodes or social contact problems. From a total of 200 consecutively referred children who were considered to be at risk, FTD criteria were rated by the clinician. For 28 children data from a standardized instrument to measure FTD (the Kiddie Formal Thought Disorder Rating Scale [K-FTDS; Caplan et al., 1989]) were not available or unreliable, which yielded a study sample of 172 children.

For the study of PDD-NOS and MCDD, the same selection sample as in the study of co-morbidity in children with PDD-NOS, was used. Of the total sample of 503 children, all MCDD and PDD-NOS research criteria were rated for 491 children. Twenty-nine children met criteria for a research diagnosis of MCDD. Four parent(s)/caretaker(s) refused to participate in the study which yielded a sample of 25 children with MCDD. A further 86 children were assigned a PDD-NOS diagnosis. Thus, the sample included in this sub study consisted of 101 children.

Finger length ratio

The length of the index finger, compared to the length of the ring finger, the 2D:4D ratio, is a sexually dimorphic trait, not only in humans (Manning & Bundred, 2000) but also in mice (Brown et al., 2002), and baboons (McFadden & Bracht, 2003). The relative length of fingers is fixed for life within the first three months of pregnancy, and remains stable thereafter (Garn et al., 1975; Manning et al., 1998). Finger length ratio is considered a marker of the levels of testosterone the fetus was exposed to in the womb. A large amount of studies have related the 2D:4D ratio to a variety of variables (i.e., assertiveness, breast cancer, fertility, hand preference, homosexuality) (Manning & Bundred, 2000; McFadden et al., 2005; Robinson & Manning, 2000; Williams et al., 2000). Further, 2D:4D ratios have been associated with psychiatric traits, personality and social behaviors that show sex differences, which are the topic of this part of our study.

It is known that children with autism have a very low 2D:4D ratio, but it is unknown whether this is specific for autism. Further, associations between social contact problems and finger length ratio have been studied in normal children, but not yet in child

psychiatric samples. Therefore, the aims of this third part of the study were the following: (1) to compare finger length ratios in school-aged children with different child psychiatric disorders, and, (2) to correlate finger length ratios with autistic features in a child psychiatric sample.

Sample

For the study of finger length comparisons in different child psychiatric groups, only boys were included. Between July 2003 and September 2005, 314 boys, aged 6 – 14 years, had been referred to the university outpatient department of child and adolescent psychiatry, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, the Netherlands. All of those who received a DSM-IV diagnosis of autism, Asperger syndrome, PDD-NOS, Attention Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), or an anxiety disorder were selected. Boys with co-morbid disorders were excluded (e.g., ADHD plus a co-morbid anxiety disorder). This yielded 154 boys. For 144 of them, at least one hand scan was available. For eight boys a hand scan was not available due to refusal of the child or the parent(s)/caretaker(s), and two scans were missed due to scanning problems. The boys in the different child psychiatric groups, were compared with 96 control boys (out of 103) who were recruited from a primary school in Rotterdam, the Netherlands.

For the study of correlations between autistic features and finger length ratios in a child psychiatric sample, 182 children, aged 6 – 13 years, were included. Selection was made from children, referred to our department as mentioned in the study above, and for whom the Autism Diagnostic Observation Schedule-Generic (ADOS-G; Lord et al., 1999) was administered (n = 199). Three children were unable or unwilling to participate in the ADOS-G, eight of the parent(s)/caretaker(s) refused to participate, and six of the hand scans were insufficiently clear for the left hand and the right hand, and therefore 2D:4D measurements could not be carried out. This yielded 182 children for whom at least one measured hand scan and ADOS-G data were available.

Structure of this dissertation

In *Chapter 2* and *Chapter 3*, the rate of co-morbid psychiatric disorders and intelligence profiles in school-aged children with PDD-NOS are described.

Chapter 4 and *Chapter 5* are related to thought disorders. In *Chapter 4* the clinician's judgment of FTD is compared with the ratings of the K-FTDS. The aim is to assess the clinician's sensitivity in the detection of FTD. In *Chapter 5*, a group of children with MCDD is compared to a group with PDD-NOS. The aim is to assess whether these two groups can be delineated with respect to symptom factors.

Chapter 6 and *Chapter 7* describe the finger length studies. In *Chapter 6* it was assessed whether a low 2D:4D ratio is specific for autism. Finger length ratios of children with autism are compared to those with PDD-NOS, ADHD, and anxiety disorders. In *Chapter 7*, autistic features in a child psychiatric sample are associated with finger length ratios of the left and the right hand, and sex differences in these associations are assessed.

Finally, in *Chapter 8* the main findings and conclusions of *Chapters 2-7* are presented and discussed. Clinical implications and recommendations for future studies are given.

2 High rates of psychiatric co-morbidity in PDD-NOS

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Journal of Autism and Developmental Disorders, in press

Abstract

Introduction

Rates of co-morbid psychiatric conditions in children with PDD-NOS are hardly available, although these conditions are often considered as more responsive to treatment than the core symptoms of PDD-NOS.

Method

Ninety-four children with PDD-NOS, aged 6 – 12 years were included. The DISC-IV-P was administered.

Results

At least one co-morbid psychiatric disorder was present in 80.9% of the children; 61.7% had a co-morbid disruptive behavior disorder, and 55.3% fulfilled criteria of an anxiety disorder. Compared to those without co-morbid psychiatric disorders, children with a co-morbid disorder had more deficits in social communication.

Discussion

Co-morbid disorders occur very frequently in children with PDD-NOS, and therefore clinical assessment in those children should include assessment of co-morbid DSM-IV disorders.

Introduction

A diagnosis of Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) applies when an individual fails to meet specific criteria for autistic disorder or another explicitly defined pervasive developmental disorder (PDD), but has similar difficulties in social interaction, reciprocal communication, and/or stereotypical behavior (APA, 1994). These difficulties may be milder or of different quality than those seen in autistic disorder (Towbin, 1997). Like children with autistic disorder, children with PDD-NOS may have stereotyped interests, preoccupations, or limitations in imaginative play, although such features may also be mild or even absent. And also in contrast with autistic disorder, PDD-NOS does not have to be associated with a language deficit (Towbin, 1997).

DSM-IV (APA, 1994) provides 12 explicit criteria for autistic disorder, divided over the domains of social interaction, communication, and stereotyped interests and repetitive behaviors. A child must display at least six criteria for a diagnosis of autistic disorder to be assigned. For a DSM-IV diagnosis of PDD-NOS, criteria are not explicit and are somewhat ambiguous. No specific items or scoring algorithms are provided. As a consequence, children with PDD-NOS may have different combinations of symptoms (Walker et al., 2004) and therefore constitute of a very heterogeneous group. Buitelaar and colleagues (1999) developed more standardized research criteria for PDD-NOS that differentiated reliably between PDD-NOS and non-PDD children. These explicit criteria are used in the current study.

Studies that provide information on the prevalence rates of PDD-NOS often fall short of strict diagnostic criteria, and assessment procedures differ per study and change over time, which makes prevalence rates difficult to compare (Fombonne, 1999). As Wing and Potter (2002) pointed out, prevalence rates of all types of PDDs in recent studies seem considerably higher than in older studies. Recently, Chakrabarti and Fombonne (2001) suggested that PDD-NOS is at least twice as common as autistic disorder in the general population and that this substantial group may have similar treatment needs as the autistic group (Fombonne, 1999). The paradox is that, although PDD-NOS may be much more common, the disorder is much less frequently studied than autistic disorder (Volkmar & Lord, 1998).

Despite the high prevalence, knowledge about psychiatric co-morbidity patterns associated with PDD-NOS is hardly available. Knowledge about specific types of co-morbidity that occur frequently with PDD-NOS would be useful to efficiently focus clinical assessment. Such additional symptoms may cause considerable distress, interfere markedly with daily functioning, and may respond favorably to treatment. For instance, pharmacotherapy can play a role in treatment of co-morbid attention and hyperactivity problems, may be helpful in reducing anxiety, aggression and obsessive preoccupations (e.g., Keen & Ward, 2004; Santosh & Baird, 2001), but has a limited effect on improving

social communication deficits in PDDs (Tanguay, 2000). Medication is also beneficial for reducing these interfering co-morbid symptoms, and may subsequently facilitate effective application of treatments, such as behavioral intervention (McDougle et al., 2003). Early use of behavioral interventions in children with PDD may lead to reductions of aggression, tantrums, and self-injurious behavior up to 80-90% (e.g., Horner et al., 2002; Iwata et al., 1994).

Knowledge of co-morbidity patterns in PDD-NOS may also enhance further research regarding subtypes of PDD-NOS. For instance, PDD-NOS that is associated with specific types of co-morbidity, such as anxiety or mood disorders, may have different genetic or neurobiological correlates, may differ with respect to prognosis, or may warrant different treatment approaches than, for instance, PDD-NOS with co-morbid disruptive behavior disorders.

Some studies investigated co-morbidity between PDD-NOS and symptoms of Attention-Deficit/-Hyperactivity Disorder (ADHD) in school-aged children. However, exact data on rates of ADHD in children with PDD-NOS are not available. This may be partly related to the priority rules of DSM-IV, which only permit the use of a co-morbid ADHD classification when the symptoms do not occur during the course of any PDD (APA, 1994). Therefore, it seems nearly impossible to simultaneously apply a classification of both PDD-NOS and ADHD. Luteijn et al. (2000) compared 5 to 12 year old children with PDD-NOS (n = 190) and with ADHD (n = 152), from an outpatients' clinic for child and adolescent psychiatry. Classifications of PDD-NOS and ADHD were based on DSM-IV criteria (APA, 1994). Parents filled out the Child Behavior Checklist 4-18 (CBCL; Achenbach, 1991). It was found that average scores of the PDD-NOS group on the CBCL Attention Problems scale equaled those of the ADHD group. Hence, this study indicated that co-morbid attention problems seemed to occur frequently in children with PDD-NOS.

To the present authors' knowledge no data are available about the co-morbidity of PDD-NOS and other externalizing disorders such as Oppositional-Defiant Disorder (ODD) or Conduct Disorder (CD). Gilmour et al. (2004) showed a substantial co-morbidity of PDD in children with CD, but no conclusions could be drawn about the reverse: rates of co-morbid CD in children with PDD-NOS.

Muris and colleagues (1998) investigated the prevalence of co-morbid anxiety disorders in children with autistic disorder (n = 15) and PDD-NOS (n = 29), aged between 5 and 14 years. Classification of PDD-NOS or autistic disorder was based on DSM-III-R criteria (APA, 1987). All children had undergone extensive psychological and psychiatric screening, and a multidisciplinary team of professionals of the Center of Autism assigned the diagnoses. Co-morbid anxiety disorders were investigated using the Diagnostic Interview Schedule for Children-Parent version 2.3 (DISC-P; Shaffer et al., 1996). Results indicated that 84.1% of the children met diagnostic criteria for at least one anxiety disorder. The most common anxiety disorder was simple phobia (63.3%), and the least frequent

anxiety disorder was panic disorder (9.1%), although panic attacks occurred regularly (56.8%). Furthermore, 11.4% of the children met diagnostic criteria for obsessive compulsive disorder (OCD). Some anxiety disorders (e.g., simple phobia, separation anxiety disorder, avoidant disorder, and overanxious disorder) were significantly more prevalent among children with PDD-NOS than among children with autistic disorder. The sample size of this study was small, which limits its generalizability. Further, diagnosis of PDD-NOS was not based on standardized assessment.

Further information regarding the co-morbidity of psychiatric disorders in children with PDD-NOS would be very useful for clinical and research purposes. Therefore the aim of this study was to investigate psychiatric co-morbidity patterns in school-aged children with PDD-NOS.

Methods

Participants

Participants were 94 children, 6 to 12 year old, who fulfilled PDD-NOS research criteria (age range 6; 5 – 12; 11 years, $M = 8.5$, $SD = 1.9$, 88.3% boys; $n = 83$, and 11.7% girls; $n = 11$). All patients visited the outpatients' department of child and adolescent psychiatry, Erasmus Medical Center Rotterdam, the Netherlands. Co-morbidity was assessed with the DISC-IV-P (Shaffer et al., 1998). Subsequently, subgroups of PDD-NOS children with different co-morbid disorders were compared on measures of severity of PDD related social contact and communication problems (i.e., Autism Diagnostic Observation Schedule-Generic [ADOS-G]; Lord et al., 1999; Children's Social Behavior Questionnaire [CSBQ]; Luteijn et al., 1998; Luteijn et al., 2002).

All consecutive referrals between July 2002 and September 2004 ($n = 503$) were screened for the presence or absence of a PDD-NOS research diagnosis. One hundred and eight children met sufficient criteria for a research diagnosis of PDD-NOS and were therefore eligible to participate in the study. Two of them were excluded due to parental language difficulties. A further nine parents refused to take part in the DISC-IV-P assessment, and three children were excluded because of severe neurological or physical problems (e.g., blindness). This yielded 94 children with a research diagnosis of PDD-NOS for whom reliable DISC-IV-P data were available.

Assessment

PDD-NOS research criteria

In the current study, a diagnosis of PDD-NOS was based on explicit research criteria. Buitelaar et al. (1999) compared children with clinical diagnoses of autistic disorder (*n*

= 205), PDD-NOS (*n* = 80), and non-PDD diagnoses such as mental retardation and language disorders (*n* = 174) on the 12 criteria for autistic disorder. Both ICD-10 (WHO, 1993) and DSM-IV (APA, 1994) classification systems were used. They found that a short set of seven criteria, derived from the 12 original criteria for autistic disorder, discriminated best between the PDD-NOS group and the group of non-PDD children. These seven items were divided over the domains of social interaction (four items), communication (two items), and stereotyped interests and repetitive behavior (one item). To diagnose PDD-NOS, at least three items had to be present including at least one social interaction item, and the child should not meet criteria for autistic disorder or other types of PDD.

Child psychiatrists, registrars, and psychologists supervised by child psychiatrists rated the research criteria. Twenty-four different raters were involved. Rating was based on assessment of early development through current level of social, communicative, and adaptive functioning, obtained from semi-structured interviews carried out with the parent(s) or caretaker(s) as well as psychiatric observation of the child in a one-to-one situation. School and relevant medical information was obtained, as well as psychological assessment information. Immediately after all diagnostic procedures were finished, a multidisciplinary team obtained consensus with regard to the final DSM-IV (APA, 1994) classification, and PDD-NOS research criteria were rated subsequently.

We carried out an inter rater reliability study on 30 randomly selected children (32%). Two clinicians independently rated all the PDD-NOS research criteria. Agreement between the raters on the presence or absence of a PDD-NOS diagnosis was moderate to good (κ = .62, 80.77% agreement). Further, we computed a score for the total number of PDD-NOS criteria rated positive by each rater for each child. The correlation between these scores by the two raters was high (Spearman's rho = .79), indicating excellent agreement (Cichetti & Sparrow, 1981).

DISC-IV

The Dutch version of the DISC-IV (Ferdinand & Van der Ende, 1998; Shaffer et al., 1998) is a highly structured respondent based interview to assess DSM-IV Axis I psychiatric disorders in the past year, in children and adolescents. The DISC-IV has a parent version (DISC-IV-P) for parents of children aged 6 to 17, and a child version (DISC-IV-C) to be administered to children aged 11 to 17. In this study, the DISC-IV-P was used to assess anxiety disorders, mood disorders, schizophrenia, and disruptive behavior disorders. DISC-IV diagnoses are solely based on parent reports about the presence or absence of symptoms. Clinical observations of the interviewer are not used.

The complete Dutch DISC-IV (Ferdinand & Van der Ende, 1998) contains just fewer than 3000 questions of which around 10% are considered 'stem' questions that are always asked. The stem questions are concerned with broad symptom descriptions and are designed to lead to false-positive answers. Subsequently, there are many 'contingent'

questions that are asked if a stem question is answered positively. Contingent questions assess whether symptoms meet the intensity, frequency, and duration criteria as specified by DSM or ICD classification systems. Thus, the contingent questions improve the accuracy of the stem questions (Shaffer et al., 2000). To obtain a Dutch version of the DISC-IV, the original American version was translated into Dutch, and then translated back by an independent translator. Subsequently, the original version and the back translation were compared by the developers of the original version at Columbia University New York, as well as by the Dutch translators, after which the translation was adapted.

Studies of earlier versions of the DISC-P have shown good test-retest and inter rater reliability (Schwab-Stone et al., 1993; Shaffer et al., 1993; Shaffer et al., 1996). The DISC-IV showed moderate to good reliability (Shaffer et al., 2000). Psychometric properties of the Dutch DISC-IV are not available yet.

In this study, psychologists, research assistants, and psychology undergraduate students (supervised by psychologists) had all been trained by the authors of the Dutch DISC-IV (Ferdinand & Van der Ende, 1998) who, in turn, had been trained as trainers at Columbia University New York by the authors of the original DISC. The interviewers were blind to any other diagnostic information about the child. In 69.1% ($n = 65$) of the cases the mother of the child has been interviewed, in 5.3% ($n = 5$) the father, in 24.5% ($n = 23$) both parents, and in 1.1% ($n = 1$) a different caretaker has been interviewed.

WISC-R

The Dutch version of the Wechsler Intelligence Scale for Children-Revised (WISC-R; Van Haasen et al., 1986; Wechsler, 1974) was administered. As the original version, the Dutch version has shown sufficient reliability and validity. The WISC-R generates a Full Scale Intelligence Quotient (FSIQ), a Verbal Intelligence Quotient (VIQ), and a Performance Intelligence Quotient (PIQ) ($M = 100$, $SD = 15$). For 95.7% ($n = 90$) of the children WISC-R data were available. FSIQ varied between 55 and 120 ($M = 91.22$, $SD = 17.43$). PIQ varied between 49 and 129 ($M = 92.84$, $SD = 18.90$), and VIQ varied between 51 and 122 ($M = 91.57$, $SD = 16.60$). For four children WISC-R could not be administered due to mental retardation ($n = 2$), hearing problems ($n = 1$), and insufficient knowledge of the Dutch language ($n = 1$).

ADOS-G

The ADOS-G (Lord et al., 1999) provides a standardized context to observe PDD related behaviors in the domains of social interaction, communication, and stereotyped behavior. In this study, subgroups of PDD-NOS children with different co-morbid disorders were compared on the subscales Reciprocal Social Interaction (i.e., eye contact) and Communication (i.e., stereotyped language) of the ADOS-G. These two subscales have shown high reliability and validity. The diagnostic algorithm of the ADOS-G allows classification of participants as having autistic disorder or ASD. The distinction between the

categories depends on symptom severity. For 93.6% (n = 88) of the children in this study ADOS-G data were available. An ADOS-G classification of autistic disorder was assigned in 10.2% (n = 9) of the cases, and a further 47.7% (n = 42) had an ADOS-G classification of ASD. The remaining 42.1% (n = 37) received scores that were below the threshold for an ASD classification. Six children were unable (i.e., severe communication deficits) or unwilling to take part in the ADOS-G assessment.

CSBQ

The CSBQ (Luteijn et al., 1998; Luteijn et al., 2002) is a 49-item parent questionnaire that covers a wide range of PDD features of a child in the past two months. The items refer to problem behaviors seen in children with milder variants of PDD (Luteijn et al., 2000). The score format is 'does not apply' (score 0), 'sometimes or somewhat applies' (score 1), or 'clearly or often applies' (score 2). The items are divided over six subscales, referring to Behaviors not tuned to situation (e.g., Doesn't know when to stop), Withdrawn (e.g., Acts as if others are not there), Orientation problems in time, place, or activity (e.g., Easily gets lost), Difficulties understanding social information (e.g., Does not understand jokes), Stereotyped behavior (e.g., Flaps arms/hands when excited), and Fear of and resistance to changes (e.g., Opposes change).

Psychometric properties of the CSBQ have been studied in a large Dutch sample (n = 3407) (Hartman et al., 2006). Three types of reliability were studied. Cronbach's α, that reflects internal consistency was good (α = .94 for total score, and between .76 and .90 for the subscales). Intraclass Correlation Coefficients (ICC), reflecting inter rater reliability (mother versus father information) was good (ICC = .86 for total score, and between .75 and .89 for the subscales). Further, test-retest reliability (interval of approximately four weeks) was good as well (r = .90 for total score, and between .80 and .88 for the subscales) (Hartman et al., 2006).

For 97.9% (n = 92) of the children in this study, CSBQ data were available. For two children, CSBQ data were not available due to refusal of the parent(s) to fill out the questionnaire. In the current sample Cronbach's α was good; alphas were between .81 and .88 for the six subscales, and .94 for the total score.

Data analyses

To determine which co-morbid psychiatric disorders were present in children with PDD-NOS, rates and 95%-confidence intervals were calculated for each co-morbid diagnosis.

To compare four different co-morbidity groups in the total sample of PDD-NOS children, on IQ, ADOS-G, and CSBQ data, analysis of variance (ANOVA) and multivariate analysis of variance (MANOVA) were used. To further compare the four groups on number of PDD-NOS criteria that were present, non-parametric statistics were used. For these additional analyses, mood and anxiety disorders were summed as internalizing disorders.

Ethics

Parent(s) or caretaker(s) of the children had all signed informed consent forms prior to participation in the study. Children who were 12 years old signed the consent forms themselves too. The Medical Ethics Committee of the Erasmus Medical Center has approved the study.

Results

PDD-NOS research criteria

In Table 2.1. the percentage of children who were scored positively on each research criterion for PDD-NOS is listed. Although all 94 children were assigned a research diagnosis of PDD-NOS, not necessarily every criterion was present in each child. Criterion 1a (marked impairment in the use of multiple non-verbal behaviors to regulate social interaction) and criterion 1b (failure to develop peer relationships appropriate to developmental level) received the highest percentages of positive scores (77.7% and 92.5% respectively).

Co-morbidity

Table 2.2. shows rates of co-morbid DISC-IV-P diagnoses. Overall, 80.9% (*n* = 76) of the children had at least one co-morbid psychiatric disorder, and 54.3% (*n* = 51) had two or more co-morbid psychiatric disorders.

In 61.7% (*n* = 58) of the children with PDD-NOS, criteria for at least one disruptive behavior disorder (ADHD, ODD, and/or CD) were met. ADHD was present in 44.7% (*n* = 42) of the children, ODD in 37.2% (*n* = 35), and CD in 9.6% (*n* = 9) of the children. In 14.9% (*n* = 14) of the children, the criteria for the inattentive type of ADHD were met, whereas the criteria for the hyperactive-impulsive type were met in 8.5% (*n* = 8) of

Table 2.1. PDD-NOS research criteria and percentages of children who were scored positively on each criterion.

Item	
Item 1a: Marked impairment in the use of multiple non-verbal behaviors to regulate social interaction	77.7%
Item 1b: Failure to develop peer relationships appropriate to developmental level	92.5%
Item 1c: A lack of spontaneous seeking to share enjoyment, interests, or achievements with others	52.7%
Item 1d: Lack of social or emotional reciprocity	26.6%
Item 2a: In individuals with adequate speech, impaired ability to initiate/sustain conversation	55.9%
Item 2b: Stereotyped and repetitive use of language or idiosyncratic language	46.2%
Item 3a: Stereotyped and repetitive motor mannerisms	40.4%

Note. PDD-NOS = Pervasive Developmental Disorder Not Otherwise Specified. Data for criteria 1b, 1c, 2a, and 2b are based on n = 93 instead of n = 94.

Table 2.2. DISC-IV diagnoses in children with PDD-NOS.

Co-morbid diagnosis	percentage of children with co-morbid diagnosis	95%-confidence interval
Social phobia	11.7% (n = 11)	5% - 18%
Separation anxiety disorder	8.5% (n = 8)	3% - 14%
Simple phobia	38.3% (n = 36)	28% - 48%
Agoraphobia	6.4% (n = 6)	1% - 11%
Panic disorder	1.1% (n = 1)	0% - 3%
Generalized anxiety disorder	5.3% (n = 5)	1% - 10%
Selective mutism	0.0% (n = 0)	0% - 0%
Obsessive compulsive disorder	6.4% (n = 6)	1% - 11%
Posttraumatic stress disorder	0.0% (n = 0)	0% - 0%
Major depression	10.6% (n = 10)	4% - 17%
Dysthymic disorder	2.1% (n = 2)	0% - 5%
Mania	3.2% (n = 3)	0% - 7%
Hypomania	3.2% (n = 3)	0% - 7%
Schizophrenia	0.0% (n = 0)	0% - 0%
ADHD, inattentive type	14.9% (n = 14)	8% - 22%
ADHD, hyperactive/impulsive type	8.5% (n = 8)	3% - 14%
ADHD, combined type	21.3% (n = 20)	13% - 30%
Oppositional defiant disorder	37.2% (n = 35)	27% - 47%
Conduct disorder	9.6% (n = 9)	4% - 16%

Note. ADHD = Attention Deficit Hyperactivity Disorder; DISC-IV = Diagnostic Interview Schedule for Children – version IV; PDD-NOS = Pervasive Developmental Disorder Not Otherwise Specified.

the children, and the criteria for the combined type were met in 21.3% (*n* = 20) of the children.

After disruptive behavior disorders, anxiety disorders were the most prevalent. In 55.3% (*n* = 52) of the children, at least one anxiety disorder was present. The highest rates were for simple phobia (38.3%, *n* = 36). Simple phobias were mostly related to fear of the dark (*n* = 11), fear of insects (*n* = 3), and fear of needles and injections (*n* = 3). Social phobia was present in 11.7 % (*n* = 11) of the children, followed by separation anxiety disorder (8.5%, *n* = 8), agoraphobia (6.4%, *n* = 6), OCD (6.4%, *n* = 6), and generalized anxiety disorder (5.3%, *n* = 5).

With regard to mood disorders, 13.8% (*n* = 13) of the children with PDD-NOS had at least one mood disorder according to the DISC-IV-P, of which major depression occurred most frequently (10.6%, *n* = 10).

It can also be seen in Table 2.2. that none of the children fulfilled sufficient criteria for a diagnosis of schizophrenia. However, when psychotic symptoms such as delusions or hallucinations were investigated separately, it appeared that in 5.4% (*n* = 5) of the children hallucinations were present, followed by delusions (3.2%, *n* = 3).

Groups of co-morbidity

When the children with one or more co-morbid anxiety disorder (n = 52) and one or more disruptive behavior disorder (n = 58) were further investigated, it was found that a high degree of overlap occurred. In Figure 2.1. it can be seen that in 19.1% (n = 18) of the children, no co-morbid disorders were present. In 19.1% (n = 18) of the cases only co-morbid internalizing disorders (sum of mood and anxiety disorders) were present, in 21.3% (n = 20) only co-morbid disruptive behavior disorders were present, and in the majority of the cases (40.5%, n = 38) internalizing and disruptive behavior disorders occurred simultaneously.

ANOVA showed no significant difference on FSIQ between the four groups ($p > .05$), and MANOVA showed no significant difference on VIQ or PIQ between the four groups ($p > .05$). MANOVA indicated that the groups did not differ significantly on scores on the Reciprocal Social Interaction or the Communication domain of the ADOS-G ($p > .05$). And non-parametric statistics showed that the groups did not differ in the number of PDD-NOS symptoms that were present ($p > .05$).

Furthermore, ANOVA indicated a significant difference in total CSBQ score between the four groups ($F(3, 88) = 5.879$, $p < .01$). Hochberg's GT2 post hoc analyses subsequently revealed that the total CSBQ score in the PDD-NOS group with internalizing and disruptive behavior disorders was higher than in the PDD-NOS group without co-morbid disorders ($p < .01$), and higher than in the PDD-NOS group with co-morbid internalizing disorders ($p < .05$). MANOVA showed that CSBQ subscale scores differed significantly between the four groups ($F(18, 255) = 3.219$, $p < .001$). Hochberg's GT2 post hoc analyses indicated that the group with co-morbid internalizing and disruptive behavior disorders had significantly higher scores on the CSBQ subscale Behaviors not tuned to situation, than the other three groups ($p < .001$, $p < .001$, and $p < .05$). Further, on the subscales Orientation problems in time, place, or activity and Stereotyped behavior, the scores of the group with co-morbid internalizing and disruptive behavior disorders were higher

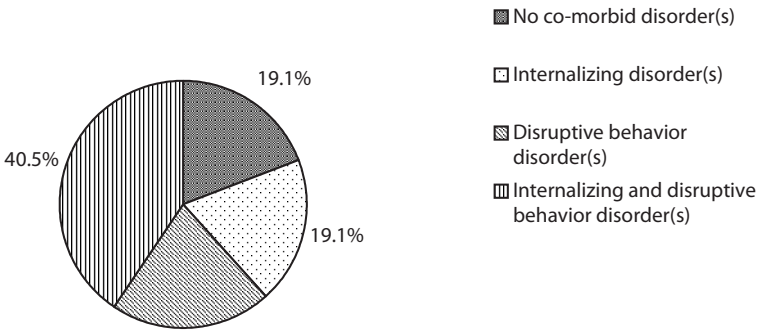

Figure 2.1. Percentages of different co-morbid disorders in children with PDD-NOS (n = 94).

than the scores of the group with internalizing disorders ($p < .05$), and higher than the scores of the group without co-morbid disorders ($p < .05$).

Discussion

To our knowledge this was the largest study thus far that investigated rates of co-morbid anxiety, mood, and disruptive behavior disorders, and schizophrenia, in school-aged children with PDD-NOS, in which PDD-NOS was classified by using explicit standardized criteria. Previous studies focused more on medical or sometimes psychiatric conditions associated with autistic disorder, used smaller samples, or did not use explicit criteria for PDD-NOS. At least one co-morbid psychiatric disorder was present in 80.9% of the children. In general, disruptive behavior disorders were most prevalent, followed by anxiety disorders, and mood disorders.

Co-morbid disruptive behavior disorders were present in 61.7% of the children, of which ADHD occurred in 44.7% (divided over three types of ADHD), and ODD occurred in 37.2% of the children. Rates for disruptive behavior disorders in the present study's sample were very high, compared to for instance ADHD prevalence rates of 2% to 11% in the general population (e.g., Shaywitz et al., 1994; Szatmari et al., 1989).

Luteijn et al. (2000) showed that children with ADHD and children with PDD-NOS both had severe problems in executing appropriate social behavior, and that attention problems did not differ between the groups. This indicated a high degree of overlap between features of PDD and ADHD but frequencies of ADHD in PDD-NOS children were not provided, all the more because DSM-IV does not permit this combination (APA, 1994). Barkley (1990) reported that children with PDD-NOS are often first diagnosed with ADHD. Possibly, differences between ADHD and PDD-NOS children become more evident at higher ages (Roeyers et al., 1998). For treatment purposes it is important to be aware of the high rate of ADHD in PDD-NOS, because the associated symptoms of inattention or impulsiveness may be responsive to pharmacological treatment (Keen & Ward, 2004; Santosh & Baird, 2001), whereas the deficits in social interaction and communication are not (Tanguay, 2000). This also applies to co-morbid ODD and CD symptoms, since additional symptoms such as aggression and tantrums can be greatly reduced with early behavior interventions (Horner et al., 2002). Optimal management of aggression in children with PDD involves both behavioral and pharmacological treatment (McDougle et al., 2003). An overlap between features of ODD, CD and PDD has been demonstrated before (Gilmour et al., 2004; Moffitt et al., 2001), but these studies focused more on the social and communication deficits in children with CD, and the exact rates of co-morbid ODD or CD in children with PDD-NOS have not been studied before.

Besides disruptive behavior disorders, anxiety disorders also occurred frequently. At least one co-morbid anxiety disorder was present in 55.3% of the children. Muris et al. (1998) previously demonstrated a high occurrence of anxiety disorders in children with PDD-NOS, significantly more than in children with autistic disorder, but the sample was very small, PDD-NOS was not classified by using explicit research criteria, and the overlap with disruptive behavior disorders was not assessed. Currently, DSM-IV guidelines do not permit the co-morbid diagnoses of generalized or separation anxiety disorder, or social phobia with a PDD. Anxiety symptoms, similarly to attention problems, may not be the core symptoms of PDD, but comprehensive guidelines for pharmacotherapy and behavioral interventions on how to treat these symptoms in children with PDD are available (e.g., Horner et al., 2002; Posey & McDougle, 2000; Santosh & Baird, 2001). It is thus important to be aware of the high rates of anxiety disorders in children with PDD-NOS, because besides being treatable, these additional symptoms may result in extra burden. Additional anxiety symptoms might inhibit the potential of mastering educational or daily life skills.

With regard to mood disorders, findings of a previous study in autistic disorder were not confirmed in the current sample of children with PDD-NOS. Ghaziuddin et al. (2002) described depression as possibly the most common psychiatric disorder in autistic disorder. In the current sample, mood disorders were present, but to a much lesser extent than disruptive behavior or anxiety disorders. Ghaziuddin et al. (2002) mentioned that the rate of depression in autistic disorder and related disorders may rise with age, whereas attention and aggressive symptoms could be more prevalent at younger ages. Possibly this applied to the current sample of school-aged children as well.

No children in this study met the criteria for schizophrenia, which is not very surprising as the majority of cases of schizophrenia have their onset in late adolescence or adulthood (Rosenbaum Asarnow et al., 2004). However, a small part of the current sample of children with PDD-NOS showed isolated symptoms of delusions and/or hallucinations. These symptoms may be a forerunner of future psychotic episodes and they may therefore be very important to identify. For instance, Poulton et al. (2000) showed that the presence of psychotic symptoms at age 11 predicted a schizophreniform disorder in adulthood.

Most previous studies focused on co-morbidity of one group of disorders (e.g., PDD and anxiety disorders), whereas in the current study the high degree of overlap of co-morbid disorders was remarkable. Co-morbid internalizing and disruptive behavior disorders were present simultaneously in 40.5% of the children with PDD-NOS. This group with double co-morbid disorders did not differ from the other co-morbidity groups, or the group without co-morbid disorders, on deficits in social contact or communication as rated by clinicians (e.g., ADOS-G, number of PDD-NOS criteria). According to the parents (e.g., CSBQ) however, the PDD-NOS children with double co-morbidity showed

more PDD related behaviors (e.g., stereotyped behaviors). Thus, apparently, a child with PDD-NOS and more co-morbid disorders is experienced by the parent as more severely disturbed in social contact and communication, than a child with PDD-NOS without co-morbid disorders.

To conclude, the way a diagnosis of PDD-NOS was obtained in this study should be taken into consideration when interpreting the findings, as well as the fact that standardized criteria for PDD-NOS, as used in this study, are generally not used in clinical or research settings. PDD-NOS diagnoses are often not based on clear and standardized criteria, but on the fact that a child does not meet the severity, intensity or number of criteria for a diagnosis of autistic disorder, whereas nevertheless, problems in social interaction and communication are present. Hence, it is unknown to which extent the findings of the present study apply to children who receive a diagnosis of PDD-NOS in regular clinical practice. This underscores the need for application of standardized criteria by clinicians, which is further underlined by other difficulties classification of PDD-NOS suffers from. PDD-NOS is often regarded as the most complex diagnosis to make in the autistic spectrum and is difficult to differentiate from autism (e.g., Allen et al., 2001; Buitelaar et al., 1999; Prior et al., 1998; Volkmar et al., 1994; Volkmar & Wiesner, 2004). Inter rater reliability of diagnosing PDD-NOS within the autistic spectrum is low (e.g., Mahoney et al., 1998; Towbin, 1997; Volkmar et al., 1997). This was also illustrated by the finding in the present study that, although raters agreed on the number of PDD-NOS criteria that were present (r = .79), kappa reflecting agreement between raters on the presence of a PDD-NOS diagnosis was only moderate (κ = .62), and the association between PDD-NOS and ADOS-G classifications was far from perfect.

Limitations

Children from only one outpatients' department were included which may have limited the generalizability of the results. Also, a university outpatients' department of child and adolescent psychiatry is generally not the first mental health service that children with psychiatric problems are referred to. Less severe cases may visit community mental health centers first. Therefore, the current study sample may not represent the target population of all children with PDD-NOS. It is possible that less severe cases display less signs of co-morbid disorders and that estimates of co-morbidity in the present study are higher than average. Future multi-center and epidemiological studies in possibly more representative samples are needed to test the present study's findings.

To the present authors' knowledge this study in a separate group of school-aged children with PDD-NOS was the largest study that used standardized assessments thus far, but nevertheless confidence intervals were still relatively broad.

Clinical implications

High rates of co-morbid psychiatric disorders in school-aged children with PDD-NOS were found. This is important when it comes to treatment planning. No single treatment is effective for all children with PDD-NOS. This is due to the large variety of symptoms and deficits demonstrated by these children. No cure seems to be available yet to treat the core deficits in PDD-NOS of social contact and communication deficits, but behavioral interventions and pharmacological treatment decisions are often based on the presence of associated symptoms, such as hyperactivity, inattention, or anxiety. The present study underscores that assessment of these associated symptoms is important.

3 WISC-R subtest but no overall VIQ – PIQ difference in Dutch children with PDD-NOS

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Abstract

Introduction

VIQ – PIQ differences have been studied in children with autism and Asperger syndrome but have not been studied in a separate group of children with PDD-NOS. Though, PDD-NOS has a much higher prevalence rate than autism and deficits in communication and social interaction are severe.

Method

The Wechsler Intelligence Scale for Children-Revised (WISC-R) was administered to 100 children, aged 6 – 12 years, with PDD-NOS (n = 76), autism (n = 13), and Asperger syndrome (n = 11). PDD-NOS was diagnosed using explicit research criteria.

Results

No overall differences between VIQ and PIQ were found in PDD-NOS and autism. Peaks in the subtest scores on Information, Similarities, Picture Arrangement, and Mazes, and troughs in the subtest scores on Comprehension, Digit Span, and Coding were demonstrated in children with PDD-NOS. Their score on the Freedom from Distractibility factor was lower than the scores on the Verbal Comprehension factor and the Perceptual Organization factor.

Discussion

Children with PDD-NOS seemed to have a similar VIQ – PIQ profile as children with autism, and on the subtest level children with PDD-NOS showed some similarities to children with Asperger syndrome or autism. It was not possible to distinguish PDD-NOS from autism or Asperger syndrome by using IQ scores.

Introduction

Since the seventies, many studies (e.g., Ehlers et al., 1997; Happé, 1994; Lincoln et al., 1995; Lincoln et al., 1988; Siegel et al., 1996; Venter et al., 1992) have investigated intelligence profiles of children with autism, using the Wechsler Intelligence Scale for Children-Revised (WISC-R; Wechsler, 1974). On the contrary, hardly any standardized studies exploring the intelligence profiles of children with Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) are available. This is all the more striking as PDD-NOS has a much higher prevalence rate than autism and, although to a lesser extent than children with autism, children with PDD-NOS show serious shortcomings in social interaction and communication. These deficits are considered to be pervasive and have severe consequences for their school, social, work and family life. This very substantial group may have similar treatment needs as the autistic group, but is nevertheless much less studied. Chakrabarti and Fombonne (2001) suggested that PDD-NOS is at least twice as common as autism in the general community.

To our knowledge hardly any studies assessing Verbal Intelligence Quotient (VIQ) versus Performance Intelligence Quotient (PIQ) of children with PDD-NOS as a separate group are available. Such knowledge is important however, to establish a focus in clinical assessment. If it would appear that VIQ in children with PDD-NOS differs from their PIQ, diagnostic procedures should pay more attention to this. Or the opposite, if no differences in VIQ versus PIQ appear, clinical judgment should be careful not to overestimate the diagnostic value of the intelligence profile in these children

Over the years, VIQ – PIQ discrepancies in children and adults with autism have been studied frequently. Results of a few of the larger studies will be mentioned below and details of the studies are summarized in Table 3.1.

Lincoln et al. (1988) found that PIQ was significantly higher than VIQ in autistic subjects. However, the age range in this study was large, the sample was very small, and WISC-R and WAIS-R scores were used, which hampered interpretation of the findings. As opposed to these findings, Venter et al. (1992), Siegel et al. (1996), and Ehlers et al. (1997) demonstrated that VIQ did not differ significantly from PIQ in autism. Venter et al. (1992) included a relatively large sample of autistic subjects, but the sample consisted of a very large age range, and scores of adult and children's intelligence tests were interpreted together. Furthermore, 23 of the 58 subjects were females, whereas rates of autistic disorder are four to five times higher in males than in females (APA, 1994). These characteristics of the sample limited the generalizability of the results. Ehlers et al. (1997) found that VIQ was significantly higher than PIQ in children with Asperger syndrome, and their FSIQ, VIQ, and PIQ were significantly higher in comparison to autistic children. Joseph and colleagues (2002) recently investigated VIQ – PIQ patterns in a sample of 47 children (6 – 10 years) with a DSM-IV diagnosis of autism or PDD-NOS. They found that 62% of

Table 3.1. Summary of some IQ profile studies in autism and Asperger syndrome.

Authors and year of publication	n and age range	Disorder and classification system	IQ Test	VIQ	PIQ	FSIQ
Lincoln et al. (1988)	n = 33 8 – 29 years	Autism DSM-III	WISC-R WAIS-R	M = 71.04 SD = n.k.	M = 83.25 SD = n.k.	M = 75.66 SD = n.k.
Venter et al. (1992)	n = 58 10 – 37 years	Autism ADI	WISC-R WAIS-R	M = 79.85 SD = 21.68	M = 83.31 SD = 22.16	M = 79.21 SD = 22.15
Siegel et al. (1996)	n = 45 6 – 16 years	Autism DSM-III-R	WISC-R	M = 96.20 SD = 16.22	M = 96.60 SD = 13.69	M = 96.02 SD = 14.49
Ehlers et al. (1997)	n = 40 6 – 15 years	Autism DSM-III, DSM-III-R, ICD-10	WISC-R	M = 81.30 SD = 16.80	M = 80.10 SD = 14.20	M = 78.80 SD = 14.00
Ehlers et al. (1997)	n = 40 5 – 15 years	Asperger syndrome Gillberg & Gillbergs criteria	WISC-R	M = 108.40 SD = 21.30	M = 95.60 SD = 21.70	M = 102.50 SD = 21.00

Note. n.k. = not known.

the children displayed significant VIQ – PIQ differences. The discrepancies occurred in the VIQ > PIQ direction nearly as often as in the PIQ > VIQ direction. Therefore, they concluded that in school-aged children with autism a high degree of unevenness in cognitive abilities was present. Although children with PDD-NOS were included in their study, they were not studied as a separate group and therefore it remained unknown whether children with PDD-NOS showed a separate pattern of cognitive strengths and weaknesses.

Summarized, data on VIQ - PIQ patterns in autism provided contrasting results, suffered from different methodological shortcomings, and data on VIQ - PIQ or intelligence patterns in PDD-NOS children as a separate group seem hardly available, despite the much higher prevalence rate of PDD-NOS. The aim of this study is therefore to investigate VIQ – PIQ and subtest patterns in children with PDD-NOS as a separate group, and to compare findings for this group with IQ results in children with autism and Asperger syndrome.

Method

Participants

The sample consisted of 76 children with PDD-NOS, aged 6 years – 12 years (M = 8.39, SD = 1.86), 85.53% boys (n = 65) and 14.47% girls (n = 11), 13 children with autism, aged 6 years – 12 years (M = 8.62, SD = 1.81), 100% boys (n = 13), and 11 children with Asperger syndrome, aged 6 – 12 years (M = 8.60, SD = 1.78), 90.9% boys (n = 10) and 9.1% girls (n = 1). All 100 children visited the outpatient department of child and adolescent psychiatry, Erasmus Medical Center Rotterdam, the Netherlands, between July 2002 and April

2004. In this period, for 396 consecutively referred 6 – 12 year old children, the PDD-NOS research criteria were rated. Also, DSM-IV (APA, 1994) diagnoses were assigned. Referrals were comprised of a large variety of child psychiatric disorders (e.g., externalizing disorders, internalizing disorders, PDD's). Eighty-five children met the criteria for a research diagnosis of PDD-NOS. Exclusion criteria were severe neurological problems, or severe difficulties in either understanding or speaking the Dutch language. For seven children, reliable data from the WISC-R (Wechsler, 1974) were not available due to refusal, or inability to complete the tests. For two children, WISC-R and WISC-III (Wechsler, 1991) were both administered within a one year period. Because of a possible learning effect, and therefore unreliable data, the results of these two children were excluded from further analyses. This yielded 76 children with a research diagnosis of PDD-NOS for whom WISC-R data were available. A further twenty children fulfilled a DSM-IV diagnosis of autism and for 13 of them reliable data from the WISC-R were available. The other seven children with autism were unable to complete the WISC-R due to communication deficits. Another 11 children were assigned a DSM-IV diagnosis of Asperger syndrome and for all of them reliable WISC-R data were obtained. Thus, in total, WISC-R data were available for 100 children.

Parent(s)/caretaker(s) of the children had all signed informed consent forms prior to participation in the study. Children of 12 years old signed the consent forms themselves as well. The Medical Ethics Committee of the Erasmus Medical Center approved the study.

Assessment

A diagnosis of PDD-NOS was based on explicit research criteria (Buitelaar et al., 1999). Nine different child psychiatrists were responsible for the rating. Rating was based on assessment of early development through current level of social, communicative, and adaptive functioning, obtained via semi-structured interviews carried out with the parent(s) or caretaker(s) as well as psychiatric observation of the child in a one-to-one situation. School and other relevant medical information was obtained, as well as standardized psychological assessment information.

Buitelaar et al. (1999) created specific research criteria for PDD-NOS. Children with clinical diagnoses of autistic disorder, PDD-NOS, and children with non-PDD diagnoses such as mental retardation and language disorders were compared on the 12 criteria for autistic disorder. Both ICD-10 (WHO, 1993) and DSM-IV (APA, 1994) classification systems were used. They found that a short set of seven criteria, derived from the 12 original criteria for autistic disorder, discriminated best between the PDD-NOS group and the group of non-PDD children. These seven criteria were divided over the domains of social interaction (four criteria), communication (two criteria), and stereotyped interests and repetitive behavior (one criterion). To diagnose PDD-NOS, at least three criteria had to

Table 3.2. PDD-NOS research criteria scored positive for each diagnostic group.

Item	PDD-NOS (n = 76)	Autism (n = 13)	Asperger syndrome (n = 11)
Total number of PDD-NOS research criteria	M = 3.97 SD = .88 Range 3-6	M = 5.69 SD = 1.60 Range 2-7	M = 4.09 SD = 1.22 Range 3-7
Item 1a: Marked impairment in the use of multiple non-verbal behaviors to regulate social interaction	86.8%	100%	90.9%
Item 1b: Failure to develop peer relationships appropriate to developmental level	93.3%	100%	100%
Item 1c: Lack of spontaneous seeking to share enjoyment, interests, or achievements with other people	46.7%	92.3%	54.5%
Item 1d: Lack of social or emotional reciprocity	32.9%	46.2%	27.3%
Item 2a: In individuals with adequate speech, impaired ability to initiate/sustain conversation	62.7%	76.9%	45.5%
Item 2b: Stereotyped and repetitive use of language or idiosyncratic language	46.7%	69.2%	36.4%
Item 3a: Stereotyped and repetitive motor mannerisms	30.3%	84.6%	54.5%

Note. PDD-NOS = Pervasive Developmental Disorder Not Otherwise Specified.

be present, including at least one social interaction criterion and the child was not allowed to meet criteria for autism or for another PDD.

We carried out an inter rater reliability study on 30 randomly selected children of the total sample (30%). Agreement between two independent raters on the presence or absence of a PDD-NOS diagnosis was good (κ = .62, 80.77% agreement). Further, we computed a score for the total number of PDD-NOS criteria rated positive by each rater for each child. The correlation between these scores by the two raters was high (Spearman's rho = .79), indicating excellent agreement (Cichetti & Sparrow, 1981). In Table 3.2. the mean number of PDD-NOS criteria per diagnostic group and the percentages of children who were scored positive on each criterion are listed. Analysis of variance (ANOVA) showed that the three groups differed significantly in number of PDD-NOS criteria that were present ($F(2, 95) = 15.37$, $p < .001$). Children with autism fulfilled significantly more PDD-NOS criteria than children with PDD-NOS ($p < .001$), and than children with Asperger syndrome ($p < .01$).

WISC-R

Psychologists administered the Dutch version of the WISC-R (Van Haasen et al., 1986; Wechsler, 1974). As the original version, the Dutch version has sufficient reliability and validity (Van Haasen et al., 1986). The WISC-R generates a FSIQ, a VIQ, and a PIQ (M = 100, SD = 15) and is composed of 12 subtests. VIQ consists of the subtests Information, Similarities, Arithmetic, Vocabulary, Comprehension, and Digit Span (M = 10, SD = 3). PIQ consists of the subtests Picture Completion, Picture Arrangement, Block Design,

Object Assembly, Coding, and Mazes (M = 10, SD = 3). Further, Kaufman factors were calculated (Kaufman, 1975). Kaufman factors are known as Verbal Comprehension factor (Information, Similarities, Vocabulary, and Comprehension), Perceptual Organization factor (Picture Completion, Block Design, Object Assembly, and Mazes), and Freedom from Distractibility factor (Arithmetic, Digit Span, and Coding) (M = 100, SD = 15).

ADOS-G

The Autism Diagnostic Observation Schedule Generic (ADOS-G; Lord et al., 1999) was administered as part of the standard diagnostic assessment, and was used to obtain a sample characteristic that can be used to compare the present study's sample to other samples. With the ADOS-G, social-communicative behavior of individuals is observed in a standardized context. The children in this study were assessed on the four ADOS-G domains (Communication, Reciprocal Social Interaction, Imagination/Creativity, and Stereotyped Behaviors and Restricted Interests). The diagnostic algorithms of the ADOS-G allow classification of participants as having social and communicative deficits of autism, or autism spectrum disorder (ASD). It is important to distinguish between ADOS-G classification and DSM-IV diagnosis. The ADOS-G does not include information about onset, early history and functioning in daily life, does not offer sufficient opportunity to measure restricted and repetitive behaviors, and does not provide information on the degree of cognitive impairment. For 92% (n = 92) of the children in this study ADOS-G results were available. For eight children ADOS-G data were not available due to refusal of the parent(s)/caretaker(s) or the child to participate. In Table 3.3. means and standard deviations on all ADOS-G domains for each diagnostic group are given.

Multivariate analysis of variance (MANOVA) showed that the three groups differed on the ADOS-G domains (F(8, 174) = 3.37, p < .01). Children with autism had higher scores on the Communication, Reciprocal Social Interaction, and Stereotyped Behaviors and Restricted Interests domains than children with PDD-NOS (p < .001, p < .01, and p < .001 respectively), and showed higher scores than children with Asperger syndrome on the

Table 3.3. Group characteristics: ADOS-G domain scores.

ADOS-G domains	PDD-NOS (n = 68)		Autism (n = 13)		Asperger syndrome (n = 11)	
	M	SD	M	SD	M	SD
Communication	2.01	1.07	3.77	1.69	2.55	1.04
Reciprocal Social Interaction	5.09	2.61	7.69	3.40	5.36	2.54
Imagination/Creativity	.87	1.38	1.62	2.10	1.09	2.39
Stereotyped Behaviors/ Restricted Interests	1.03	1.07	2.46	1.71	1.00	1.00

Note. ADOS-G = Autism Diagnostic Observation Schedule-Generic; PDD-NOS = Pervasive Developmental Disorder Not Otherwise Specified.

Communication ($p < .05$) and Stereotyped Behaviors and Restricted Interests domains ($p < .01$).

Data analyses

Parametric tests were carried out as FSIQ, VIQ, and PIQ were normally distributed in all three groups (Shapiro-Wilk test; $p > .05$). To establish whether FSIQ differed between the three groups, ANOVA was carried out, and to compare the three groups on VIQ and PIQ, on the 12 subtests, and on the three Kaufman factors, three separate MANOVA's were carried out. Due to large differences in group sizes, Hochberg's GT2 post hoc analyses were used.

To assess VIQ - PIQ differences within each group, paired-samples *t* tests were used. To reveal peaks or troughs in the subtest profile of children within the group of PDD-NOS a General Linear Model (GLM) repeated measures design with one within subjects factor was applied, using the 12 scaled subtest scores as the different levels of the factor IQ. This analysis was not carried out in the comparison groups of autism or Asperger syndrome as group sizes were too small. To reveal possible peaks or troughs in combinations of subtests, differences between Kaufman factors were assessed in post hoc analyses in each separate group, using paired-samples *t* tests.

Results

IQ differences between the three groups

Means and standard deviations of FSIQ, VIQ, PIQ, the Kaufman factors, and the different subtests, of children with PDD-NOS, autism, or Asperger syndrome are summarized in Tables 3.4. and 3.5.

Although ANOVA showed that FSIQ did not differ significantly between the three groups ($p > .05$), MANOVA showed that VIQ and/or PIQ differed significantly between the three groups ($F(4, 194) = 2.91$, $p < .05$). Hochberg's GT2 post hoc analyses subsequently revealed that VIQ in Asperger syndrome was significantly higher than VIQ in PDD-NOS ($p < .05$). PIQ did not differ significantly between the three groups ($p > .05$).

MANOVA showed that subtest scores differed significantly between the three groups ($F(24, 172) = 1.87$, $p < .05$). Hochberg's GT2 post hoc analyses revealed that children with Asperger syndrome had significantly higher scores on the subtest Information and Vocabulary compared to children with autism and children with PDD-NOS ($p < .05$). Children with Asperger syndrome also had significantly higher scores on the subtest Similarities compared to children with PDD-NOS ($p < .05$), and had significantly higher scores on the subtest Mazes compared to children with autism ($p < .05$).

Table 3.4. WISC-R IQ scores for each diagnostic group.

	PDD-NOS (n = 76)			Autism (n = 13)			Asperger syndrome (n = 11)		
	M	SD	Range	M	SD	Range	M	SD	Range
Full Scale IQ	89.58	19.38	49 – 131	83.62	22.63	48 – 122	102.91	24.12	66 - 152
Verbal Scale IQ	90.12	18.26	51 – 138	88.92	24.79	48 – 144	106.27	21.08	75 - 148
Performance Scale IQ	91.37	20.82	48 – 129	80.77	20.86	49 – 110	97.91	21.52	61 - 138
Kaufman factors	M	SD	Range	M	SD	Range	M	SD	Range
Verbal Comprehension	92.40	17.04	54 – 131	89.77	23.73	48 – 140	109.18	18.37	76 - 138
Perceptual Organization	91.79	20.24	48 – 134	82.69	21.44	48 – 114	101.50	19.64	65 - 134
Freedom from Distractibility	85.32	19.34	48 – 134	83.31	26.59	48 – 137	91.27	26.12	57 - 149

Note. IQ = Intelligence Quotient; PDD-NOS = Pervasive Developmental Disorder Not Otherwise Specified; WISC-R = Wechsler Intelligence Scale for Children-Revised.

Table 3.5. WISC-R subtest scores for each diagnostic group.

Subtests	PDD-NOS (n = 76)			Autism (n = 13)			Asperger syndrome (n = 11)		
	M	SD	Range	M	SD	Range	M	SD	Range
Information	9.29	3.32	2 - 19	8.69	4.13	3 - 19	13.36	3.85	6 - 19
Similarities	9.28	3.97	1 - 18	8.77	4.36	1 - 15	12.45	3.48	7 - 17
Arithmetic	8.05	3.91	1 - 18	7.54	5.04	1 - 18	9.55	4.28	3 - 15
Vocabulary	8.43	3.07	1 - 14	7.69	4.72	1 - 19	11.09	3.62	5 - 19
Comprehension	7.93	3.00	2 - 16	7.92	4.19	1 - 15	9.09	3.36	5 - 15
Digit Span	7.32	3.37	1 - 15	8.38	5.04	1 - 19	9.45	3.33	5 - 17
Picture Completion	8.33	3.67	1 - 15	7.23	3.63	2 - 12	8.91	3.27	3 - 15
Picture Arrangement	9.80	3.59	1 - 17	8.23	3.61	3 - 13	11.00	3.41	3 - 15
Block Design	8.45	4.01	1 - 15	7.77	4.95	1 - 15	10.45	3.73	5 - 17
Object Assembly	8.29	3.77	1 - 16	6.69	4.11	1 - 12	9.64	3.72	4 - 16
Coding	7.79	3.92	1 - 15	5.77	3.75	1 - 12	6.55	4.70	1 - 16
Mazes	9.75	3.55	1 - 17	7.46	3.97	1 - 15	11.36	3.30	6 - 17

Note. PDD-NOS = Pervasive Developmental Disorder Not Otherwise Specified; WISC-R = Wechsler Intelligence Scale for Children-Revised.

Finally, MANOVA showed that Kaufman factors did not differ significantly between the three groups ($p > .05$).

IQ profiles within the three groups

PDD-NOS

No significant difference between VIQ and PIQ was found ($p > .05$) for children with PDD-NOS. With regard to different subtests scores in PDD-NOS, GLM demonstrated a main effect ($F(11, 64) = 7.07$, $p < .01$). Tests of within-subjects deviation contrasts demonstrated that scores on Information ($p < .01$), Similarities ($p < .05$), Picture Arrangement ($p < .01$), and Mazes ($p < .01$) were significantly higher than the mean of all subtest scores. Scores on Comprehension ($p < .05$), Digit Span ($p < .01$), and Coding ($p < .05$) were significantly lower than the mean of all subtest scores. However, overall, the range of subtest scores was relatively small (7.32 - 9.80). The mean of the Freedom from Distractibility factor was significantly lower than the mean of the Verbal Comprehension factor ($t = 4.18$, $p < .01$), and also significantly lower than the mean of the Perceptual Organization factor ($t = 3.01$, $p < .01$). The means of the Verbal Comprehension factor and the Perceptual Organization factor did not differ significantly ($p > .05$).

Autism

No significant difference between VIQ and PIQ was found ($p > .05$) for children with autism. The means of the three Kaufman factors did not differ significantly from each other ($p > .05$) and the range of subtests scores was quite small (5.77 – 8.77).

Asperger syndrome

VIQ was significantly higher than PIQ ($t = 2.99$, $p < .05$) in children with Asperger syndrome. Subtest scores ranged from 6.55 – 13.36. The mean of the Verbal Comprehension factor was significantly higher than the mean of the Perceptual Organization factor ($t = 3.09$, $p < .05$), and also significantly higher than the mean of the Freedom from Distractibility Factor ($t = 3.33$, $p < .01$). The means of the Perceptual Organization factor and the Freedom from Distractibility factor did not differ significantly ($p > .05$).

Discussion

The results of this study showed, that although children with PDD-NOS did not show overall VIQ – PIQ differences and their range of subtest scores was relatively narrow, they did show peaks and troughs in subtest scores compared to their own overall mean. They showed strengths in subtests measuring factual knowledge, logical sequencing of social situation pictures, reasoning via similarities, and weaknesses on subtests measuring understanding of social situations, graphomotor skills, memory for numbers, attention, and distractibility.

The children with autism showed no VIQ – PIQ differences and no differences between Kaufman factors, and the children with Asperger syndrome showed the characteristic higher VIQ compared to PIQ, and a higher Verbal Comprehension factor. When the three groups were compared, FSIQ, PIQ, and Kaufman factors did not differ, only VIQ was higher in the Asperger syndrome group as compared to PDD-NOS. Furthermore, children with Asperger syndrome showed higher scores on subtests measuring factual knowledge, vocabulary, and reasoning via similarities than children with autism or PDD-NOS.

Thus, the findings of this study, like some previous studies in autism (Ehlers et al., 1997; Siegel et al., 1996; Venter et al., 1992) demonstrated no VIQ – PIQ differences in children with PDD-NOS. On the subtest level, children with PDD-NOS showed similarities to subtest scores found in children with autism and Asperger syndrome in previous studies. High scores on Information and low scores on Comprehension were found before in autism (Ehlers et al., 1997; Happé, 1994; Lincoln et al., 1995; Siegel et al., 1996) and also applied to children with PDD-NOS in this study. This indicated that children with PDD-NOS, like children with autism, have difficulties understanding social situations but have a high level of factual knowledge.

Furthermore, it was found that children with PDD-NOS in this sample had graphomotor, concentration and distractibility difficulties (i.e. a low Freedom from Distractibility factor), similarly to what has been demonstrated before in autism or Asperger syndrome (Ehlers et al., 1997; Happé 1994; Lincoln et al., 1995; Mayes & Calhoun, 2003; Mayes & Calhoun, 2004; Siegel et al., 1996). When interpreting a low Freedom from Distractibility factor, care should be taken as this factor has been subject to different interpretations, varying from distractibility (Cohen, 1952), memory (Cohen, 1957), to numerical ability (Osborne & Lindsey, 1967) back to distractibility (Kaufman, 1975).

Besides many similarities, children with PDD-NOS also showed a few differences compared to what has been found in autism before. Strengths on Digit Span and Block Design, and a weakness on Picture Arrangement have been demonstrated in autism (Ehlers et al., 1997; Happé, 1994; Lincoln et al., 1995; Siegel et al., 1996). In PDD-NOS however, this particular strength on Block Design did not appear, and more remarkable, Digit Span was a significant weakness and Picture Arrangement a significant strength. The latter is a non-verbal subtest which required logical organization and sequencing of a series of pictures on which a social situation was depicted. Possibly, the children in this study have put the pictures in the correct order in this subtest, simply by logical theoretical reasoning. However, this theoretical strength needs to be integrated in socially adaptive behaviors to function adequately in social situations of every day life. The transfer of theoretical knowledge to a daily situation might be difficult for children with PDD-NOS.

Clinical significance

The main findings of this study showed that VIQ and PIQ did not differ in children with PDD-NOS or autism, whereas the group with Asperger syndrome showed a VIQ higher than PIQ, as often described before. FSIQ did not differ between the three groups. Thus, apart from the specific findings for Asperger syndrome, VIQ - PIQ data can not be used to distinguish between PDD-NOS and autism.

Although nearly all subtest scores in children with PDD-NOS were higher than in children with autism, this difference was not significant. There were no specific strengths or weaknesses that distinguished PDD-NOS from the other groups in this study. Compared to their own overall mean, children with PDD-NOS showed specific strengths and weaknesses. More specifically, children with PDD-NOS in this sample showed a high level of factual knowledge and a theoretical insight in sequencing of different aspects of a social situation, but a weak understanding of daily social situations. Thus, clinicians should be aware that on the surface children with PDD-NOS may seem to have a lot of knowledge, while their actual understanding of a social situation might be less well developed.

The clinical significance of the relative peaks and troughs in IQ profiles that were found in the present study should not be overestimated. The range of IQ subtest scores was quite narrow, thus an overall stable intelligence pattern seemed to prevail. In this study individual subtests were compared to the overall mean, but according to WISC-R guidelines (Wechsler, 1974) a difference of at least 2 to 3 (or more) points between subtest scores is considered significant. According to these guidelines, many of the subtest scores of PDD-NOS children would not differ significantly from other subtest scores.

Finally, similarly to what has been demonstrated in children with autism and Asperger syndrome, children with PDD-NOS performed poorly on subtests that were associated with attention and distractibility. If their behavior at home and at school is also characterized by deficits in attention and high distractibility, these characteristics should be taken into account when planning treatment.

Limitations

Important limitations in this study were the low numbers of children in the comparison groups of autism and Asperger syndrome. Also, very low IQ values were analyzed together with very high IQ values which provided no information on potential profiles of lower functioning and higher functioning children.

Furthermore, the choice of instrument may have had an effect on some of the results. By choosing the Wechsler Scales (Wechsler, 1974), the study subjects were by definition higher-functioning children as most lower functioning children may have had problems with the relatively verbal character of this instrument due to their communication deficits. This applied particularly to our group of autism, in which nearly a third of the children could not be tested with the WISC-R due to communication prob-

lems. However, the problem with other tests is that, mostly, they do not yield separate VIQ and PIQ scores. Further, at the time of testing, WISC-III (Wechsler, 1991) or WISC-IV (Wechsler, 2003) were not available for the Dutch population. However, current findings seemed to be consistent with findings from studies on the WISC-III and autism (Mayes & Calhoun, 2003; Mayes & Calhoun, 2004) and with WISC-IV data on children with autism and Asperger syndrome as reported in the WISC-IV Technical and Interpretive manual (Wechsler, 2003).

The inclusion of children from only one outpatient department limited the generalizability of the findings, and also referral biases could have played a role. A university department of outpatient child and adolescent psychiatry is generally not the first institution that children with psychiatric problems are referred to. Therefore, the sample of the present study may not represent the target population of all children with PDD-NOS. Also, samples of children with PDD-NOS may vary across different sites and countries. The research criteria used in this study to classify PDD-NOS were considered reliable and standardized, but were nevertheless developed mainly by Dutch authors and are not necessarily used at other national or international sites. Future multi-center and epidemiological studies in possibly more representative samples are needed to test the present study's findings.

Finally, only cognitive profiles of school-aged children were investigated. In previous studies it has been shown that VIQ – PIQ differences in children with autism possibly change with age. In pre-school children a VIQ < PIQ pattern might prevail and VIQ > PIQ is infrequently observed, whereas in school-aged children VIQ < PIQ and VIQ > PIQ patterns are more evenly distributed (Joseph et al., 2002). Therefore, it should be realized that the present study's findings may not be generalized to other age groups.

Conclusion

The results of this study demonstrated that although children with PDD-NOS, similarly to children with autism, did not show overall VIQ – PIQ differences, they did show peaks and troughs in subtest scores compared to their own overall mean. Children with Asperger syndrome showed a higher VIQ than PIQ. It is not possible to distinguish PDD-NOS from autism or Asperger syndrome by using IQ scores.

4 Assessment of formal thought disorder: The relation between the Kiddie Formal Thought Disorder Rating Scale and clinical judgment

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Abstract

Objective

The presence of formal thought disorder (FTD) in childhood is sometimes viewed as a possible precursor of psychotic symptoms or adult schizophrenia. It is possible to assess FTD in childhood in a valid and reliable manner, by using the Kiddie Formal Thought Disorder Rating Scale (K-FTDS). However, training and rating procedures are very time consuming, and may be particularly difficult during clinical assessment. The aim of this study was therefore to compare the clinician's rapid judgment of FTD to the detailed ratings of the K-FTDS.

Methods

The K-FTDS was administered to 172 consecutively referred children, aged 6 to 12 years and subsequently rated by two blind raters. The same criteria, as used in the K-FTDS (illogical thinking, loose associations, incoherence, and poverty of content of speech), were rated by nine clinicians.

Results

The overall agreement between K-FTDS scores and FTD scores as rated by the clinician was low.

Conclusion

The clinician's judgment of FTD did not correspond very highly with ratings on the K-FTDS. Thus, although detecting FTD has important clinical value, the assessment of its presence or absence seemed to depend highly on which measure was used.

Introduction

Formal thought disorder (FTD) has been a central characteristic of schizophrenia since the first descriptions of this disorder by Bleuler (1911). The presence of FTD prior to the onset and during the whole course of the disorder, suggests that it is connected to the core pathophysiology of schizophrenia (Ott et al., 2002). It remains one of the core symptoms of schizophrenia, and refers to a disturbance in thought processes (APA, 1994). In DSM-III (APA, 1980), FTD is described as the presence of illogical thinking, loose associations, incoherence, and poverty of content of speech. Speech is considered to reflect the underlying thought processes, thus symptoms of FTD are represented in how a person verbally presents his/her thoughts to a listener (Asarnow and Karatekin, 2001; Werry, 1996).

FTD was originally considered as part of the positive symptoms of schizophrenia and referred to the structural characteristics of speech, such as illogical associations and incoherence. This type of thought disorder was distinguished from disturbance of thought content (e.g., delusions) and perceptions (e.g., hallucinations). More recently FTD has been divided into two subtypes: negative, characterized by poverty of expression in speech production, and positive, characterized by loosening of associations (Ott et al., 2001).

FTD in children has been demonstrated to be a possible precursor of future psychotic episodes and even of schizophrenia (Ott et al., 2001; Parnas et al., 1982). FTD can be reliably assessed in childhood (Caplan et al., 1989). For instance, the Thought Disorder Index (TDI) has been shown to be a valid and reliable assessment tool to measure thought disorder in children (Arboleda & Holzman, 1985). Results from a follow-up study showed that thought disorder as measured with the TDI remained stable over time (Metsänen et al., 2005). Many other studies of childhood schizophrenia used another standardized instrument to measure FTD in children, the Kiddie Formal Thought Disorder Rating Scale (K-FTDS) (Asarnow & Karatekin 2001; Caplan et al., 1989; Caplan et al., 2000; Hollis, 2002; Remschmidt, 2002; Rosenbaum Asarnow et al., 2004; Van der Gaag, 1993; Volkmar, 2001; Volkmar & Tsatsanis, 2002; Werry, 1996). The K-FTDS assesses four symptoms of FTD, based on DSM-III criteria (APA, 1980): illogical thinking, loose associations, incoherence, and poverty of content of speech. Illogical thinking is rated when the child uses inappropriate causal utterances and provides the listener with unfounded or illogical explanations. Loose associations are rated when the child suddenly changes the topic of conversation, to an unrelated topic, without preparing the listener for this topic change. Incoherence is rated when a rater is unable to understand the contents of the child's speech, because of a scrambled syntax. And poverty of content of speech is rated when the child provides the listener with adequate length of speech, but does not elaborate on the topic (Caplan et al., 1989; Caplan et al., 2000).

Caplan et al. (1989) compared K-FTDS scores of 4- to 12-year-olds with DSM-III schizophrenia (n = 16) and schizotypal personality disorder (n = 4), to those of normal control children (n = 29). Results indicated that scores of illogical thinking and loose associations, differentiated children with schizophrenia from normal controls. These findings were replicated by Caplan et al. (2000) in a larger study of 88 children with DSM-IV (APA, 1994) schizophrenia and 190 normal controls aged between 7 and 13 years. Blind ratings of the K-FTDS correctly classified 85% to 87% of the children with schizophrenia, and 73% to 82% of the normal controls.

The K-FTDS was also used to assess FTD in other child psychiatric groups. Recently, Van der Gaag et al. (2005) showed that high FTD scores were found in children with autism, lower rates were found in children with Attention Deficit Hyperactivity Disorder (ADHD), and children with anxiety disorders showed no signs of FTD on the K-FTDS. The K-FTDS, although valuable, can be considered a 'laboratory test' (Werry, 1996), or 'research instrument' (Hollis, 2002), and it is often not practical for clinicians to perform the detailed rating process (Caplan, 1994), because training and rating itself are very time consuming. Therefore, the K-FTDS is not likely to become part of a clinician's regular psychiatric evaluation. Nevertheless, symptoms of FTD are clinically important, and it would be relevant to know whether the clinician is able to rapidly rate these symptoms without extensive training and rating procedures. However the sensitivity of the clinician's ability to detect FTD and the correspondence of this evaluation with an independent measure of (i.e., the K-FTDS) has not been studied before.

Therefore, the aim of this study was to determine the association between blindly rated K-FTDS scores, and clinicians' ratings of FTD based on standardized psychiatric assessment. We hypothesized that the agreement between the clinician and the K-FTDS would not be high. A K-FTDS rater was specifically instructed to focus on the formality of the speech only. Although the clinician was provided with the same descriptions of the FTD signs, we expected clinical judgment to also be influenced by the content of the child's speech, and not only the formality. If for instance, the child would show signs of hallucinations or delusions, we would expect the clinician to rate signs of FTD to be present, whereas a K-FTDS rater would not attend to signs that reflect the mere content of the speech, but would only judge whether the speech is logically sound.

The main focus of this study was to assess agreement between two different instruments in rating FTD. Sample characteristics such as age and IQ may have influenced the results. Therefore, a secondary aim of this study was to assess whether age and IQ correlated with FTD.

Methods

Participants

The sample consisted of 172 children, aged between 6 and 12 years (M = 9.4, SD = 1.8), 78.5% boys (n = 135) and 21.5% girls (n = 37). All 172 children visited the outpatient department of child and adolescent psychiatry, Erasmus Medical Center Rotterdam, the Netherlands, between July 2002 and July 2004. All children participated in a larger study regarding the identification of children at risk for the development of psychotic episodes, for which they underwent extensive and highly standardized psychiatric and psychological evaluation. The screening for the presence of disturbed thought processes was carried out by using the Thoughts subscale of the Child and Adolescent Functional Assessment Scale (CAFAS; Hodges, 1997). The CAFAS is a rating scale which assesses the youth's degree of impairment in functioning due to emotional, behavioral, or psychiatric problems. Psychometric properties of the CAFAS were extensively studied (Hodges & Wong, 1996). The CAFAS consists of eight scales, divided over a list of items from which the rater chooses those items that describe the child's most severe functioning. For each scale there are four levels of severity: severe (score 30), moderate (score 20), mild (score 10), or no impairment (score 0). No intermediate scores were assigned. All children with a score of 10 or above on the subscale Thoughts (i.e., paranoia, incoherent thoughts, loose associations, delusions, hallucinations) were eligible for the current study. In this way, a threshold was applied which would include all children with at least mild forms of thought problems.

For 200 consecutively referred children, FTD criteria were rated by the child's clinician (child and adolescent psychiatrist), and K-FTDS ratings were made by two independent raters. Exclusion criteria were severe neurological problems, or severe difficulties in either understanding or speaking the Dutch language. For nine children, reliable data from the K-FTDS were not available due to communication deficits related to their diagnosis of autism. For another 16 children, reliable K-FTDS data were missing due to refusal to participate, or incomplete K-FTDS assessment. For three children criteria were rated incompletely by the clinician and were therefore excluded from further analyses. This yielded 172 children for whom valid K-FTDS data and FTD criteria as rated by the clinician were available.

All 172 children were also assigned DSM-IV classifications by child psychiatrists, which are presented in Table 4.1. In order to demonstrate a medium effect size, the power of this study was over 0.90 (Cohen, 1988). For 170 children, reliable data from the Wechsler Intelligence Scales for Children (WISC-R; Wechsler, 1974) were available. The average Full Scale Intelligence Quotient (FSIQ) was 91.46 (SD = 19.10), Verbal Intelligence Quotient (VIQ) was 92.24 (SD = 16.98), and Performance Intelligence Quotient (PIQ) was 93.08 (SD = 18.80). WISC-R data were not available for two children due to refusal or inability to complete the tests.

Table 4.1. Diagnostic characteristics of the study sample (n = 172).

DSM-IV classification	Number of children (%)
Pervasive developmental disorder (autism, Asperger syndrome, or PDD-NOS)	n = 68 (39.5%)
Disruptive behavior disorder (ADHD, ODD, or CD)	n = 35 (20.3%)
Anxiety or mood disorder	n = 15 (8.7%)
Pervasive developmental disorder + disruptive behavior disorder	n = 21 (12.2%)
Pervasive developmental disorder + anxiety or mood disorder	n = 8 (4.7%)
Disruptive behavior disorder + anxiety or mood disorder	n = 8 (4.7%)
Other DSM-IV classifications	n = 17 (9.9%)

Note. ADHD = Attention Deficit Hyperactivity Disorder; CD = Conduct Disorder; ODD = Oppositional Defiant Disorder; PDD-NOS = Pervasive Developmental Disorder Not Otherwise Specified.

Assessment

K-FTDS

Children were presented two audio taped stories for which they were asked to answer some standard questions (i.e., "What did you like about this story?"). Subsequently, the child was asked to make up his/her own story about one of four given topics. Assessment took approximately 20 to 30 minutes and the speech samples were videotaped. At a later stage the number of FTD signs was rated which took on average 1.5 to 2 hours per rater per child. The rater was never the same person as the psychologist who administered the K-FTDS. The rater had no prior knowledge of the child and was not aware of the aims of the study. A total raw K-FTDS score was derived by summing frequency counts for illogical thinking, loose associations, incoherence, and poverty of content of speech. Subsequently, the raw scores were divided by the number of utterances per minute which yielded the final K-FTDS scores. This procedure was carried out to correct for the variability of speech elicited in different children.

Caplan et al. (1989) assessed reliability of the K-FTDS scores in a group of children with schizophrenia (n = 17), children with schizotypal personality disorder (n = 4), and normal control children (n = 7). They reported a kappa of 0.77 for the total K-FTDS score, of 0.78 for illogical thinking and 0.71 for loose associations. According to Cicchetti and Sparrow (1981), reliability values above 0.70 are good and values higher than 0.75 are considered excellent. Due to a low base rate, reliability of incoherence and poverty of content of speech was not studied. Undergraduate student raters obtained similarly reliable K-FTDS scores as experienced raters (κ ranged between 0.66 and 0.87). Thus, inter rater reliability was independent of prior clinical experience. Further, Caplan et al. (1989) calculated sensitivity and specificity values for illogical thinking, loose associations, and total K-FTDS score and 'cut points for pathology' were derived from optimal points for sensitivity and specificity values. Therefore, a score above the cut point indicated a higher likelihood of pathology (diagnosis of schizophrenia). By using the cut point

values, continuous K-FTDS scores were dichotomized as falling above or below the cut point. Again, due to a low base rate, cut points for pathology were not calculated for incoherence and poverty of content of speech.

The first author of the present study (EdB) was trained and supervised by Caplan, and subsequently trained a student rater (TW). Both raters were blind for DSM-IV diagnosis. The student rater (TW) rated all the videotapes (n = 172), and the other rater (EdB) independently rated a random selection of 39.0% of the videotapes (n = 67). Agreement between the two raters was high. Intra class correlation coefficients (ICCs; McGraw & Wong, 1996) for illogical thinking, loose associations, total K-FTDS scores, and utterance counts were respectively 0.97, 0.90, 0.97, and 0.97. Inter rater reliability was also calculated by using the dichotomous data of scores above or below the cut points for pathology. In this way, kappa's of 0.87, 0.82, and 0.78 were obtained for illogical thinking, loose associations, and total K-FTDS score respectively which also indicated high agreement between the raters (Cichetti & Sparrow, 1981).

FTD as rated by the clinician

The clinician rated the four signs of FTD as present or absent. The descriptions of the signs were identical to the descriptions used in the K-FTDS. A total score was derived by summing illogical thinking, loose associations, incoherence, and poverty of content of speech (range 0 to 4). Also, the total FTD score was dichotomized. When one or more signs were rated positive by the clinician, FTD was considered present, and when all four signs were rated negative by the clinician, FTD was considered absent. The clinician's ratings were based on a semi-structured psychiatric interview (Semi structured Clinical Interview for Children and Adolescents [SCICA], McConaughy & Achenbach, 2001). Directly after this interview with the child, the clinician rated the FTD criteria, which took at most five minutes per child. Subsequently, questionnaires were administered to the parent(s) or caretaker(s), as well as extensive psychological evaluation of the child (i.e., assessment of intelligence, and neuropsychological tasks to assess theory of mind, flexibility of thinking, and central coherence). School and other relevant medical information was obtained. After all diagnostically relevant information was integrated, a DSM-IV (APA, 1994) diagnosis was assigned.

For 30 randomly selected children, FTD signs were rated by three independent clinicians. Agreement between the three raters was high. Intra class correlations for illogical thinking, loose associations, incoherence and total FTD were respectively 0.69, 0.78, 0.83, and 0.80. Due to a low base rate, reliability of poverty of content of speech was not studied.

Data analyses

Kappa's were calculated as a measure of agreement between K-FTDS scores below or above the cut point for pathology and the clinician's dichotomous FTD scores. Further, Spearman correlations were computed between continuous K-FTDS scores and the clinician's FTD scores.

To assess the accuracy of the clinician's FTD ratings, sensitivity and specificity values were calculated by using receiver operating characteristic (ROC) analyses. For these analyses, the dichotomous K-FTDS scores were used. As no cut points for incoherence and poverty of content of speech were available, these two signs were not included.

Further, Spearman correlations were computed to assess the relation between IQ, age, K-FTDS scores, and FTD scores as rated by the clinician.

Ethics

Parent(s)/caretaker(s) of the children had all signed informed consent forms prior to participation in the study. Children of 12 years old signed the consent forms themselves as well. The Medical Ethics Committee of the Erasmus Medical Center approved the study.

Results

K-FTDS and FTD scores as rated by the clinician

The means and standard deviations of the K-FTDS and the clinician's FTD scores are presented in Table 4.2. In Table 4.3., kappa's and correlations between the K-FTDS and the clinician's FTD scores are summarized.

Table 4.4. provides an overview of sensitivity, specificity, and related values, for illogical thinking, loose associations, and total FTD. The area under the curve (AUC) is used as a measure of test accuracy. Areas of 0.5 to 0.7 indicate low test accuracy, 0.7 to

Table 4.2. K-FTDS and FTD scores as rated by the clinician (n = 172).

	ILL	LA	INC	POC	Total K-FTDS
K-FTDS score	M = 0.34	M = 0.04	M = 0.02	M = 0.01	M = 0.40
	SD = 0.36	SD = 0.11	SD = 0.05	SD = 0.03	SD = 0.46
	Range 0 - 3.10	Range 0 - 1.06	Range 0 - 0.38	Range 0 - 0.22	Range 0 - 3.91
	ILL	LA	INC	POC	Total FTD
FTD score	M = 0.24	M = 0.48	M = 0.26	M = 0.24	M = 1.22
	SD = 0.43	SD = 0.50	SD = 0.44	SD = 0.43	SD = 1.26
	Range 0 - 1	Range 0 - 1	Range 0 - 1	Range 0 - 1	Range 0 - 4

Note. FTD = Formal thought disorder; ILL = Illogical thinking; INC = Incoherence; K-FTDS = Kiddie Formal Thought Disorder Rating Scale; LA = Loose association; POC = Poverty of content of speech.

Table 4.3. Kappa's and correlations between K-FTDS scores and FTD scores as rated by the clinician.

	ILL (n = 172)	LA (n = 164)	Total (n = 172)
K-FTDS (> or < cut point) versus FTD clinician	κ = 0.08	κ = 0.30	κ = 0.14
	p = 0.13	p = 0.00	p = 0.07
K-FTDS (continuous) versus FTD clinician	rho = 0.21	rho = 0.28	rho = 0.41
	p = 0.06	p = 0.00	p = 0.00

Note. FTD = Formal thought disorder; ILL = Illogical thinking; K-FTDS = Kiddie Formal Thought Disorder Rating Scale; LA = Loose association.

Table 4.4. Sensitivity, specificity and related values of FTD signs as rated by the clinician.

	ILL	LA	Total FTD
Sensitivity	28.2%	86.2%	68.3%
Specificity	82.3%	63.0%	45.6%
PPV	73.8%	33.3%	65.7%
NPV	39.2%	95.5%	48.4%
AUC	0.55 (p = 0.26)	0.75 (p = 0.00)	0.57 (p = 0.13)

Note. AUC = area under the curve; FTD = Formal thought disorder; ILL = Illogical thinking; LA = Loose association; NPV = negative predictive value; PPV = positive predictive value.

0.9 moderate accuracy, and areas above 0.9 indicate high test accuracy (Swets, 1988). Data for illogical thinking and total FTD were based on *n* = 172, and data for loose associations were based on *n* = 164. The reason for this discrepancy is that for children below 6 years of age (*n* = 8), no cut point for loose associations is available (Caplan et al., 1989).

Age and IQ

In Table 4.5. correlations between total K-FTDS score, age, and IQ are presented, as well as the correlations between the clinician's total FTD score, age, and IQ.

Table 4.5. Correlations between K-FTDS, FTD scores as rated by the clinician, age, and IQ.

	Correlations
Total K-FTDS versus age	rho = -0.44; p = 0.00
Total FTD score clinician versus age	rho = -0.30; p = 0.00
Total K-FTDS versus FSIQ	rho = -0.28; p = 0.00
Total FTD score clinician versus FSIQ	rho = -0.21; p = 0.00

Note. FSIQ = Full Scale Intelligence Quotient; FTD = Formal thought disorder; IQ = Intelligence Quotient; K-FTDS = Kiddie Formal Thought Disorder Rating Scale.

Discussion

In the present study, the relation between blindly rated K-FTDS scores and the clinician's ratings of FTD was investigated in different ways. In general, there was weak agreement between K-FTDS and clinician's FTD scores. Older children and children with higher IQs had lower FTD scores but, overall, agreement between the clinician's ratings and the K-FTDS remained poor.

There are a few possible explanations for this weak agreement. Most important, FTD was rated in a slightly different manner by the K-FTDS rater than by the clinician. In accordance with Caplan et al.'s (1989) rating procedures, the K-FTDS rater was instructed to only investigate signs of the formality of the speech, and was specifically trained not to attend to the content of the child's speech. The clinician may have paid less attention to this difference between formal and content aspects of the speech, and may therefore have been distracted by the content of a child's speech. The K-FTDS rater rated the speech sample word by word, and had no prior knowledge of the child's diagnosis.

With respect to the separate FTD signs, agreement, association, and accuracy of the clinician's FTD scores as compared to the K-FTDS, seemed highest, although overall still relatively poor, for loose associations. When loose associations were present, there was a high chance that the clinician would detect this (high sensitivity). High sensitivity is a characteristic of a test that is required for disease screening (Henderson, 1993), and thus the clinician's judgment about the presence of loose associations can be considered as a good screening tool. However, when the clinician decided that loose associations were present, this was only confirmed by the K-FTDS in about one third of the cases. A reason for this discrepancy could be that a loose association was only rated in the K-FTDS when the child suddenly changed the topic of conversation, without informing the listener first (Caplan et al., 1989). When the child was simply distracted (e.g., by a clock in the room) and started talking about this distracter, this was not considered as a loose association in the K-FTDS. However, children who displayed signs of hyperactivity and difficulties concentrating might have been frequently distracted, and therefore changed topics regularly, which might have been rated as loose associations by the clinician.

Further, it was found that sensitivity of the clinician was much lower for illogical thinking than for loose associations, and agreement between the K-FTDS and the clinician's ratings of illogical thinking were very low. When illogical thinking was present, there was only a small chance that the clinician would detect this (low sensitivity) and therefore the clinician's judgment of illogical thinking is not considered a good screening measure. However, when the clinician did detect illogical thinking, the chance of this being confirmed by the K-FTDS was relatively high. This was related to the high base rate of illogical thinking in the study sample. A high prevalence leads to an increase of positive test results and therefore a relatively high predictive value of a positive test result

(Henderson, 1993). This high base rate was also demonstrated in previous studies, where illogical thinking was the most commonly found sign of FTD in the K-FTDS (Caplan et al., 1989; Van der Gaag, 1993). Given the high base rate, the chance that the clinician would miss a case of illogical thinking in the K-FTDS became very unlikely. Contradicting oneself, making illogical inferences, or reaffirming the question was counted as illogical thinking in the K-FTDS. Perhaps the clinician considered these aspects of speech as being signs of language immaturity, or insecurity about oneself, and might not have rated this as illogical thinking. Another possibility could simply be that the clinician was right, and the precise rating guidelines of the K-FTDS caused raters to over rate the presence of illogical thinking. Or the clinician's low sensitivity could have been related to confusion between illogical thinking and incoherence. When logical causal statements were lacking in the speech of the child, which made the speech seem incoherent, the clinician might have considered this a form of incoherence whereas the K-FTDS considered it as illogical thinking. However, caution applies to this inference as sensitivity values for incoherence were not known due to its infrequent nature.

Due to the low base rates and the absence of cut points for incoherence and poverty of content of speech, no agreement, association or sensitivity values were known for these signs. One issue however, was the low occurrence of poverty of content of speech in the K-FTDS, and the much higher ratings by the clinicians. This is possibly related to the high number of children with pervasive developmental disorders (PDD) in the study sample (39.5%). Children with PDD often display stereotyped interests and persevere on their favorite topics (APA, 1994; Volkmar & Lord, 1998). Possibly, this led to repetitive talking without elaboration, which might have caused the clinician to score poverty of content of speech.

Older children in the present study showed fewer signs of FTD. This is in accordance with previous studies which demonstrated that the speech of children up to 7 or even 10 years of age is often less coherent and logical (Arboleda & Holzman, 1985; Caplan et al., 2000). Further, a higher IQ was associated with fewer signs of FTD. This finding was also in agreement with previous findings of Van der Gaag et al. (2005) who found a significant negative correlation between full-scale IQ and illogical thinking and loose associations on the K-FTDS.

Clinical implications

Detecting FTD in childhood is clinically relevant, particularly because it may indicate an increased risk of future psychotic disorders (Ott et al., 2001; Parnas et al., 1982). It is important to realize however that although once considered as a core feature of schizophrenia, FTD is not present in all schizophrenic patients, and is also not a unique characteristic of schizophrenia but occurs in other disorders as well (Arboleda & Holzman, 1985; Caplan et al., 2001). The presence of FTD in children in the current sample does

not imply that all of these children would be considered psychotic by the clinician at the time of testing. FTD is only one aspect of psychosis and the presence of signs of FTD alone is not sufficient to assign a diagnosis of psychosis or childhood schizophrenia.

Limitations

Although administration and rating of the K-FTDS occurred in a highly standardized manner, FTD rating by the clinician was based on less standardized assessment. However, inter rater agreement between clinicians was good. Although the rating process was based on a semi-structured psychiatric interview, different child psychiatrists may have focused on different aspects of the child's speech. This may limit the generalizability of the results. In other settings, where assessments are likely to be less standardized, agreement would possibly be even lower.

Further, FTD in this study was equated to the score on the K-FTDS, and FTD was considered to be a possible precursor and primary symptom of schizophrenia. Yet, there are no adequate studies available that have examined how well the ratings of the K-FTDS predict eventual schizophrenia. The nearest findings come from studies that have demonstrated that FTD is a possible precursor of psychotic episodes, and schizophrenia (Ott et al., 2001; Parnas et al., 1982).

A final limitation concerns the comparison of two different types of rating scales. The clinician's ratings were made in a present/absent manner, whereas the K-FTDS ratings were more complicated. For instance, they were corrected for number of utterances. This raises concerns about the validity of this comparison. Due to time limits, in practice it would be impossible for a clinician to correct his ratings for number of utterances. However, it might be possible to create a more dimensional FTD rating scale for the clinician instead of the dichotomous scale used in the current study.

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5 Multiple Complex Developmental Disorder (MCDD) delineated from PDD-NOS

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Abstract

Objective

Children with MCDD have difficulties with affect regulation, social behavior, and thought processes. MCDD is not a DSM-IV classification, but is often considered as a pervasive developmental disorder (PDD), due to its early onset, social deficits, and pervasive character. Previous research showed that MCDD differs from autistic disorder. PDD-NOS occurs more often that autistic disorder, but it has never been investigated if MCDD can be delineated from PDD-NOS. Therefore the objective of this study was to ascertain whether behavioral differences could be demonstrated between children with MCDD and those with PDD-NOS.

Methods

Twenty-five children (6 – 12 years) with MCDD and 86 children with PDD-NOS were compared with respect to psychiatric co-morbidity, psychotic thought problems and social contact problems, using the Child Behavior Checklist/4-18 (CBCL), the Dutch version of the Diagnostic Interview Schedule for Children – version IV (DISC-IV), the Child and Adolescent Functional Assessment Scale (CAFAS), and the Autism Diagnostic Observation Schedule-Generic (ADOS-G).

Results

MCDD was associated with anxiety disorders, disruptive behavior, and psychotic thought problems, and PDD-NOS with deficits in social contact.

Conclusion

MCDD differs from autistic disorder, and can also be delineated from PDD-NOS. This has implications for research regarding etiology and treatment.

Introduction

The combination of early onset impairment in affect regulation, high levels of anxiety, disturbed social relationships, and periods of thought problems has been recognized by child psychiatrists throughout the past five decades and is not a rare phenomenon (Towbin et al., 1993). In the past 'childhood schizophrenia' and 'borderline syndrome of childhood' were the most common labels to describe this group of children, and more recently, 'childhood schizotypal disorder' or 'schizoid personality' were used (Petti & Vela, 1990). Cohen et al. (1986) suggested the term Multiplex Developmental Disorder (MDD) for which they proposed a specific set of diagnostic criteria. They emphasized that the social impairment seen in these children was suggestive of autism, and they therefore considered MDD as belonging to the group of Pervasive Developmental Disorders (PDDs) (Cohen et al., 1986; Towbin et al., 1993).

MDD was defined by disturbances in three domains. First, impaired regulation of affective states, which was manifested by anxiety and fears. Second, impairment in social behavior, which was manifested by detachment, social disinterest, withdrawal, and aggression. This second domain was most reminiscent of PDD. And third, impaired thought processes, which were manifested by magical thinking, unusual thoughts, and difficulties in separating fantasy from reality (Cohen et al., 1986). Though Cohen et al. (1986) positioned the MDD concept under the umbrella of the PDDs, they also recognized the overlap with several DSM-III (APA, 1980) personality disorders (i.e., Avoidant Disorder, Overanxious Disorder, and Schizotypal Disorder).

Towbin et al. (1993) modified the criteria slightly, and changed the term MDD to Multiple Complex Developmental Disorder (MCDD). To validate the MCDD construct and its distinct position from other psychiatric disorders, Towbin et al. (1993) compared a group of 5-13 year old children who fulfilled criteria of MCDD (n = 30) with a group of children with DSM-III-R dysthymic disorder (n = 30), and conduct disorder (CD, n = 30). Children with MCDD were significantly younger at their first mental health contact, had significantly higher scores on internalizing and externalizing problems on the Child Behavior Checklist (CBCL; Achenbach, 1991), and showed significantly more difficulties in relating to peers.

These data showed that MCDD differed from externalizing (e.g., CD), and from internalizing (e.g. dysthymic disorder) disorders on symptom variables, but did not elucidate whether MCDD children can be differentiated from PDDs. Van der Gaag et al. (1995) found that children with MCDD (n = 105) showed more anxiety and thought disorders, but were less disturbed on social responsiveness, interest in non-functional aspects of objects, and resistance to change, compared to children with autistic disorder (n = 32). This study was limited by the selection procedure of children with MCDD. They were selected only from a larger group of children with Pervasive Developmental Disorder-

Not Otherwise Specified (PDD-NOS). This seemed to implicate that MCDD can not occur outside PDD-NOS, whereas Towbin et al. (1993) already showed that only a third of their children with MCDD had a clinical diagnosis of PDD-NOS.

Currently, MCDD is not a separate construct in DSM-IV (APA, 1994). The early onset of the symptoms, impairments in multiple areas of development, the related social deficits, and its pervasive character make that the diagnostic classification mostly used for these children, is PDD-NOS (Ad-Dab'bagh & Greenfield, 2001; Towbin et al., 1993). Previous research indicated that MCDD can be delineated from autistic disorder (Van der Gaag et al., 1995). However, the question whether MCDD can be separated from other PDDs has not been answered yet. In this study, children with PDD-NOS were compared to children who fulfilled research criteria of MCDD on several standardized, valid, and reliable measures of psychiatric disorders, thought problems, and social contact and communication problems. Based on the previous findings by Towbin et al. (1993) and Van der Gaag et al. (1995), we hypothesized that children with MCDD would have more psychiatric disorders, and more thought problems than children with PDD-NOS. Further, we expected children with PDD-NOS to show more social contact and communication problems than children with MCDD.

Methods

Participants

The study sample was selected from 503 children, aged 6 – 12 years who were consecutively referred to the outpatient department of child and adolescent psychiatry, Erasmus Medical Center Rotterdam, the Netherlands, between July 2002 and September 2004 and who were all rated on MCDD and PDD-NOS criteria. Referrals were comprised of a large variety of child psychiatric disorders (e.g., externalizing disorders, internalizing disorders, PDDs). For 12 (2.4%) children the MCDD and/or PDD-NOS research criteria were rated incompletely and these children were excluded from further analyses. This eventually yielded 491 children for whom all MCDD and PDD-NOS criteria were rated.

Twenty-nine (5.9%) children met research criteria for a diagnosis of MCDD. The parents of four of these children refused to participate in the study, thus in the MCDD group, 25 children were included (mean age = 9.12, *SD* = 1.56, 88% boys, and 12% girls). Eleven of them (44%) met research criteria for PDD-NOS as well, but they remained included in the MCDD group. Of the remaining children, 86 (17.5%) met research criteria for a diagnosis of PDD-NOS (mean age = 8.48, *SD* = 1.83, 86% boys, and 14% girls). Intelligence quotients (IQs) of all children were assessed by using the Dutch version of the Wechsler Intelligence Scale for Children-Revised (WISC-R; Van Haasen et al., 1986; Wechsler, 1974). Children in the MCDD group had a Full Scale Intelligence Quotient (FSIQ) of 92.42 (*SD*

= 15.40), a Verbal Intelligence Quotient (VIQ) of 94.67 (*SD* = 18.27), and a Performance Intelligence Quotient (PIQ) of 92.13 (*SD* = 13.40). Children in the PDD-NOS group had a FSIQ of 90.06 (*SD* = 18.34), a VIQ of 91.05 (*SD* = 18.45), and a PIQ of 92.39 (*SD* = 20.43). The MCDD group did not differ significantly in age, gender, FSIQ, VIQ, or PIQ ($p > .05$) from the PDD-NOS group. Further, children within the MCDD or the PDD-NOS group did not show significant VIQ – PIQ differences ($p > .05$). With respect to PDD-NOS, a recent study confirmed these findings. No VIQ –PIQ differences were found in Dutch children with PDD-NOS (De Bruin et al., 2006).

Ethics

Parents or caretakers of the children had all signed informed consent forms prior to participation in the study. Children of 12 years old signed the consent forms themselves as well. The Medical Ethics Committee of the Erasmus Medical Center approved the study.

Assessment

PDD-NOS research criteria

DSM-IV (APA, 1994) provides 12 explicit criteria, equally divided over the three domains of social interaction, communication, and stereotyped interests and repetitive behaviors. At least six criteria must be met for a diagnosis of autistic disorder. However, for a DSM-IV diagnosis of PDD-NOS, criteria are not specified as such. The PDD-NOS category should be used when there is a severe and pervasive impairment in the development of reciprocal social interaction, plus either deficits in verbal or non-verbal communication skills, or stereotyped interests and repetitive behavior, but the criteria for a specific PDD are not met. No specific items or scoring algorithms are provided.

Buitelaar et al. (1999) created research criteria for PDD-NOS. Children with clinical diagnoses of autistic disorder (*n* = 205), PDD-NOS (*n* = 80), and non-PDD diagnoses such as mental retardation and language disorders (*n* = 174) were compared on the 12 criteria for autistic disorder. Both ICD-10 (WHO, 1993) and DSM-IV (APA, 1994) classification systems were used. They found that a short set of seven criteria, derived from the 12 original criteria for autistic disorder, discriminated best between the PDD-NOS group and the group of non-PDD children. These seven items were divided over the domains of social interaction (four items), communication (two items), and stereotyped interests and repetitive behavior (one item). The items are listed in Table 5.1. To diagnose PDD-NOS, at least three items had to be present including at least one social interaction item, and the child should not meet criteria for autistic disorder or other types of PDDs. This classification rule resulted in a sensitivity of 94%, specificity of 83% and yielded a total predictive value of 89%. The onset item, impairment prior to the age of 3, differentiated significantly between children with PDD-NOS and non-PDD, but did not improve the

overall classification rule and was therefore not included. With this scoring rule, children could meet criteria for PDD-NOS by only showing impairments in social interaction and no impairments in communication or stereotyped interests. However, if criteria from these other two domains were set as mandatory, sensitivity would be reduced to 84% and total predictive value would diminish to 83%. Therefore, impairments in communication and stereotyped interests were not set as mandatory in the classification rule (Buitelaar & Van der Gaag, 1998).

In the current study, a diagnosis of PDD-NOS was based on these explicit research criteria (Buitelaar et al., 1999). Nine different child and adolescent psychiatrists were responsible for rating the research criteria. Rating was based on assessment of early development through current level of social, communicative, and adaptive functioning, obtained via semi-structured interviews, carried out with the parents or caretakers, as well as psychiatric observation of the child in a one-to-one situation (e.g., Semi structured Clinical Interview for Children and Adolescents [SCICA], McConaughy & Achenbach, 2001). School and other relevant medical information was obtained, as well as psychological assessment information. Immediately after all diagnostic procedures were finished, a multidisciplinary team obtained consensus with regard to the final DSM-IV (APA, 1994) classification, and PDD-NOS research criteria were ticked as present or absent. Subsequently, the algorithm, of which the rater was unaware, was used to decide whether the threshold for a research diagnosis of PDD-NOS was met.

MCDD research criteria

In an attempt to better differentiate PDDs, Cohen et al. (1986) introduced heuristic diagnostic criteria for an early onset developmental disorder characterized by anxiety and deficits in affective regulation, and impaired social relationships. These symptoms were identified from a review of 400 children characterized by 'deviant human relationships and disorganized, bizarre thinking' (Dahl et al., 1986). The term MCDD was proposed by Cohen et al. (1986) to describe these young children. The original criteria were divided over three domains; impaired regulation of affective state (six criteria of which two had to be present), impaired social behavior (four criteria of which one had to be present), and thought disorder (four criteria of which one had to be present). The symptoms had to be present longer than 6 months and the child should not meet criteria for autistic disorder.

Buitelaar and Van der Gaag (1998) subsequently examined the sensitivity and discriminative power of these 14 MCDD criteria in children with MCDD (i.e., who scored above the threshold for MCDD criteria) (n = 103), autistic disorder (n = 32), and non-PDD diagnoses such as mental retardation and language disorders (n = 96). They found that the contribution of several criteria in establishing the classification of MCDD was redundant, and constructed a simplified scoring rule. A short set of eight MCDD criteria

Table 5.1. PDD-NOS and MCDD research criteria (Buitelaar & Van der Gaag, 1998).

PDD-NOS
1. Qualitative impairments in social interaction:
a. Marked impairments in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
b. Failure to develop peer relationships appropriate to developmental level
c. A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people
d. A lack of social or emotional reciprocity
2. Qualitative impairments in communication:
a. In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
b. Stereotyped and repetitive use of language or idiosyncratic language
3. Restricted, repetitive, and stereotyped patterns of behavior, interests, and activities:
a. Stereotyped and repetitive motor mannerisms
MCDD
1. Impaired regulation of affective state and anxieties:
a. Unusual or peculiar fears and phobias, or frequent idiosyncratic or bizarre anxiety reactions
b. Recurrent panic episodes or flooding with anxiety
c. Episodes of behavioral disorganization punctuated by markedly immature, primitive, or violent behaviors
2. Impaired social behavior:
a. Social disinterest, detachment, avoidance, or withdrawal
b. Markedly disturbed and/or ambivalent attachments
3. The presence of thought disorder:
a. Irrationality, magical thinking, sudden intrusions on normal thought process, bizarre ideas, neologism, or repetition of nonsense words
b. Perplexity and easy confusability
c. Overvalued ideas, including fantasies of omnipotence, paranoid preoccupations, over engagement with fantasy figures, referential ideation

Note. MCDD = Multiple Complex Developmental Disorder; PDD-NOS = Pervasive Developmental Disorder Not Otherwise Specified.

had the strongest discriminative power (three criteria for affective dysregulation and anxiety, two for impaired social interaction, and three for thought disorder). The MCDD criteria are listed in Table 5.1. When at least five out of eight criteria were present, the total percentage of correctly classified children was 95% for the differentiation between MCDD and non-PDD, and 87% for the differentiation between MCDD and autism.

In the present study, the procedure of rating the MCDD research criteria was identical to the aforementioned rating of PDD-NOS research criteria. We carried out an inter rater reliability study on 30 randomly selected children (27%). Two clinicians independently rated all MCDD and PDD-NOS research criteria. Agreement between the raters on the presence or absence of a PDD-NOS diagnosis was good ($\kappa = .62$). Agreement for MCDD diagnosis could not be calculated as MCDD did not occur once in this sub sample. Fur-

ther, we computed a score for the total number of PDD-NOS and MCDD criteria rated positive by each rater for each child. The intra class correlation coefficient (ICC) between these scores by the two raters was high (ICC = .89 and .79 respectively), indicating excellent agreement for PDD-NOS and MCDD criteria (Cichetti & Sparrow, 1981).

Psychiatric symptoms and disorders

CBCL/4-18

The Child Behavior Checklist/4-18 (CBCL; Achenbach, 1991) was used to obtain standardized parent-reports on children's problem behaviors. The CBCL covers 118 problem items, and for the present study, groups were compared on the scores on eight syndrome scales (Withdrawn, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior, and Aggressive Behavior). Average scores from mothers and fathers were used. CBCL data were available for 84.9% of the children (of which 48.7% was rated by mother only, 41.4% by father only, 6.3% by both parents, and for 3.6% it was unknown who filled in the CBCL). For the other 15.1%, parents did not fill out the CBCL.

DISC-IV

The Dutch version of the Diagnostic Interview Schedule for Children – version IV (DISC-IV; Ferdinand & Van der Ende, 1998; Shaffer et al., 1998) is a highly structured interview to assess DSM-IV Axis I psychiatric disorders in the past year, in children and adolescents. The parent version of the DISC-IV (DISC-IV-P) for parents of children aged 6 to 17, was used to assess how many percent of the children in each group had anxiety disorders, mood disorders, schizophrenia, and disruptive behavior disorders. Also the presence of hallucinations and delusions was assessed, as well as the total number of DISC/DSM-IV disorders in each group. Studies of earlier versions of the DISC-P have shown good test-retest and inter rater reliability (Schwab-Stone et al., 1993; Shaffer et al., 1993; Shaffer et al., 1996). The DISC-IV compared well with its earlier versions (Shaffer et al., 2000).

In this study, psychologists, research assistants, and psychology undergraduate students (supervised by psychologists) had all been trained by the authors of the Dutch DISC-IV (Ferdinand & Van der Ende, 1998) who, in turn, had been trained as trainers at Columbia University New York by the authors of the original DISC. The interviewers were blind to any other diagnostic information about the child. DISC-IV data were available for 99.1% of the children. The other 0.9% was not available due to parent's refusal to be interviewed.

Thought problems

CAFAS

The CAFAS (Hodges, 1997) is a valid and reliable rating scale (Hodges & Wong, 1996) which assesses the child's degree of impairment in functioning due to emotional, behavioral, or psychiatric problems. Only the Thoughts subscale of the CAFAS (i.e., obsessions, eccentric speech, paranoia, incoherent thoughts, loose associations, delusions, hallucinations) was included in this study. It was scored in the same manner and by the same clinicians as the MCDD and PDD-NOS research criteria. The CAFAS was available for 100% of the children.

FTD criteria

Van der Gaag et al. (1995) showed that in MCDD children formal thought disorder (FTD) was present. Thought disorder can be interpreted differently by different clinicians. In order to obtain an unambiguous judgment of FTD, DSM-III criteria in the section form of thought, under Schizophrenic Disorders (APA, 1980): illogical thinking, loose associations, incoherence, and poverty of content of speech (criterion A6) were used. Illogical thinking was rated when inappropriate causal utterances were used and explanations were illogical. Loose association was rated when the child suddenly changed the topic of conversation, to an unrelated topic, without preparing the listener for this topic change. Incoherence was rated when the rater was unable to understand the contents of the child's speech, and poverty of content of speech was rated when the child did provide the listener with adequate length of speech, but did not elaborate on the topic. The clinician rated the four signs of FTD as present or absent. A total FTD score (range 0 – 4) was also calculated. This was carried out by the same clinicians as the rating of the MCDD and PDD-NOS criteria. The clinician's ratings were made immediately after administration of the SCICA (McConaughy & Achenbach, 2001) which is a semi-structured respondent based interview with the child. Assessment took 45-60 minutes and focused on issues such as difficulties in school, the home situation, or with friends. Rating of the FTD criteria took at most five minutes per child.

For 30 (27%) randomly selected children, FTD signs were rated by two independent clinicians. Agreement between the raters was fair to good (κ = .52 for illogical thinking, κ = .63 for loose associations, κ = .71 for incoherence, and κ = .54 for total FTD). Due to a low base rate, reliability of poverty of content of speech was not studied. FTD criteria were rated for 99% of the children.

Social contact and communication problems

ADOS-G

The Autism Diagnostic Observation Schedule-Generic (ADOS-G; Lord et al., 1999) provides a standardized context to observe PDD related behaviors in the domains of social interaction, communication, imagination, and stereotyped behavior. In this study, the different groups were compared on the subscales Communication (i.e., stereotyped language), Reciprocal Social Interaction (i.e., eye contact), the combination of Communication and Reciprocal Social Interaction (which constitutes the algorithm), Imagination/Creativity, and Stereotyped Behaviors and Restricted Interests (i.e., unusual sensory interest in play material or person).

Lord et al. (1999) showed that the psychometric properties of the ADOS-G were good. The diagnostic algorithm of the ADOS-G allows for classification of participants as having a non-spectrum disorder (N.S.), autism spectrum disorder (ASD), or autism. The distinction between the three categories depends on symptom severity. Non-spectrum disorder indicates that the child may have another psychiatric disorder, but a PDD is not present according to observations in the ADOS-G. The ADOS-G is particularly effective in differentiating between autism or ASD and N.S. (sensitivity 90%-97% and specificity 87%-94%), and is a little less effective in the differentiation between autism and ASD (sensitivity 87%-100% and specificity 68%-79%). A false positive classification of autism on the ADOS-G was considered more acceptable than a false negative classification of N.S. on the ADOS-G.

Psychologists who conducted the ADOS-G in this study were all trained by certified ADOS-G trainers. ADOS-G classifications were available for 97.3% of the children. In 2.7% of the children the ADOS-G could not be completely administered due to the child's refusal to cooperate.

Data analyses

Independent-samples *t*-tests (two-tailed) were used to compare the two groups on CBCL syndrome scale scores, total number of DISC/DSM-IV disorders, CAFAS Thought Problems scores, FTD total scores, and ADOS-G domain scores. Further, chi-square tests were performed to assess differences between the two groups in separate DISC/DSM-IV disorders, the four FTD criteria, and ADOS-G classifications.

In addition to these tests for statistical significance, effect sizes were calculated in order to evaluate the magnitude of the differences. An effect size of .20 was considered as small, of .50 as medium, and an effect size of .80 and above was considered as large (Cohen, 1988). For the independent samples *t*-tests, Cohen's d was calculated as a measure of effect size. To estimate the magnitude of the association in the contingency tables of the chi-square tests, the phi-coefficient was calculated. Phi is a Pearson prod-

uct-moment coefficient calculated on two nominal, dichotomous variables. Phi of .10 - .20 is considered a weak association, of .20 - .40 is a moderate, of .40 - .60 is relatively strong, of .60 - .80 is strong, and phi above .80 is considered a very strong association (Rea & Parker, 1992).

Results

Psychiatric symptoms and disorders

In Table 5.2. means and standard deviations of the two groups on the different CBCL syndrome scales are shown. Apart from the syndrome scale Thought Problems which was higher for the MCDD group (t[98] = 2.453, $p < .05$, $d = .57$), groups did not differ on the syndrome scales ($p > .05$). Small, albeit non-significant effect sizes were found for Anxious/depressed, Delinquent Behavior and Social Problems, i.e. higher scores for the MCDD group on the first two syndrome scales and higher scores for the PDD-NOS group on the latter scale. These scores were in the expected direction.

In Table 5.3. the percentages of children with DISC/DSM-IV disorders in each group are shown. Children in the MCDD group had an average of 3.80 DISC/DSM-IV disorders ($SD = 3.11$) whereas children in the PDD-NOS group had an average of 2.21 DISC/DSM-IV disorders ($SD = 2.04$). The difference was significant (t[30.335] = 2.406, $p < .05$) with a medium effect size ($d = .68$).

Further, chi-square tests indicated there was an association between group membership and some of the DISC/DSM-IV disorders. In Table 5.3. it can be seen that in the PDD-NOS group only 5.9% had a Separation anxiety disorder, whereas in the MCDD group this was 20.0% (χ^2[1, $N = 110$] = 4.659, $p < .05$). The phi-coefficient indicated a moderate association. Similarly, Obsessive compulsive disorder was present in 36.0% of the MCDD group and in 7.1% of the PDD-NOS group (χ^2[1, $N = 110$] = 13.739, $p < .01$), which showed that children in the MCDD group had much higher rates of obsessive thoughts and compulsive behaviors than children in the PDD-NOS group. Children in the MCDD group also had higher frequencies of disruptive behavior disorders. Oppositional defiant disorder was present in 60.0% of the MCDD group, and in 37.6% of the PDD-NOS group (χ^2[1, $N = 110$] = 3.944, $p < .05$), Conduct disorder in 24.0% of the MCDD group and in 5.9% of the PDD-NOS group (χ^2[1, $N = 110$] = 7.046, $p < .05$). Thus, compared the PDD-NOS group, children in the MCDD group showed significantly higher rates of aggressive, violent, and oppositional behaviors according to their parents. The associations (Φ) were all weak to moderate.

Although none of the children received a DISC/DSM-IV disorder of Schizophrenia, 8.0% of the MCDD group (and 1.2% of the PDD-NOS group) had at least one delusional experience (i.e., people spying on you, people talking about you, holding a conspiracy

Table 5.2. CBCL syndrome scale scores of the PDD-NOS (n = 72) and MCDD (n = 22) groups.

CBCL syndrome scales	PDD-NOS		MCDD		p-value	ES (d)
	M	SD	M	SD		
Withdrawn	6.20	3.70	5.91	2.64	.563	.08
Somatic Complaints	2.03	2.45	2.41	2.70	.379	.15
Anxious/depressed	8.28	6.16	10.09	6.22	.091	.29
Social Problems	6.66	3.13	5.66	3.13	.065	.32
Thought Problems	3.59	2.59	5.10	2.76	.016	.57
Attention Problems	10.12	4.55	9.43	4.42	.374	.15
Delinquent Behavior	2.98	2.70	3.48	2.36	.272	.19
Aggressive Behavior	15.74	8.91	16.41	8.86	.661	.08

Note. CBCL = Child Behavior Check List; ES = Effect Size; MCDD = Multiple Complex Developmental Disorder; PDD-NOS = Pervasive Developmental Disorder Not Otherwise Specified.

Table 5.3. DISC/DSM-IV disorders in the PDD-NOS (n = 85) and MCDD (n = 25) groups.

DISC/DSM-IV disorders	PDD-NOS	MCDD	p-value	ES (Φ)
Social phobia	10.6%	16.0%	.475	.07
Separation anxiety disorder	5.9%	20.0%	.046	.21
Specific phobia	37.6%	56.0%	.102[a]	.16
Agoraphobia	7.1%	8.0%	1.00	.02
Panic disorder	1.2%	8.0%	.129	.18
Generalized anxiety disorder	7.1%	4.0%	1.00	.05
Selective mutism	0.0%	0.0%	n/a	n/a
Obsessive compulsive disorder	7.1%	36.0%	.001	.35
Posttraumatic stress disorder	0.0%	0.0%	n/a	n/a
Major depressive episode	9.4%	20.0%	1.00	.14
Dysthymic disorder	1.2%	4.0%	1.00	.09
Manic episode	1.2%	12.0%	.036	.24
Hypomanic episode	2.4%	8.0%	1.00	.13
Schizophrenia	0.0%	0.0%	n/a	n/a
ADHD, inattentive type	40.0%	40.0%	.100[a]	.00
ADHD, hyperactive/impulsive type	27.1%	40.0%	.215[a]	.12
ADHD, combined type	20.0%	24.0%	.666[a]	.04
Oppositional defiant disorder	37.6%	60.0%	.047[a]	.19
Conduct disorder	5.9%	24.0%	.016	.25

Note. [a] : the p-value of Chi-Square Test is stated. In all other cases the p-value of Fisher's Exact Test is stated due to expected cell counts less than five. ADHD = Attention Deficit Hyperactivity Disorder; DISC-IV = Diagnostic Interview Schedule for Children – version IV; ES = Effect Size; MCDD = Multiple Complex Developmental Disorder; n/a = not applicable; PDD-NOS = Pervasive Developmental Disorder Not Otherwise Specified.

against you) during the past year, which lasted for at least a month ($p > .05$). Further, in 12.0% of the MCDD group (and 2.3% of the PDD-NOS group) at least one hallucination (i.e., hearing voices) occurred during the past year, which also lasted for at least a month

(χ^2[1, N = 110] = 6.458, p < .05). Thus, children with MCDD had a higher rate of delusions and a significantly higher rate of hallucinations than those with PDD-NOS.

Thought problems

The mean score on the CAFAS Thoughts subscale was significantly higher in the MCDD group (M = 16.00, SD = 7.07) as compared to the PDD-NOS group (M = 10.00, SD = 8.81) (t[109] = 3.122, p < .01, d = .71). Thus, children in the MCDD group showed significantly more paranoia, incoherent thoughts, and delusions according to ratings of the clinician.

In Table 5.4. it can be seen that in 76.0% of the MCDD group the FTD criterion loose associations was present, whereas in the PDD-NOS group loose associations were present in 48.2% of the children (χ^2[1, N = 111] = 6.006, p < .05). The strength of the association was considered moderate. Thus, according to the clinician, the speech of children in the MCDD group contained higher rates of unexpected topic changes than the speech of children in the PDD-NOS group. Other FTD criteria or FTD total score did not differ significantly between the groups.

Table 5.4. FTD ratings in the PDD-NOS (n = 86) and MCDD (n = 25) groups.

FTD ratings	PDD-NOS	MCDD	p-value	ES (Φ)
Illogical thinking	28.2%	44.0%	.137	.14
Loose associations	48.2%	76.0%	.014	.23
Incoherence	25.9%	36.0%	.323	.09
Poverty of content of speech	35.3%	24.0%	.290	.10

Note. ES = Effect Size; FTD = Formal Thought Disorder; MCDD = Multiple Complex Developmental Disorder; PDD-NOS = Pervasive Developmental Disorder Not Otherwise Specified.

Social contact and communication problems

In Table 5.5. means and standard deviations of the different ADOS-G domains in the MCDD and PDD-NOS groups are presented. Whereas, children did not differ on any of the domains (p > .05), there was a significant association between group membership and ADOS-G classification. Only 36.0% of the MCDD group had ADOS-G classifications of autism or ASD, whereas this was true for 62.2% of the PDD-NOS group (χ^2[1, N = 107] = 5.337, p < .05, Φ = .22). This can be considered a moderate association (Rea & Parker, 1992). Five (55.6%) of the MCDD children with ADOS-G classifications (autism or ASD) also fulfilled PDD-NOS research criteria, but the other 4 (44.4%) did not.

Results on two of the ADOS-G domains showed a trend of differences in the expected direction (p < .10) with small to medium effect sizes. Higher scores for the PDD-NOS group were found for Reciprocal Social Interaction and for Communication plus Reciprocal Social Interaction. The latter constitutes the two domains in the algorithm.

Table 5.5. ADOS-G domai n scores in the PDD-NOS (n = 82) and MCDD (n = 25) groups.

ADOS-G domains	PDD-NOS		MCDD		p-value	ES (d)
	M	SD	M	SD		
Communication	1.99	1.04	1.68	1.63	.263	.26
Reciprocal Social Interaction	5.09	2.80	3.92	2.71	.069	.42
Communication & Reciprocal Interaction	7.07	3.46	5.64	3.96	.083	.40
Imagination/Creativity	.78	1.28	.44	.71	.203	.29
Stereotyped Behaviors/ Restricted Interests	.98	1.13	1.32	1.44	.215	.28

Note. ADOS-G = Autism Diagnostic Observation Schedule – Generic; ES = Effect Size; MCDD = Multiple Complex Developmental Disorder; PDD-NOS = Pervasive Developmental Disorder Not Otherwise Specified.

Discussion

This was the first study, to our knowledge, that tried to delineate MCDD from PDD-NOS. Children who fulfilled standardized criteria of MCDD were selected from a large sample of children referred to an outpatient mental health center. Most previous studies, a priori, considered MCDD as a pervasive developmental disorder (PDD). However, empirical evidence for this assumption was not available. Therefore, in the present study, children with MCDD were selected, independently of the presence or absence of a PDD classification. In total, 25 children with MCDD were selected. Indeed, whereas 11 of those also fulfilled criteria of PDD-NOS, 14 did not. This, in itself, already showed that MCDD should not necessarily be regarded as one of the pervasive developmental disorders. Instead, it could be a disorder that often coincides with PDD, but may also be present by itself.

However, the present study provided additional evidence for the point of view that MCDD can be delineated from PDD-NOS. Children who fulfilled criteria of MCDD clearly differed from the PDD-NOS group on a number of other symptom dimensions, which supported their divergent validity. The significance of the present study's findings becomes clear all the more because a large battery of standardized assessment procedures was used, which made the results independent of informant (clinician, parent, or child), method of data collection (interview versus questionnaire), or diagnostic construct (e.g., DSM-IV versus CBCL based taxonomy) that was used.

An important distinction between the MCDD group and the PDD-NOS group was found with respect to the number ADOS-G autism or autism spectrum disorder classifications that were yielded, which was 36.0% in the MCDD group, and 62.2% in the PDD-NOS group. This was all the more remarkable because the groups did not differ on any of the ADOS-G domains. This may be related to the fact that the algorithm for an ADOS-G classification includes items from different domains, but does not include all items from all domains. Apparently, those children in the MCDD group fulfilled criteria for ADOS-G classifications to a far lesser extent than those in the PDD-NOS group. This

can be considered as a reason to consider MCDD as a distinct construct. Of course, it can be argued that a number of MCDD children did not fulfill criteria of PDD-NOS, which automatically reduced the propensity that they would receive an ADOS-G classification. This would constitute an extra argument to consider MCDD as a separate entity. Unfortunately, our study lacked the statistical power to test if differences between MCDD children with versus without PDD-NOS were present.

On three other important domains, MCDD children showed higher problem levels than those with PDD-NOS. First, they had higher frequencies of DISC/DSM-IV anxiety disorders. For instance, they showed higher levels of separation anxiety. This may be related to the disturbed or ambivalent attachments that characterize MCDD (Cohen et al., 1986; Towbin et al., 1993). They also had a higher rate of obsessive compulsive disorder. Severe obsessions and compulsions may resemble symptoms of psychosis or thought disorder. The coexistence of obsessive compulsive symptoms and psychosis has been described extensively (e.g., Byerly et al., 2005; Eisen & Rasmussen, 1993; Ganesan et al., 2001) and seems to apply to MCDD as well. The largest effect sizes, and thus the largest differences between the groups were found on measures of psychotic thought problems (e.g., CAFAS Thoughts subscale, CBCL Thought Problems syndrome scale). Clinicians more often rated the presence of paranoia, incoherent thoughts, loose associations, delusions, and hallucinations in MCDD children, as compared to those with PDD-NOS. Also parents of MCDD children reported the occurrence of hallucinations more often than parents of children in the PDD-NOS group.

A third domain on which children with MCDD showed higher problems levels than those with PDD-NOS, was the frequency of DISC/DSM-IV disruptive behavior disorders. More specifically, they showed higher rates of oppositional defiant disorder and of conduct disorder. ODD and CD are disorders characterized by behaviors such as aggression, lying, stealing, violence, disobedience, and anger (APA, 1994) which may be reflected in the impaired regulation of affective states as seen in MCDD children (Cohen et al., 1986; Towbin et al., 1993).

Because of the social contact problems in the criteria of MCDD, its pervasive character, the early onset, and the deficits in multiple areas of development, the diagnostic classification mostly used for MCDD children is PDD-NOS (Ad-Dab'bagh & Greenfield, 2001; Towbin et al., 1993), in particular because MCDD is not an official DSM-IV or ICD-10 classification. The current study showed that MCDD children have impairments in social contact, but to a lesser extent than children with PDD-NOS, and furthermore, as discussed above, they also showed more anxiety, disruptive behavior, and psychotic disorders than children with PDD-NOS. Therefore, in our opinion, MCDD should not necessarily be placed under the PDDs. For example, one could also argue that MCDD should be regarded as a psychotic disorder, as a variety of psychotic thought problems and hallucinations seemed to be characteristic of MCDD, and showed the largest effect sizes between the groups.

Summarized, MCDD can be regarded as a disorder characterized by the presence of anxiety, disruptive behavior disorders and psychotic thought problems, that seems to constitute a diagnostic category not only different from autistic disorder, but also different from PDD-NOS. A different etiology and treatment approach may therefore apply to MCDD versus PDD-NOS.

Clinical implications

If MCDD would be a separate disorder, it would be useful to diagnose MCDD symptoms in clinical practice, independently of the presence or absence of a PDD. If clinicians considered a diagnosis of PDD-NOS as a prerequisite for the presence of MCDD, in the present study MCDD would have been missed in 56% of the cases (i.e., 56% of the children who fulfilled criteria for MCDD did not meet criteria for PDD-NOS).

Another issue related to this is whether clinicians will be able at all to reliably distinguish between MCDD and PDD-NOS. In practice PDD-NOS is often regarded as the most complex diagnosis to make in the autistic spectrum and is difficult to differentiate from autism (e.g., Buitelaar et al., 1999; Volkmar et al., 1994; Volkmar & Wiesner, 2004). Inter rater reliability of diagnosing PDD-NOS within the autistic spectrum is low (e.g., Towbin, 1997; Volkmar et al., 1997). To solve this problem, use of standardized procedures in clinical practice would be very useful.

Considering MCDD as a disorder that can be delineated from PDD-NOS also has research implications. The symptoms covered by MCDD may occur in combination with a variety of psychiatric disorders, not only PDDs, and therefore, children who fulfill criteria of MCDD should not only be selected from a group of children with PDD-NOS, but also from children with other PDDs or other psychiatric diagnoses.

Limitations

The inclusion of children from only one outpatient department limited the generalizability of the findings, and also referral biases could have played a role. A university department of outpatient child and adolescent psychiatry is generally not the first institution that children with psychiatric problems are referred to. Therefore, the sample of the present study may not represent the target population of all children with PDD-NOS and MCDD. Also, samples of children with PDD-NOS and MCDD may vary across different sites and countries. The research criteria used in this study to classify PDD-NOS were considered reliable and standardized, but were nevertheless developed mainly by Dutch authors and are not necessarily used at other national or international sites. Future multi-center and epidemiological studies in possibly more representative samples are needed to test the present study's findings.

6 Finger length ratio (2D:4D) differences between boys with autism, PDD-NOS, ADHD, and anxiety disorders

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Abstract

Objective

Children with autism have a relatively short index finger (2D) compared to their ring finger (4D). It is often presumed that the 2D:4D ratio is associated with fetal testosterone levels and that high fetal testosterone levels could play a role in the etiology of autism. It is unknown however, whether this effect is specific to autism.

Methods

Therefore, in this study, the 2D:4D ratios of 144 boys aged 6 – 14 years (mean age = 9.1, SD = 1.9), with psychiatric disorders, and control boys (n = 96, mean age = 9.1, SD = 1.8) were compared. Psychiatric disorders were divided in: autism/Asperger syndrome (n = 24), PDD-NOS (n = 26), ADHD/ODD (n = 68), and anxiety disorders (n = 26). All five groups were compared. Diagnoses were based on DSM-IV criteria and ratios were measured from hand scans using vernier calipers.

Results

It was found that boys with autism/Asperger syndrome (M = 0.934, SD = 0.033), PDD-NOS (M = 0.939, SD = 0.037), and ADHD/ODD (M = 0.943, SD = 0.031) had lower ratios than boys with an anxiety disorder (M = 0.964, SD = 0.037), and that boys with autism/Asperger syndrome had lower ratios than control boys (M = 0.956, SD = 0.034).

Conclusion

These results indicated that higher fetal testosterone levels may play a role not only in the origin of autism, but also in the etiology of PDD-NOS, and ADHD/ODD. Further, boys with anxiety disorders showed relatively high 2D:4D ratios, which suggested that they may have been exposed to lower prenatal testosterone levels.

Introduction

Since 1875 (Ecker), it is known that, the length of the index finger, compared to the length of the ring finger, the 2D:4D ratio, is a sexually dimorphic trait, not only in humans (Manning & Bundred, 2000) but also in baboons (McFadden & Bracht, 2003). Ratios close to 1 are more characteristic of women, and lower ratios are more common in men (Peters et al., 2002). A large number of studies have related the 2D:4D ratio to a variety of variables (i.e., assertiveness, breast cancer, fertility, hand preference, homosexuality) (Manning & Bundred, 2000; McFadden et al., 2005; Williams et al., 2000). Further, 2D:4D ratios have been associated with psychiatric traits, personality and social behaviors (Bailey & Hurd, 2005a; Bailey & Hurd, 2005b; Manning et al., 2001) that show sex differences, which is the topic of the present study.

The relative length of the digits is fixed for life within the first three months after conception, and remains stable thereafter (Garn et al., 1975; Manning et al., 1998). Hox genes control the development of the urinogenital system, the digits, and the testes (Kondo et al., 1997). Ingram et al. (2000) found support for the role of the Hoxa1 gene in the susceptibility to autism. However, in a study of Devlin et al. (2002) this association between Hoxa1 and autism could not be confirmed. Further, finger length ratio is a marker of the amount of testosterone the fetus was exposed to in the womb. An association was found between a low 2D:4D ratio and high levels of fetal testosterone, and vice versa, a high 2D:4D ratio and low levels of fetal testosterone (Lutchmaya et al., 2004; Manning et al., 1998).

Manning et al. (2001) found that autistic children (42 boys, seven girls) had extremely long ring fingers compared to their index fingers. Children with Asperger syndrome (20 boys, three girls) also showed a lower 2D:4D ratio, although this was less pronounced than in children with autism. Baron-Cohen and Hammer (1997) hypothesized that exposure to very high levels of testosterone in utero may lead to magnification of normal male traits, such as problems with communication and empathy. Extreme forms of these traits are often seen in individuals with autism.

To our knowledge, the 2D:4D ratio has not been assessed in any other child psychiatric disorders, and thus it remains unknown whether low 2D:4D ratios are specific for autism. Therefore, the aim of this study was to compare boys with different child psychiatric disorders and a control group with respect to their 2D:4D ratios. We only included boys because of the known sex differences in finger length ratio. If 2D:4D ratios would differentiate between the groups, careful conclusions may be drawn about fetal testosterone levels in the etiology of the different disorders. For instance, if boys with anxiety disorders would show a high 2D:4D ratio, this could indicate that they have been exposed to low prenatal levels of testosterone.

We hypothesized (1) that boys with anxiety disorders, which occur more frequently in girls than in boys, would have the highest 2D:4D ratios, (2) that boys with Attention Deficit Hyperactivity Disorder (ADHD) and Oppositional Defiant Disorder (ODD), which occur more frequently in boys than in girls, would have lower 2D:4D ratios, and (3) that boys with autism spectrum disorders (ASD: autism, Asperger syndrome, and Pervasive Developmental Disorder-Not Otherwise Specified [PDD-NOS]), which show an even more contrasting male-female difference in prevalence, would have the lowest 2D:4D ratios.

Methods

Participants

The sample consisted of boys, aged 6 – 14 years, who had been referred to the outpatients' department of child and adolescent psychiatry, Erasmus Medical Center Rotterdam, the Netherlands, between July 2003 and September 2005. In this period, 314 boys were referred who all received a DSM-IV diagnosis after clinical assessment.

All boys with DSM-IV autism/Asperger syndrome, PDD-NOS, ADHD/ODD, or an anxiety disorder were selected for the present study. Boys with co-morbid disorders were excluded (n = 45, e.g., ADHD plus a co-morbid anxiety disorder). This yielded 154 boys. PDD-NOS was separated from autism/Asperger syndrome to assess whether the low ratios as demonstrated before in children with autism or Asperger syndrome, were also present in children with a lesser variant of the autism spectrum disorders (ASD's). For 144 boys (93.5%), 2D:4D measurements of the left hand were available. For eight boys a hand scan was not available due to refusal of the child or the parent, and two scans were missed due to scanning problems at the time of visiting of the child. For the right hand, two additional scans were unavailable due to bad quality of the copy and a broken arm. Thus, 142 (92.2%) hand scans of the right hand were available.

This yielded a study sample of 144 patients for which at least one hand scan was available (mean age 9.1, SD = 1.9): autism/Asperger syndrome (n = 24, mean age = 9.0, SD = 2.2, Full Scale IQ [FSIQ] = 97.91 (SD = 18.81), Verbal IQ [VIQ] = 104.00 (SD = 25.37), Performance IQ [PIQ] = 95.62 (SD = 24.49); PDD-NOS (n = 26, mean age = 9.1, SD = 2.0, FSIQ = 87.36 [SD = 18.74], VIQ = 88.79 [SD = 18.70], PIQ = 88.86 [SD = 17.09]); ADHD/ODD (n = 68, mean age = 9.1, SD = 1.9, FSIQ = 94.70 [SD = 15.48], VIQ = 96.04 [SD = 15.66], PIQ = 94.61 [SD = 14.90]); or one or more anxiety disorders (n = 26, mean age = 9.2, SD = 1.3, FSIQ = 93.00 [SD = 30.78], VIQ = 97.60 [SD = 25.45], PIQ = 88.80 [SD = 28.73]). The different groups did not differ on any of the IQ-scores ($p > .05$). In the first group, 17 boys with autism were included and 7 with Asperger syndrome. Boys with autism did not differ in

IQ-scores from boys with Asperger syndrome ($p > .05$). In the ADHD/ODD group, 38 boys met criteria for ADHD only, 21 for ADHD plus ODD, and 9 for ODD only.

The four child psychiatric groups were compared with each other and with control boys (mean age = 9.1, $SD = 1.8$) who were recruited from a primary school in The Netherlands. For these boys IQ data were not available. For 96 boys (out of 103, 93.2%), at least one hand scan was available.

Informed consent was obtained prior to participation from all parents, caretakers, and children of 12 years and above. The Medical Ethics Committee of the Erasmus Medical Center approved the study.

Assessment

DSM-IV classifications were assigned by child and adolescent psychiatrists who based their evaluation on highly standardized assessment measures: all 144 children were assessed with the Semi structured Clinical Interview for Children and Adolescents (SCICA; McConaughy & Achenbach, 2001), and at least one interview to assess DSM-IV diagnoses; the Diagnostic Interview Schedule for Children – version IV (DISC-IV; Shaffer et al., 1998), or the Autism Diagnostic Observation Schedule-Generic (ADOS-G; Lord et al., 1999), if children were referred to the neuropsychiatric unit of our department, and the Anxiety Disorder Interview Schedule for Children (ADIS-C; Silverman et al., 2001) if referred to the anxiety/depression unit of our outpatient department. Psychometric properties of all assessment procedures are good, and the interviews were carried out by trained psychologists and research assistants, who were blind to diagnostic information about the child.

The DISC-IV is a highly structured interview to assess DSM-IV Axis I psychiatric disorders in the past year. The ADIS-C has a similar format, but only focuses on anxiety disorders, and the ADOS-G is a semi-structured observation scale for children suspected of having an ASD. For all 144 children, the responsible psychiatrist was asked to rate standardized DSM-IV research criteria to diagnose PDD-NOS. Further, IQ tests and other psychological tests were administered. After this routine clinical assessment, the psychiatrist assigned the final DSM-IV diagnosis after consulting all professionals involved in the assessment.

2D:4D ratio

Scans of the ventral surface of the left and the right hands were obtained. Finger length measurements were conducted from the basal crease to the tip of the finger with electronic vernier calipers reading to 0.01 mm. This type of measurement is highly reliable (Manning et al., 1998). The research assistants who measured the finger lengths were blind to age or diagnostic classification of the child.

We carried out an inter and intra rater reliability study. Three independent raters rated 30 randomly selected pairs of hands. Intra class correlation coefficients for 2D:4D ratios of the left (0.87) and the right hand (0.86) were good. Further, one rater rated the same 30 pairs of hands twice. Agreement for the left hand ratio (0.96) and the right hand ratio (0.96) was excellent. We also followed the method to quantify the differences between raters as described by Bland & Altman (1986), and showed that around 95% of the differences between the raters (and also within one rater) fell within the 95% confidence interval, and that the differences between the raters (or within one rater) were distributed normally.

Statistical analyses

Two univariate analyses of variance were carried out to compare the groups on 2D:4D ratios of the left and the right hand. Group variances were equal (Levene statistic: $p > .05$), all groups were compared pair-wise, and group sizes were slightly uneven. Therefore, Gabriel's post hoc analyses were carried out. Further, Cohen's *d* was calculated as a measure of effect size when means of two groups were compared. An effect size of 0.20 can be considered as small, of 0.50 as medium, and of 0.80 or above as large (Cohen, 1988). For the groups that differed significantly, we also calculated the Wald 95%-confidence intervals of pair-wise group differences in terms of 2D:4D ratio.

Finally, discriminant analysis was performed. Left and right hand ratios were used to predict group membership.

Results

In Table 6.1., descriptive variables for the left and the right hand ratios in the five different groups are presented. Overall, groups differed significantly with respect to 2D:4D ratio of the left ($F[4, 233] = 2.74$, $p < 0.05$), and right hand ($F[4, 233] = 4.44$, $p < 0.01$). Post hoc analyses showed that boys with autism/Asperger syndrome had a significantly lower 2D:4D ratio in the left hand than normal control boys ($p < 0.05$, $d = 0.57$, Wald-95%-CI: $0.004 < \text{diff} < 0.035$).

With respect to the right hand ratio, boys with autism/Asperger syndrome had a significantly lower 2D:4D ratio than boys with anxiety disorders ($p < 0.05$, $d = 0.85$, Wald-95%-CI: $0.010 < \text{difference} < 0.050$). Similarly, boys with ADHD/ODD showed a significantly lower ratio than the group with anxiety disorders ($p < 0.05$, $d = 0.66$, Wald-95%-CI: $0.007 < \text{difference} < 0.036$). Boys with PDD-NOS also had a lower ratio than boys with anxiety disorders but the difference did not reach statistical significance ($p = 0.62$, $d = 0.69$, Wald-95%-CI: $0.006 < \text{difference} < 0.046$).

Table 6.1. Descriptive variables of the five different groups.

	Autism/AS	PDD-NOS	ADHD/ODD	Anxiety disorders	Normal controls
LH 2D:4D					
M	0.939	0.944	0.948	0.960	0.958
SD	0.036	0.038	0.032	0.036	0.034
95%-CI mean	0.923 – 0.954	0.929 – 0.960	0.940 – 0.956	0.946 – 0.975	0.951 – 0.965
Median	0.941	0.949	0.952	0.958	0.953
Range	0.89 – 1.03	0.87 – 1.02	0.87 – 1.01	0.89 – 1.04	0.89 – 1.04
Interquartile range	0.060	0.056	0.048	0.059	0.051
n	23	26	67	26	86
RH 2D:4D					
M	0.934	0.939	0.943	0.964	0.956
SD	0.033	0.037	0.031	0.037	0.034
95%-CI mean	0.920 – 0.949	0.923 – 0.954	0.935 – 0.950	0.949 – 0.979	0.949 – 0.963
Median	0.934	0.945	0.941	0.971	0.952
Range	0.89 – 1.02	0.86 – 1.00	0.88 – 1.04	0.92 – 1.05	0.88 – 1.04
Interquartile range	0.054	0.042	0.038	0.062	0.042
n	23	26	67	26	86

Note. ADHD = Attention Deficit Hyperactivity Disorder; AS = Asperger syndrome; CI = confidence interval; LH = left hand; ODD = Oppositional Defiant Disorder; PDD-NOS = Pervasive Developmental Disorder Not Otherwise Specified; RH = right hand.

Further, boys with autism/Asperger syndrome had a lower ratio than normal control boys, but this difference did also not reach statistical significance ($p = 0.52$, $d = 0.64$, Wald-95%-CI: 0.006 < difference < 0.037). Effect sizes were medium to large.

In the discriminant analysis, the overall Wilk's lambda was significant when right hand ratio ($\Lambda = .93$, χ^2 (4, $n = 234$) = 17.18, $p < .01$), and left hand ratio ($\Lambda = .95$, χ^2 (4, $n = 234$) = 10.75, $p < .05$) were used separately as predictors. This indicated these predictors differentiated between the five groups. The right hand ratio correctly classified 41.9% of the boys, and the left hand ratio correctly classified 39.3% of the boys.

Discussion

To our knowledge, this was the first study that compared finger length patterns in different child psychiatric groups and control children. It was demonstrated that boys with different child psychiatric disorders differed in 2D:4D ratios of the left and the right hand. Overall, boys with autism/Asperger syndrome showed the most 'male-like' finger pattern, and boys with anxiety disorders showed the most 'female-like' finger pattern.

Boys with autism/Asperger syndrome did not differ from boys with PDD-NOS, or with ADHD/ODD. Not all differences between groups were significant, but most of them were in the expected direction.

For the left and the right hand, boys with autism/Asperger syndrome had a lower ratio than control boys, which was in agreement with previous findings (Manning et al., 2001). For the right hand only, boys with ADHD/ODD, and to a lesser extent, boys with PDD-NOS, showed the same pattern as boys with autism/Asperger syndrome: they had lower ratios than boys with anxiety disorders.

The relatively low 2D:4D ratio in boys with ADHD/ODD confirmed our hypothesis, and seems in accordance with the higher rate of aggression (which is a symptom of ODD) that was found in men with lower, more masculine, 2D:4D ratios (Bailey & Hurd, 2005a). ADHD and ODD occur more often in boys compared to girls (Szatmari et al., 1989). Low 2D:4D ratios in boys with ADHD/ODD suggested that these boys may have been exposed to high prenatal levels of testosterone.

The 2D:4D ratio of boys with PDD-NOS was not studied before. PDD-NOS is considered to be a milder form of the ASD's, and therefore it was expected that boys with PDD-NOS would also show relatively low 2D:4D ratios. We did indeed find evidence for a low 2D:4D ratio in boys with PDD-NOS (albeit not statistically different from boys with anxiety disorders) which suggested that boys with PDD-NOS may have been exposed to high fetal testosterone levels.

The fact that no differences in ratios were found between boys with autism/Asperger syndrome, PDD-NOS, and ADHD/ODD could be attributed to small and unequal sample sizes and therefore a lack of power to demonstrate group differences. Another explanation could be that although children with autism or PDD-NOS may show different symptoms than those with ADHD or ODD, in prenatal life, these children were all exposed to equally high levels of testosterone. From genetic studies it has also been suggested that ADHD and ASD's share a common genetic background (Smalley et al., 2002).

As hypothesized, boys with anxiety disorders had a higher 2D:4D ratio than boys with other child psychiatric disorders, and a higher ratio than normal control boys, although the latter finding did not reach significance. Anxiety disorders, contrary to ADHD and ODD, occur more often in girls than in boys (Lewinsohn et al., 1998). If levels of fetal testosterone influence finger length, it could be that boys with anxiety disorders were exposed to relatively low prenatal testosterone levels. To our knowledge, the association between anxiety disorders and digit ratio was not studied before. The nearest finding however, was a relation between digit ratio and depression, which also is a sexually dimorphic disorder that occurs more often in females. Bailey and Hurd (2005b) demonstrated that higher levels of depression in men were associated with higher, more feminine 2D:4D ratios.

This study showed that group differences were present in the left and the right hand, but effects were strongest for the right hand. This is in agreement with previous literature showing that relations between 2D:4D ratio and personality traits were stronger for the right hand, and that 2D:4D ratio was more sexually dimorphic in the right hand (Manning et al., 1998).

Limitations

The findings in this study are limited to boys, and thus no conclusions can be drawn about finger length ratio in girls. To keep groups as homogeneous as possible, all boys with dual psychiatric diagnoses were excluded. This resulted in relatively small sample sizes, which reduced the power of the study.

Further, the relation between the level of prenatal testosterone and psychiatric disorders is based on the assumption that 2D:4D ratio reflects the exposure of the fetus to testosterone. This ratio however, is only an indirect measurement of prenatal testosterone. It might, for instance, also be possible that the 2D:4D ratio reflects underlying early fetal abnormal brain development rather than simply that testosterone may influence behavior. Therefore, the findings should be interpreted carefully.

Conclusions and future directions

High fetal testosterone levels may play a role not only in the origin of autism, but also in the etiology of ADHD/ODD, and PDD-NOS. Boys with anxiety disorders have relatively high 2D:4D ratios, which suggested that they may have been exposed to lower prenatal testosterone levels. In future studies however, bigger samples should be included, as well as girls, and attention should be paid to other ratios than the 2D:4D ratio (for instance the 3D:5D ratio).

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7 Autistic features in girls from a psychiatric sample are strongly associated with a low 2D:4D ratio

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Abstract

Objective

Autistic features such as deficits in social interactions and communication have been associated with a low 2D:4D ratio in normal children.

Methods

This study assessed this association in a large sample of children with a variety of psychiatric disorders (n = 35 girls and n = 147 boys). Autistic features were assessed with a highly valid and reliable measure (Autism Diagnostic Observation Schedule [ADOS-G]). Correlations between the 2D:4D ratio and autistic features were computed separately for boys and girls.

Results

Particularly in girls, large negative correlations (r = -.51 to r = -.64) were found.

Conclusion

A low 2D:4D ratio in girls was highly predictive of the presence of autistic features. Thus, a low ratio could be used as a diagnostic predictor in clinical practice.

Introduction

Since more than a century, the length of the index finger (second digit = 2D) relative to the length of the ring finger (fourth digit = 4D) (the 2D:4D ratio) is being considered a sexually dimorphic trait in a variety of species, varying from humans and mice to zebra finches (e.g., Brown et al., 2002; Burley & Foster, 2004; Manning et al., 2000). Lower ratios are more common in men and ratios closer to 1 are more characteristic of women (Baker, 1888; George, 1930; Manning et al., 1998). A large number of studies have revealed associations between the 2D:4D ratio and a variety of variables and diseases (i.e., assertiveness, breast cancer, attractiveness, fertility, hand preference, female waist-hip ratio, homosexuality, reproductive success) (Manning et al., 1999; Manning et al., 2000; Manning & Bundred, 2000; McFadden et al., 2005; Robinson & Manning, 2000; Williams et al., 2000). Some studies have associated low 2D:4D ratios with deficits in social interaction in normal samples. The current study will focus on this association in a child psychiatric sample.

The relative length of fingers is fixed for life within the first three months of pregnancy, and remains stable thereafter (Garn et al., 1975; Manning et al., 1998). Finger length ratio is considered a marker of the levels of testosterone the fetus was exposed to in the womb. Fetal testosterone has an effect on cerebral lateralization in the developing brain (Garn et al., 1975; Manning et al., 1998). A low 2D:4D ratio may indicate the fetus was exposed to a high level of prenatal testosterone. Vice versa, a high 2D:4D ratio may indicate low prenatal levels of testosterone. Evidence to support this view comes from studies in patients with congenital adrenal hyperplasia (CAH). These individuals were exposed to high fetal testosterone concentrations. Later in life they exhibited more masculine digit ratios than normal controls (Brown et al., 2002; Slijper, 1984).

The following three studies in preschool children in the United Kingdom revealed relationships between levels of fetal testosterone or low 2D:4D ratios, and deficits in social interaction and communication skills, as measured by parent questionnaires. Lutchmaya et al. (2002) showed that a high level of fetal testosterone, as measured in the amniotic fluid, was associated with decreased eye contact in 1 year old children (n = 70). Subsequently, Knickmeyer et al. (2005) demonstrated an association between high levels of fetal testosterone and poor quality of social relationships, and more restricted interests in 4 year old children (n = 58). In both studies, associations applied to boys in particular, and not as much to girls. Although the authors emphasized that they could not extrapolate directly from their study in a normal sample to a sample of autistic children, they did provide evidence for a possible effect of fetal testosterone in the vulnerability to autism (Knickmeyer et al., 2005). Further, Williams and colleagues (2003) found that a low male-type 2D:4D ratio was associated with social cognition problems and peer relationships (n = 196). In all three studies deficits in social interaction and

communication were measured by parent questionnaires, and no direct standardized observations of the child were made by a clinician.

In child psychiatric samples, associations between finger length ratio and deficits in social interaction and communication skills have not much been studied yet. Only one study demonstrated that autistic children (n = 49) had extremely long ring fingers compared to their index fingers, and thus a very low 2D:4D ratio (Manning et al., 2001). Apart from these findings in autism, it is unknown whether associations between finger length ratio and autistic features are also present in children with other disorders than autism. In our opinion this would be relevant to assess. If it could be demonstrated that a low 2D:4D ratio is associated with autistic features in a child psychiatric sample, finger length could possibly be used as a diagnostic predictor of autistic traits.

Summarized, previous results were based mainly on children from normal preschool samples, and no standardized clinical observation of autistic features was made. Only parent questionnaires were used. The aim of this study therefore was to assess the relation between autistic features, as measured with the Autism Diagnostic Observation Schedule-Generic (ADOS-G; Lord et al., 1999), and 2D:4D ratio in a large child psychiatric sample. A second aim of the study was to assess sex differences in the associations between boys and girls as in previous studies findings were different for boys and girls. We hypothesized that the presence of more autistic features (i.e., more deficits in social interaction) was associated with lower digit ratios, for boys as well as for girls.

Methods

Participants

The sample consisted of 182 children, aged 6 years – 13 years (M = 8.98, SD = 1.85), 147 boys (80.77%) and 35 girls (19.23% girls). Selection was made from 199 children who were consecutively referred to the outpatients' department of child and adolescent psychiatry, Erasmus Medical Center Rotterdam, the Netherlands between July 2003 and September 2005. ADOS-G was carried out and hand scans were made. Three children were unable or unwilling to participate in the ADOS-G, eight of the parents refused to participate, and six of the hand scans were insufficiently clear for the left hand and the right hand, and therefore 2D:4D measurements could not be carried out. This yielded 182 children for whom at least one measured hand scan and ADOS-G data were available. For 171 (93.96%) children, both the left and the right hand measurements were available.

All 182 children were assigned DSM-IV (APA, 1994) classifications by child psychiatrists. Eighty (43.95%) of them were assigned a diagnosis in the autistic spectrum (autism, Asperger syndrome, or Pervasive Developmental Disorder-Not Otherwise Specified [PDD-NOS]), 25 (13.74%) children were assigned one or more externalizing disorders

(Attention Deficit Hyperactivity Disorder [ADHD], Oppositional Defiant Disorder [ODD], or Conduct Disorder [CD]), and 16 (8.79%) children were assigned one or more internalizing disorders (anxiety or depressive disorders). The other 61 (33.52%) children were divided over co-morbid disorders (e.g., a disorder in the autistic spectrum plus an externalizing disorder) and other Axis-I disorders.

Ethics

Parents or caretakers of the children had all signed informed consent forms prior to participation in the study. Children of 12 years old signed the consent forms themselves as well. The Medical Ethics Committee of the Erasmus Medical Center approved the study.

Assessment

ADOS-G

The ADOS-G (Lord et al., 1999) provides a standardized context to specifically observe the DSM-IV autism related behaviors in the domains of social interaction, communication, imagination, and stereotyped behavior. In this study, the ADOS-G domains Communication (i.e., stereotyped language), Reciprocal Social Interaction (i.e., eye contact), Imagination/Creativity, and Stereotyped Behaviors and Restricted Interests (i.e., unusual sensory interest in play material or person) were used as variables in the analyses, as well as the sum of these four domains, the ADOS-G Total Score. The sum of Communication and Reciprocal Social Interaction, which together constitute the algorithm on which the ADOS-G classification is based, was also used as a variable. Although behaviors such as restricted and repetitive behaviors are rated in the ADOS-G, the time span to measure these behaviors is limited to the ADOS-G assessment (approximately 45 minutes) which is considered insufficient to rate them reliably (Lord et al., 1999). Therefore, the ADOS-G classification is only based on social behaviors and communication. It is important to distinguish between an ADOS-G classification and an overall DSM-IV diagnosis of autism which also includes abnormalities in restricted, repetitive behavior and an early onset of the symptoms. The ADOS-G only provides a measure of current functioning.

Inter rater reliability varied from $r = .82$ on the domain of Stereotyped Behaviors and Restricted Interests to $r = .93$ on the domain of Reciprocal Social Interaction. Test-rest reliability showed good stability for Stereotyped Behaviors and Restricted Interests ($r = .59$) up to excellent stability for the algorithm ($r = .82$). Psychologists who conducted the ADOS-G in this study were trained by certified ADOS-G trainers.

2D:4D ratio

Measurements of finger length are usually made directly from the fingers or from photocopies of the fingers. Both methods show high reliability (Robinson & Manning, 2000).

Manning et al. (2005) showed that 2D:4D ratios measured from photocopies were significantly smaller than those measured directly from the fingers. Therefore, photocopies and direct measurements should not be combined within one study. For the present study, scans of the ventral surface of the left and the right hands were obtained during psychological testing. Children were requested to press their hand flat on a scanner attached to a personal computer. Images were stored and printed later. Subsequently finger length measurements were made from the basal crease to the tip of the finger with electronic vernier calipers reading to .01 mm. Manning et al. (1998) showed that this type of measurement is very reliable. If the basal crease of the finger was not clearly visible, the copy was excluded from further measurements. The research assistants who measured the finger lengths were unaware of sex, age or diagnostic classification of the child.

For 30 hand scans, an inter rater reliability study was carried out. Three independent raters rated 30 pairs of hands. Intra class correlation coefficients (ICC) for 2D:4D ratio reflected high agreement (ICC = .89 for left hand, ICC = .85 for right hand).

Further, an intra rater reliability study was carried out. One rater rated the same 30 pairs of hands twice. ICC showed excellent agreement (ICC = .95 for left hand 2D:4D ratio, and ICC = .91 for right hand 2D:4D ratio).

Statistical analyses

Means and standard deviations for the left and the right hand 2D:4D ratios were calculated for boys and girls separately. An independent samples *t*-test was used to assess the difference in left and right hand ratios between boys and girls.

Pearson correlations for boys and girls separately were calculated between the left and the right hand ratio and the following six ADOS-G scores: Communication, Reciprocal Social Interaction, Imagination/Creativity, Stereotyped behaviors/restricted interests, ADOS-G algorithm score (Communication plus Reciprocal Social Interaction), and ADOS-G Total score (sum of the four domains). Sex differences between the correlations for boys versus girls were investigated according to Hays (1988). R squared (R^2) was used to indicate effect size. R^2 between .02 - .13 is considered a small effect size, .13 - .26 indicates a medium effect size, and R^2 above .26 represents a large effect size (Cohen, 1988).

Results

Descriptives

Figure 7.1. displays means of 2D:4D ratios for boys (left hand: M = .95, SD = .04, range .86 – 1.06; right hand: M = .95, SD = .04, range .86 – 1.05), and girls (left hand: M =

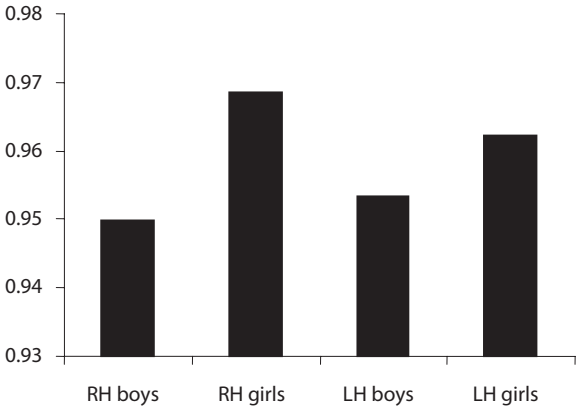

Figure 7.1. Left and right hand ratios for boys (n = 147) and girls (n = 35).
Note. LH = left hand; RH = right hand.

.96, *SD* = .04, range .83 – 1.04; right hand: *M* = .97, *SD* = .04, range .89 – 1.05). Boys had a lower 2D:4D ratio than girls, for the right hand only ($t(173) = -2.60$, $p = .01$, two-tailed).

Correlations

In Table 7.1. correlations between ADOS-G scores and the left and right hand ratios are presented, as well as the Z-scores for differences in correlations between boys and girls. Z-scores above 1.96 reflect significant effects (Hays, 1988), which indicates that correlations differed significantly for all the ADOS-G domains of the left hand ratio only.

For girls, all correlations between the ADOS-G scores and the 2D:4D ratios of the left hand were significant. Higher ADOS-G scores were related to lower digit ratios. Correla-

Table 7.1. Correlations for boys (n = 145) and girls (n = 33) between left and right hand ratio and ADOS-G scores, and Z-scores.

ADOS-G scores	LH ratio girls	LH ratio boys	Z-score	RH ratio girls	RH ratio boys	Z-score
Communication	r = -.63 p = .00	r = -.01 p = .94	3.69	r = .04 p = .82	r = -.07 p = .39	.57
Reciprocal social interaction	r = -.51 p = .00	r = -.09 p = .28	2.33	r = -.01 p = .94	r = -.19 p = .03	.87
Imagination/Creativity	r = -.59 p = .00	r = .01 p = .88	3.42	r = -.03 p = .86	r = -.06 p = .48	.14
Stereotyped behaviors and restricted interests	r = -.60 p = .00	r = -.01 p = .87	3.35	r = .07 p = .72	r = -.07 p = .42	.66
Communication + Reciprocal social interaction	r = -.61 p = .00	r = -.07 p = .41	3.15	r = .01 p = .98	r = -.17 p = .05	.86
Total score (4 domains)	r = -.64 p = .00	r = -.06 p = .51	3.52	r = .01 p = .94	r = -.15 p = .07	.84

Note. ADOS-G = Autism Diagnostic Observation Schedule-Generic; LH = left hand; RH = right hand.

tions were all large, around .60, which corresponds with R^2 around .36. For the right hand ratios in girls, none of the correlations were significant.

For boys, correlations overall were much smaller than for girls. Correlations for the left hand were not significant, and for the right hand, only small correlations were found with the ADOS-G domain Reciprocal Social Interaction (r = -.19, R^2 = .04), and the ADOS-G algorithm score (r = -.17, R^2 = .03). Higher ADOS-G scores were correlated with lower digit ratios.

Discussion

The findings of this study were twofold. First, this study contributed to the evidence for a negative association between autistic features and finger length ratio in a child psychiatric sample. Second, a remarkable sex difference in these associations was demonstrated. Not only did boys have a lower digit ratio than girls, but we also found that the negative relation between finger length ratio and autistic features was far stronger in girls than in boys.

In previous studies in samples of preschool children, a negative association between the 2D:4D ratio and deficits in social interaction and communication was found (Knickmeyer et al., 2005; Lutchmaya et al., 2002; Williams et al., 2003). Lower digit ratios were associated with more autistic features, which, in these studies, were measured by parent questionnaires only. The current study confirmed these findings in a child psychiatric sample by using a direct clinical observation of the child. The presence of more autistic features was correlated with a lower digit ratio.

However, our findings applied mainly to girls whereas in previous studies, they applied mainly to boys. In girls with a psychiatric disorder, lower digit ratios were highly associated with the lack of imagination and stereotyped behaviors as well as deficits in social interaction and communication. Over a third of the variance in autistic features was explained by the variance in the left hand ratio. Thus it seemed that when a low male-like 2D:4D ratio was present in a girl, this was highly indicative of the occurrence of autistic features. For boys however, this relation was much weaker. In clinical practice, a low ratio in girls may point in the direction of problems with social interaction and communication, whereas for boys such a relation is not necessarily present. This is particularly interesting as finger length ratio is fixed for life within the first three months after conception, and remains stable thereafter (Garn et al., 1975; Manning et al., 1998) and could therefore possibly play a role in the very early detection of autistic features.

It is difficult to explain this large difference in correlations between boys and girls. We are aware that girls constituted a much smaller portion of the total sample (n = 35) and therefore these findings would need to be confirmed in larger psychiatric samples

of girls. Additionally, a significantly higher proportion of boys, as compared to girls, had a diagnosis in the autistic spectrum ($p < .01$, 48.7% versus 22.9%), and therefore boys in the sample showed more autistic features. However, we don't think this would explain the larger correlations between finger length ratio and autistic features in girls. Further, boys are exposed to higher levels of prenatal testosterone (Collaer & Hines, 1995), and it therefore seems possible that the effect of prenatal testosterone on the later development of autistic features is different for boys and girls.

Results differed for the left and the right hand ratio. From previous literature it is known that findings are not necessarily the same for the left and the right hand ratio (Manning et al., 1998). The right hand 2D:4D ratio is often considered a stronger predictor than left hand ratio. Right hand 2D:4D ratio may be more sensitive to the effects of fetal testosterone (Lutchmaya et al., 2004). In this study however, the left hand ratio was strongly associated with autistic features, particularly in girls. We are currently unable to explain this stronger relation for the left hand ratio.

Finally, although this was not the main aim of the current study, it was also demonstrated that boys had a lower digit ratio than girls, only in the right hand. This finding is in accordance with the sex differences that have been demonstrated before in normal samples (e.g., Manning et al. 1998).

Limitations

Only children from one child psychiatric outpatient department were included. This limits the generalizability of the results. Another limitation concerns the interpretation of correlational findings. Correlations are of a bidirectional nature and no causal conclusions can be drawn. A low digit ratio can be explained by the presence of autistic features, but vice versa, a high number of autistic features can also be explained by a low finger length ratio. Therefore we can not simply conclude that a girl born with a low 2D:4D ratio has a high chance of developing autistic features. To obtain evidence for the causality of this relation longitudinal studies are needed.

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8 General discussion

Introduction

In this Chapter, the results of *Chapter 2* through *Chapter 7* will be summarized. First, issues with respect to PDD-NOS will be discussed, followed by FTD and last, issues with respect to the finger length studies will be evaluated. Subsequently, clinical implications and recommendations for future studies will be discussed.

PDD-NOS

Intelligence profiles and psychiatric co-morbidity patterns in children with PDD-NOS were described in *Chapters 2* and *3*. Although PDD-NOS occurs much more frequently than autism (Chakrabarti & Fombonne, 2001), and intelligence profiles of children with autism have been studied extensively (e.g. Ehlers et al., 1997; Happé, 1994; Lincoln et al., 1995; Siegel et al., 1996; Venter et al., 1992), nothing was known about these profiles of children with PDD-NOS. We showed that children with PDD-NOS have IQ scores in the average range, and show no difference between their VIQ and PIQ. Strengths and weaknesses found in previous studies in children with autism, do not necessarily apply to children with PDD-NOS as well.

Further, it was found that more than 80% of the children with PDD-NOS had at least one co-morbid psychiatric disorder, of which disruptive behavior disorders such as ADHD or ODD, occurred most frequently. This is important to be aware of when it comes to treatment planning. No definite cure seems available yet to treat the core deficits in communication and social interaction in children with PDD-NOS (Tanguay, 2000). However, associated symptoms such as hyperactivity or anxiety can be targeted with behavioral and pharmacological interventions (e.g., Horner et al., 2002; Keen & Ward, 2004; Santosh & Baird, 2001). Ghaziuddin (2005) dedicated a whole book to the importance of treating psychiatric conditions in people with autism. The treatment of superadded conditions of autism results in substantial improvement of general functioning, in their quality of life, whereas in the near future it will probably not be possible to cure autism itself (Ghaziuddin, 2005).

The fact that the large majority of children with PDD-NOS had co-morbid psychiatric diagnoses raises the issue whether PDD-NOS as a separate diagnosis adds sufficiently to the current classification system. In my opinion, PDD-NOS is a useful diagnostic concept, however in its current form it is not sufficiently fine-tuned. The simple fact that the rest category of PDD-NOS seems to have a much higher prevalence than autistic disorder or Asperger syndrome, and results in large daily impairments, indicates that more studies of PDD-NOS are warranted.

Although this was not studied in this dissertation, a suggestion of a more fine-tuned approach of PDD-NOS is included below. It might be possible to consider PDD-NOS as a profile, like an intelligence profile, (see Figure 8.1.), with the use of explicit criteria. The

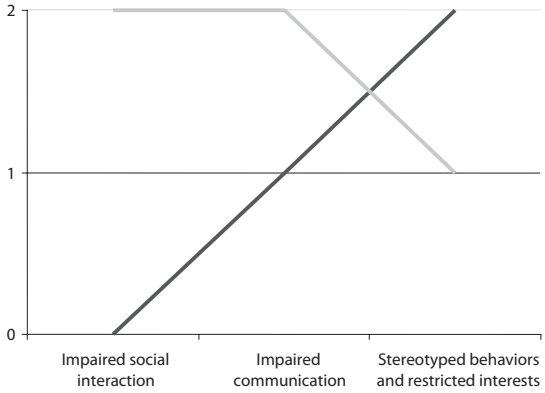

Figure 8.1. Examples of PDD-NOS profiles.

current classification alone does not convey where the patient's condition is positioned on an extensive spectrum (Towbin, 1997). Both children in the graph would be assigned a classification of PDD-NOS plus it is then known which domains (x-axis) are disturbed and to what extent (y-axis). To obtain a more detailed picture of how disturbed the child would be, in this example, PDD-NOS symptoms would be rated on a more continuous scale (0-1-2), such as used in the CBCL (Achenbach, 1991), or the ADOS-G (Lord et al., 1999) instead of on a dichotomous scale.

Such a symptom profile could subsequently be combined with an IQ profile and co-morbidity assessment, and would result in a more fine-tuned picture of the individual child to which treatment could better be tailored.

Formal thought disorder

In this dissertation *Chapters 4* and *5* were related to FTD. First, a low agreement between a clinician's ratings of FTD and ratings of the K-FTDS was found for which several explanations were given. I consider the detection of FTD in childhood as clinically relevant, particularly because it may indicate an increased risk of future psychotic disorders (Ott et al., 2001; Parnas et al., 1982). However, despite its clinical value, the absence or presence of FTD seemed to depend highly on which measure was used. To use assessments such as the K-FTDS as a part of routine clinical assessment would be too time consuming. Another less time consuming possibility to higher awareness and reliability of FTD ratings among clinicians, would be to set up inter rater reliability studies for groups of clinicians on a regular basis.

Second, the concept of MCDD was studied. Currently, MCDD is not a separate construct in DSM-IV (APA, 1994). The early onset of the symptoms, impairments in multiple areas of development, the related social deficits, and its pervasive character, make that the diagnostic classification mostly used for these children is PDD-NOS (Ad-Dab'bagh & Greenfield, 2001; Towbin et al., 1993). In my opinion this is not always correct.

When the research criteria for MCDD and PDD-NOS are compared, some overlap (e.g., impairment in social behavior), but also some differences (e.g., thought disorder in the MCDD criteria and stereotyped behavior in the PDD-NOS criteria) can be seen. Also, in our study we showed that children with MCDD differ from children with PDD-NOS. Children with MCDD showed more anxiety disorders, disruptive behavior, and thought problems as compared to children with PDD-NOS. And vice versa, children with PDD-NOS showed more deficits in social contact than children with MCDD.

Ad-Dab'bagh and Greenfield (2001) summarized arguments to capture MCDD under the personality disorders, or under the PDDs. They suggested a more neutral term: 'emoto-cognitive dys-social disorder', which simply referred to the disturbed areas of functioning of these children. In my opinion, this neutral approach is the best way to assess the concept of MCDD. This way, the term does not imply any pre-existing assumption of etiology, classifications or outcome.

Finger length ratio

Chapter 6 and *7* described studies about the role of finger length ratios in child psychiatry. It was already shown before that children with autism had a very low 2D:4D ratio (Manning et al., 2001) and this was considered an indication that children with autism have been exposed to very high levels of testosterone in the womb (Baron-Cohen & Hammer, 1997). One of our studies showed however, that not only boys with autism or Asperger syndrome, but also boys with ADHD/ODD, or with PDD-NOS to a lesser extent, had relatively low 2D:4D ratios. Thus, higher fetal testosterone levels may play a role not only in the origin of autism, but also in the etiology of ADHD/ODD, and PDD-NOS. In contrast, boys with anxiety disorders showed relatively high 2D:4D ratios, which suggested that they were exposed to lower prenatal testosterone levels.

Further, negative associations between the 2D:4D ratio and deficits in social interaction and communication were demonstrated before in normal samples (Knickmeyer et al., 2005; Lutchmaya et al., 2002; Williams et al., 2003), and our study confirmed this in a child psychiatric sample. When boys and girls were compared, a large negative correlation between 2D:4D ratio and autistic features was found for girls in particular. A low 2D:4D ratio in girls was highly predictive of the presence of autistic features.

Clinical implications

The clinical significance for each of the three main topics of this thesis will be discussed below. First, the studies with respect to PDD-NOS underscored the importance of clinical assessment of associated symptoms. Although the hierarchichal structure of the DSM does not always allow co-morbid classifications with the PDDs, the large majority of

children with PDD-NOS suffered from co-morbid psychiatric symptoms or disorders. Treatment for these associated symptoms is often available, whereas the core deficits in communication and social interaction are considered as more resistant to treatment. PDD-NOS is a life-long disorder and most patients do not outgrow their symptoms. The outcome of the disorder is determined by intelligence levels, the level of verbal skills, but also by the presence of somatic or psychiatric complications. Therefore, in clinical practice, some form of standardized assessment of co-morbid symptoms in children with PDD-NOS should always be included.

Further, when tailoring treatment to the individual child with PDD-NOS, a practitioner should have some knowledge about the intelligence profile of the child. Children with PDD-NOS have IQ scores in the average range and show no differences between their VIQ and PIQ as often seen in children with autism or Asperger syndrome. They seem to have a lot of factual knowledge which may lead to overestimation of their abilities, while their actual understanding of social situations might be less well developed. And last, children with PDD-NOS seemed to perform poorly on tests that are associated with attention and distractibility. High distractibility might interfere with their learning abilities. Although this is also often found in children with autism or Asperger syndrome, it should be taken into account when planning treatment.

Second, it was shown that although detection of FTD in childhood is clinically relevant, careful interpretation should be made. The absence or presence of FTD seemed to depend highly on which measure was used. In my opinion, it is not the case that the clinician is unable to make a good judgment of FTD, but it is important to realize that different clinicians or FTD measurements might show different results, and therefore miscommunication about what is considered as FTD may play a role in clinical practice. To increase awareness and reliability of FTD ratings, it may be possible to set up inter rater reliability studies for groups of clinicians on a regular basis. Simple, short measurements of FTD should then be used. Also, it is important not to overestimate the clinical importance of the presence of FTD. FTD is only one aspect of psychosis, and the presence of FTD alone is not sufficient to assign a diagnosis of psychosis or childhood schizophrenia.

Further, it would be useful to rate the presence of MCDD symptoms in clinical practice, irrespective of the presence of a PDD. Children who fulfill criteria for MCDD should not necessarily receive a DSM-IV classification of PDD-NOS. It is also be possible that they, for instance, receive a classification of ODD, and meet criteria for MCDD.

Third, clinical implications can be drawn from the finger length studies. Although finger length ratio should never be used alone to classify children with psychiatric disorders, it could be used as an additional measurement. As a measurement of the level of testosterone the fetus was exposed to, finger length ratio provides us with an insight in hormonal effects in the etiology of different disorders. It's a very quick, easy and non-in-

vasive biological measure to acquire at any given time during clinical practice. Different psychiatric disorders seemed to be characterized by different finger length ratios, and, particularly for girls, a low ratio could be used as a diagnostic predictor of autistic behavior. It is therefore recommended to include finger length measurements more routinely in clinical practice.

Recommendations for future studies

Some of the recommendations described below apply to all studies described in this thesis, and others are more specific to one or two of the studies.

First, children from only one outpatients' department were included which may have limited the generalizability of the results. A university outpatients' department of child and adolescent psychiatry is generally not the first mental health service that children with psychiatric problems are referred to. Therefore, the current study samples may not have been representative of their target populations. For instance, it is possible that the children with PDD-NOS in our samples represented the cases with the higher intelligence levels and therefore we should be careful to conclude that children with PDD-NOS in general have IQ scores in the average range. Also, if less severe cases were included in our PDD-NOS samples, it is possible that estimates of co-morbidity were higher than average. Thus, in the future, multi-center studies in possibly more representative samples are needed to test the present study's findings.

Second, more studies of intelligence profiles in children with PDD-NOS should be carried out to establish whether our findings can be replicated. In these future studies, larger comparison groups of children with autism and Asperger syndrome should be included, as well as children with other psychiatric disorders than PDDs. Also, children of different age groups should be included as our study only investigated intelligence profiles in school-aged children with PDD-NOS.

Third, for future studies in children with PDD-NOS, standardized criteria for PDD-NOS should always be used. PDD-NOS is regarded as the most complex diagnosis to make within the autistic spectrum, PDD-NOS is difficult to differentiate from autism, and inter rater reliability of a diagnosis of PDD-NOS is low. These aspects may improve by using standardized criteria. Also, samples of children with PDD-NOS may vary across different sites and countries. The research criteria used in our study to classify PDD-NOS were considered reliable and standardized, but were nevertheless developed mainly by Dutch authors and are not necessarily used at other national or international sites. To be able to compare future studies from different institutions, it is important that the same criteria for PDD-NOS are used.

Fourth, the same applies to MCDD research criteria. MCDD is not an official DSM-classification and therefore different sets of criteria might be used in different settings and countries. To be able to compare studies of children with MCDD from different sites, the same criteria should be used. Further, considering MCDD as a disorder that can be delineated from PDD-NOS has research implications. The symptoms covered by MCDD may occur in combination with a variety of psychiatric disorders, not only PDDs, and therefore, children who fulfill criteria of MCDD should not only be selected from a group of children with PDD-NOS, but also from children with other PDDs or other psychiatric classifications.

Fifth, finger length ratio has been related to a variety of medical, psychological, and psychiatric traits and therefore one should be careful about drawing conclusions about the specificity of findings in this field. Also, when comparing children with different psychiatric disorders, very large groups should be included. The differences between groups are likely to be very small and will only be detected when large numbers of children are included. Further, it is recommended that future studies also assess other ratios, not only the 2D:4D ratio, but for instance the 2D:3D ratio, or the 3D:5D ratio. Last, findings of finger length ratio should be interpreted with caution as they are based on the assumption that the 2D:4D ratio reflects the exposure of the fetus to testosterone. This ratio however, is only an indirect measurement of prenatal testosterone. It might, for instance, also be possible that the 2D:4D ratio reflects underlying early fetal abnormal brain development rather than simply that testosterone may influence behavior.

Finally, more longitudinal studies are needed to test some of the present study's findings. If for instance, a large percentage of children with MCDD develop psychotic disorders, schizophrenia, or personality disorders in adult life, this would provide us with information about the etiology and prognosis of children with MCDD. Furthermore, finger length studies can be carried out at a very early age, and hypothetical predictions could be made for development of psychiatric behaviors in the future. Currently, only associations are found between finger length ratio and psychiatric traits, but correlations are of a bidirectional nature. To obtain evidence for the causality between the 2D:4D ratio and the development of psychiatric behaviors, follow-up studies are required.

Conclusion

The main findings of the studies described in this thesis can be summarized as follows. First, knowledge about children with PDD-NOS is acquired with this study. On a behavior level it was demonstrated that the majority of these children suffer from co-morbid psychiatric disorders. On a cognitive level it was found that children with PDD-NOS do not show VIQ – PIQ differences as sometimes seen in autism and Asperger syndrome.

With respect to the biological level, it was found that boys with PDD-NOS show similar finger length patterns as boys with autism or externalizing disorders, and that they differ from boys with anxiety disorders. In girls we found an association between autistic features and a low finger length ratio.

Second, this study provided more information about the dimensions of social contact problems as seen in pervasive developmental disorders, and thought disorders. It was demonstrated that children with MCDD can be distinguished from those with PDD-NOS, whereas before these children were usually classified as PDD-NOS. In children with MCDD the emphasis lies on thought disorders whereas in children with PDD-NOS the emphasis lies on social contact and communication problems. However, we also showed that the clinician's judgment and objective assessment do not necessarily agree on what should be considered as formal thought disorder.

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Summary

Summary

The objective of the studies described in this dissertation was threefold. In *Chapter 1*, the main aims were presented. First, the aim was to provide more information about children with PDD-NOS, from a behavioral, as well as from a cognitive perspective. Due to the lack of explicit, standardized criteria, this large and heterogeneous group of children has not been studied much before. The specific aims of this part of the study were (1) to assess the rate of co-morbid psychiatric disorders in children with PDD-NOS, and (2) to investigate intelligence profiles in children with PDD-NOS. The second aim of this dissertation was to get a better understanding of what is considered as FTD, and how thought disorders play a role in children with social contact problems. Special attention was paid to children with MCDD, who suffer from impairments in social contact as well as from thought disorders. More specifically, (3) the association between a standardized research based measurement and the clinician's judgment of FTD was assessed, and (4) an attempt was made to delineate children with PDD-NOS from those with MCDD. The third aim of this dissertation was based on a biological point of view. The role of finger length ratios in child psychiatric samples was studied. Previous studies associated finger length measures with a variety of somatic diseases, or psychological traits in normal samples, but psychiatric samples were not yet studied as much. Therefore, the aims of this part of the study were (5) to compare finger length ratios in school-aged children with different child psychiatric disorders, and (6) to correlate finger length ratios with autistic features in a child psychiatric sample.

In *Chapter 2*, rates of co-morbid psychiatric conditions were assessed in 94 children with PDD-NOS, aged 6-12 years. PDD-NOS was assigned by using explicit, valid, and reliable research criteria and the DISC-IV was administered to the parent(s)/caretaker(s) to evaluate DSM-IV diagnoses. More than 80% of the children had at least one co-morbid disorder, of which disruptive behavior disorders occurred most frequently, followed by anxiety disorders. Associated symptoms are often more responsive to treatment than the core deficits in social interaction and communication. It was therefore concluded that, clinical assessment of children with PDD-NOS should include assessment of co-morbid psychiatric symptoms or disorders.

In *Chapter 3*, intelligence profiles were studied in 76 children with PDD-NOS, 13 with autism and 11 children with Asperger syndrome. Children were aged 6-12 years. The WISC-R was administered and PDD-NOS was diagnosed using explicit, valid, and reliable research criteria. Children with PDD-NOS showed no difference between their VIQ and PIQ as seen in previous studies of children with autism or Asperger syndrome. Further, children with PDD-NOS showed overall subtest scores in the average range, and, compared to the other Kaufman factors, they had a lower score on the Freedom from Dis-

tractibility factor. In our sample it was not possible to distinguish children with PDD-NOS from those with autism or Asperger syndrome by using IQ scores.

In *Chapter 4*, the clinician's rapid judgment of FTD was compared to the detailed and time consuming ratings of the K-FTDS, in 172 children, aged 6-12 years. Clinicians rated the same DSM-criteria of FTD as were used in the K-FTDS (illogical thinking, loose associations, incoherence, and poverty of content of speech). Overall agreement between K-FTDS scores and FTD scores as rated by the clinician was low. It was concluded that although detecting FTD has important clinical value, all the more because the presence of FTD in childhood can be a possible forerunner of psychotic symptoms later in life, the presence or absence of FTD seemed to depend highly on which measure was used.

In *Chapter 5*, the aim was to delineate children, aged 6-12 years, with MCDD from those with PDD-NOS based on behavioral variables. Twenty-five children with MCDD and 86 children with PDD-NOS were compared with respect to psychiatric co-morbidity, psychotic thought problems and social contact problems, using the CBCL/4-18, the DISC-IV, the CAFAS, and the ADOS-G. Children with MCDD showed more anxiety disorders, disruptive behavior, and thought problems, whereas children with PDD-NOS were characterized by deficits in social contact. Currently, MCDD is not a DSM-classification, but is usually classified under PDD-NOS, due to its early onset, social deficits, and pervasive character. However, it was concluded from this study that MCDD should be delineated from PDD-NOS, and that MCDD might co-occur with other child psychiatric disorders as well.

In *Chapter 6*, the 2D:4D ratios of boys, aged 6 – 14 years, with DSM-IV autism/Asperger syndrome (n = 24), PDD-NOS (n = 26), ADHD/ODD (n = 68), and anxiety disorders (n = 26), were compared with each other and with control boys (n = 96). Boys with autism/Asperger syndrome, ADHD/ODD, and boys with PDD-NOS to a lesser extent, had lower ratios than boys with an anxiety disorder, and control boys. It is often presumed that a low 2D:4D ratio is associated with high fetal testosterone levels and that these high levels could play a role in the etiology of autism. It was concluded from our study that high fetal testosterone levels may play a role not only in the origin of autism, but also in the etiology of PDD-NOS, and ADHD/ODD. Further, it was concluded that boys with anxiety disorders, who showed relatively high 2D:4D ratios, may have been exposed to lower prenatal testosterone levels.

In *Chapter 7*, the association between autistic features and 2D:4D ratio was assessed in a child psychiatric sample (n = 35 girls and n = 147 boys). Autistic features were assessed with the ADOS-G. Particularly in girls, negative correlations were found. A low 2D:4D ratio in girls was highly correlated with the presence of autistic features. Deficits in social interaction and communication have been associated with low 2D:4D ratios in normal children before. From this study it was concluded that this association was also

present in a child psychiatric sample, and more importantly, in clinical practice, a low 2D:4D ratio could be used as a diagnostic predictor of autistic features in girls.

In *Chapter 8*, the main findings and conclusions of this dissertation were discussed. First, the present study showed that the majority of children with PDD-NOS suffer from co-morbid psychiatric disorders, and that they don't show VIQ-PIQ differences as sometimes seen in children with autism and Asperger syndrome. Further, boys with ADHD/ODD, and boys with PDD-NOS to a lesser extent, showed low finger length ratios, similar to boys with autism/Asperger syndrome. Thus, testosterone might play a similar role in the etiology of autism, Asperger syndrome, PDD-NOS, ADHD and ODD. In girls an association between autistic features and a low finger length ratio was found. This indicated that a low finger length ratio could possibly be used as a diagnostic predictor in girls from a psychiatric sample. Second, this study combined assessment of social contact and communication problems, as well as thought disorders. It was demonstrated that children with MCDD can be distinguished from those with PDD-NOS, whereas before these children were usually classified under PDD-NOS. Children with MCDD were characterized by thought problems, whereas children with PDD-NOS were characterized by impairments in social contact and communication. However, it was also found that the clinician's judgment and objective assessment do not necessarily agree on what should be considered as FTD. What is considered as FTD seemed to depend highly on which measurement was used.

Samenvatting

Samenvatting

De doelstellingen die zijn beschreven in dit proefschrift waren drieledig. In *hoofdstuk 1* werden deze drie hoofddoelstellingen toegelicht.

Het eerste doel was om meer informatie over kinderen met PDD-NOS te verschaffen, zowel vanuit een gedragsmatig als ook vanuit een cognitief perspectief. Mede vanwege een gebrek aan expliciete, gestandaardiseerde criteria, is deze grote, heterogene groep kinderen eerder nog niet veel onderzocht. De specifieke doelstellingen binnen dit eerste deel van het onderzoek waren (1) het in kaart brengen van de frequentie van voorkomen van comorbide psychiatrische stoornissen in kinderen met PDD-NOS en (2) het in kaart brengen van intelligentieprofielen van kinderen met PDD-NOS.

Het tweede doel van dit proefschrift was om een beter begrip te verkrijgen van wat verstaan wordt onder formele denkstoornissen en hoe deze een rol spelen in kinderen met problemen in het sociale contact. Hierbij werd specifiek aandacht besteed aan kinderen met MCDD die lijden aan zowel gebreken in het sociale contact als ook aan denkstoornissen. De specifieke doelstellingen binnen dit tweede deel van het onderzoek waren (3) het onderzoeken van de associatie tussen een gestandaardiseerd onderzoeksinstrument en het oordeel van de clinicus wat betreft de aanwezigheid van denkstoornissen en (4) het onderscheid maken tussen kinderen met PDD-NOS en MCDD.

Het derde doel van dit proefschrift was meer gebaseerd op een biologisch perspectief. De rol van vingerlengte ratio in kinderpsychiatrische samples werd bestudeerd. Eerdere studies lieten associaties tussen vingerlengte ratio en somatische aandoeningen of psychologische kenmerken in normale populaties zien, maar in hoeverre deze associaties ook aanwezig waren in kinderen met psychiatrische stoornissen was nog niet onderzocht. De specifieke doelstellingen binnen dit laatste deel van het onderzoek waren (5) het vergelijken van vingerlengte ratio van kinderen met verschillende psychiatrische stoornissen in de basisschoolleeftijd en (6) het correleren van vingerlengte ratio aan autistische kenmerken in een kinderpsychiatrisch sample.

In *hoofdstuk 2* werd de frequentie van verschillende comorbide psychiatrische stoornissen in kaart gebracht bij 94 kinderen met PDD-NOS, variërend in leeftijd van 6 tot en met 12 jaar. PDD-NOS werd gediagnosticeerd door gebruik te maken van expliciete, valide en betrouwbare onderzoekscriteria en de DISC-IV werd afgenomen bij de ouder(s)/verzorger(s) om de DSM-IV diagnoses in kaart te brengen. Meer dan 80% van de kinderen voldeed aan de criteria voor tenminste één comorbide diagnose, waarvan disruptieve gedragstoornissen het meeste voorkwamen, gevolgd door angststoornissen. Geassocieerde symptomen zijn vaak beter te behandelen dan de kernproblemen als beperkingen in de sociale interactie en communicatie. Daarom werd geconcludeerd dat tijdens klinisch onderzoek bij kinderen met PDD-NOS, altijd gekeken moet worden naar comorbide psychiatrische symptomen of stoornissen.

In *hoofdstuk 3* werden intelligentieprofielen van 76 kinderen met PDD-NOS, 13 kinderen met een autistische stoornis en 11 kinderen met de stoornis van Asperger in kaart gebracht. Alle kinderen hadden een leeftijd van 6 tot en met 12 jaar. De WISC-RN werd afgenomen en PDD-NOS werd gediagnosticeerd met behulp van expliciete, valide en betrouwbare onderzoekscriteria. Kinderen met PDD-NOS lieten geen contrast zien tussen hun VIQ en PIQ, zoals in eerdere studies van kinderen met een autistische stoornis of de stoornis van Asperger vaak wel getoond werd. Verder behaalden kinderen met PDD-NOS in het algemeen subtestscores in de gemiddelde range en hadden ze een lagere score op de Afleidbaarheidsfactor vergeleken bij de andere Kaufmanfactoren. Het was binnen ons onderzochte sample niet mogelijk om kinderen met PDD-NOS te onderscheiden van kinderen met een autistische stoornis of de stoornis van Asperger gebaseerd op IQ scores.

In *hoofdstuk 4* is, in een groep van 172 kinderen, 6 tot en met 12 jaar, het oordeel van de clinicus wat betreft de aanwezigheid van formele denkstoornissen vergeleken met de gedetailleerde en tijdrovende scores van de K-FTDS. Clinici werd gevraagd om dezelfde DSM-criteria van formele denkstoornissen te scoren als werden gebruikt binnen de K-FTDS (onlogisch denken, losse associaties, incoherentie en spraakarmoede). De overeenkomst tussen scores van de K-FTDS en de clinicus was laag. Er werd geconcludeerd dat hoewel detectie van formele denkstoornissen van groot klinisch belang is, te meer omdat de aanwezigheid ervan in de kindertijd een mogelijke voorspeller is van latere psychotische symptomen, de aan- of afwezigheid van formele denkstoornissen af lijkt te hangen van welk meetinstrument gebruikt werd.

Het doel van *hoofdstuk 5* was om kinderen, van 6 tot en met 12 jaar, met MCDD te onderscheiden van kinderen met PDD-NOS op basis van gedragsvariabelen. Vijfentwintig kinderen met MCDD en 86 kinderen met PDD-NOS werden vergeleken wat betreft psychiatrische comorbiditeit, psychotische denkproblemen en problemen in het sociale contact. Hierbij werden de CBCL/4-18, de DISC-IV, de CAFAS en de ADOS-G gebruikt. Kinderen met MCDD lieten meer angststoornissen, disruptief gedrag en psychotische denkproblemen zien, terwijl kinderen met PDD-NOS meer gekarakteriseerd werden door problemen in het sociale contact. Op dit moment is MCDD geen DSM-classificatie en wordt het beeld veelal geclassificeerd onder PDD-NOS vanwege de vroege onset, de sociale gebreken en het pervasieve karakter. Echter, uit deze studie kan geconcludeerd worden dat onderscheid gemaakt moet worden tussen MCDD en PDD-NOS en dat MCDD ook samen met andere kinderpsychiatrische stoornissen kan voorkomen.

In *hoofdstuk 6* werden de 2D:4D ratios van jongens, in de leeftijd van 6 tot en met 14 jaar, met DSM-IV diagnoses autistische stoornis/stoornis van Asperger ($n = 24$), PDD-NOS ($n = 26$), ADHD/ODD ($n = 68$) en angststoornissen ($n = 26$) met elkaar vergeleken, en de ratios werden vergeleken met die van controlejongens ($n = 96$). Jongens met een autistische stoornis/stoornis van Asperger, ADHD/ODD en jongens met PDD-NOS in mindere

mate, hadden lagere ratios dan jongens met een angststoornis en controlejongens. Vanuit eerder onderzoek werd verondersteld dat een lage 2D:4D ratio geassocieerd is met een hoog niveau van prenataal testosteron en dat dit hoge testosteronniveau een rol speelt in de etiologie van autisme. Uit deze studie werd geconcludeerd dat een hoog prenataal testosteron niveau niet alleen in de origine van autisme een rol kan spelen, maar ook in de etiologie van ADHD/ODD en PDD-NOS. Verder werd geconcludeerd dat jongens met angststoornissen, die een relatief hoge 2D:4D ratio hadden, mogelijk bloot hebben gestaan aan lagere prenatale testosteron niveaus.

In *hoofdstuk 7* werd de associatie tussen autistische kenmerken en de 2D:4D ratio in een kinderpsychiatrisch sample onderzocht (n = 35 meisjes en n = 147 jongens). Autistische kenmerken werden meetbaar gemaakt met behulp van de ADOS-G. Een lage 2D:4D ratio in meisjes was sterk gecorreleerd met de aanwezigheid van autistische kenmerken. Beperkingen in de sociale interactie en communicatie zijn al eerder geassocieerd met lage 2D:4D ratios in normale kinderen. Uit deze studie kan geconcludeerd worden dat deze associatie ook aanwezig is in een kinderpsychiatrisch sample, en nog belangrijker, dat in de klinische praktijk een lage 2D:4D ratio mogelijk gebruikt kan worden als diagnostische predictor voor autistische kenmerken bij meisjes.

In *hoofdstuk 8* werden de belangrijkste bevindingen en conclusies uit dit proefschrift beschreven. Ten eerste toonde huidig onderzoek aan dat de meerderheid van de kinderen met PDD-NOS lijdt aan comorbide psychiatrische stoornissen en dat deze kinderen geen verschil tussen hun VIQ en PIQ laten zien, zoals soms wel gezien wordt bij kinderen met een autistische stoornis of de stoornis van Asperger. Verder hadden jongens met ADHD/ODD vergelijkbare lage vingerlengte ratios als jongens met een autistische stoornis/stoornis van Asperger of met PDD-NOS. Dus, mogelijk speelt testosteron een overeenkomstige rol in de etiologie van autisme, de stoornis van Asperger, ADHD, ODD en PDD-NOS. Bij meisjes werd een associatie tussen autistische kenmerken en een lage vingerlengte ratio gevonden. Deze bevinding geeft aan dat een lage vingerlengte ratio mogelijk als diagnostische predictor gebruikt kan worden bij meisjes in een psychiatrische groep. Ten tweede werden in huidig onderzoek studies naar de dimensies sociaal contact en communicatieproblemen gecombineerd met studies naar denkstoornissen. Er werd getoond dat kinderen met MCDD onderscheiden kunnen worden van kinderen met PDD-NOS terwijl kinderen met MCDD voorheen meestal werden geclassificeerd onder PDD-NOS. Kinderen met MCDD werden gekenmerkt door denkproblemen en kinderen met PDD-NOS door beperkingen in het sociale contact en de communicatie. Echter, ook werd gevonden dat het oordeel van een clinicus over het aanwezig zijn van formele denkstoornissen niet altijd overeenkomt met de scores van een objectief meetinstrument voor denkstoornissen. Wat werd verstaan onder formele denkstoornissen leek sterk af te hangen van welke maat gebruikt werd.

Dankwoord

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Zonder de grote bereidheid van ouders en kinderen om aan dit onderzoek deel te nemen was dit onderzoek niet mogelijk geweest. Ik wil hen dan ook allemaal bedanken. In totaal werd er bij ouders en kinderen bijna 10 uur aan testmateriaal verzameld. Dit vroeg niet alleen een grote bereidwilligheid van ouders en kinderen, maar ook een aantal jaar keihard werken door vele studenten, stagiaires en onderzoeksassistenten. Het kwam bij medewerkers van dit onderzoek nooit voor dat ze even wat minder te doen hadden. Op de één of andere manier renden afstudeerstudenten, stagiaires en onderzoeksassistenten altijd verhit door de gang, van de ene naar de andere patiënt of van het ene naar het andere databestand. Ik vroeg veel van ze, maar het resultaat is er dan ook naar. Vele goede scripties zijn er geschreven en binnen twee jaar tijd waren alle testresultaten verzameld, verwerkt en zelfs deels geanalyseerd. In het bijzonder wil ik de volgende studenten bedanken: Lucy de Vries, Boukje Haas, Michiel van der Hout, Sieds Dieleman, Carlien Bos, Esther van der Vegt, Debora Verhagen en Wendy van Dorp. Daarnaast wil ik Tamar Wiegman, Sjifra Meester en Janine Driessen apart bedanken voor hun hulp tijdens het onderzoek. Tamar, inmiddels heb ik al vele jaren met jou samengewerkt en jouw nauwkeurigheid, kalmte en 'speurneuzentalent' hebben bijgedragen aan dit proefschrift. Sjifra, met jou heb ik ongeveer alle varianten van samenwerken doorlopen; onderzoek, diagnostiek, SoVa trainingen, vele treinreizen tussen Amsterdam en Rotterdam en nu de GZ-opleiding in Leiden. Ik waardeerde ook jouw precisie, doorzettingsvermogen en zelfstandigheid tijdens de soms eindeloos lang lijkende dataverzameling en verwerking.

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Curriculum Vitae

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Esther Irene de Bruin werd geboren op 23 juli 1974 te Bussum. In 1993 behaalde zij het VWO diploma op R.S.G. Broklede te Breukelen. Na een jaar gereisd en gewerkt te hebben in Israël begon zij haar studie psychologie in 1994 aan de Universiteit van Amsterdam. Zij studeerde in 2000 cum laude af in de richtingen Psychonomie en Klinische Psychologie. Tevens behaalde zij de specialisatie Klinische Psychobiologie en Neuropsychologie en de basisaantekening Psychodiagnostiek van het Nederlands Instituut voor Psychologen (NIP). Een praktijkstage werd voltooid aan het State Child Development Centre te Perth, Australië en gefinancierd vanuit beurzen van het Hendrik Muller Vaderlandsch Fonds, het Freederik van Eeden fonds en een VSB-Talenten beurs. Het doctoraalonderzoek werd uitgevoerd in het AMC en in het VU ziekenhuis te Amsterdam.

Tijdens en na haar studie was zij werkzaam als supervisor bij call center ITM Research te Amsterdam, als psycholoog i.o. bij stress management bureau Delahay & Van der Pool te Amsterdam en als neuropsycholoog op de revalidatieafdeling voor CVA patiënten, van het Gulden Huis te Den Haag.

Vanaf november 2000 is zij aangesteld als psycholoog op de afdeling Kinder- en Jeugdpsychiatrie van het Erasmus MC-Sophia Kinderziekenhuis/Erasmus Universiteit Rotterdam. Zij werkte als onderzoekscoördinator mee aan de Genetic Research in Isolated Populations (GRIP) studie en was nauw betrokken bij het opzetten van eigen promotieonderzoek en het schrijven van de bijbehorende ZonMw subsidieaanvraag. Vanaf juli 2002 tot en met december 2004 werkte zij halftime als onderzoeker aan haar dataverzameling en halftime als psychodiagnosticus in het poliklinische team voor pervasieve ontwikkelingsstoornissen. In 2005 werkte zij vrijwel fulltime als onderzoeker aan haar promotieonderzoek (projectleiders Prof.dr. F. Verheij en Dr. R.F. Ferdinand), waarvan de resultaten in dit proefschrift beschreven staan.

Sinds januari 2006 volgt zij de opleiding tot gezondheidszorg (GZ-) psycholoog met als opleidingsplaats de Universiteit van Leiden (hoofdopleider Dr. E.H.M. Eurelings-Bontekoe) en als praktijkplaatsen de polikliniek Kinder- en Jeugdpsychiatrie en de adolescentenkliniek (praktijkopleider Drs. E.W.C. Aendekerk) van het Erasmus MC-Sophia Kinderziekenhuis.