Exploring the labyrinth of the brain

Neurobiological parameters in Multiple Complex Developmental Disorder, a subtype of the Pervasive Developmental Disorder-Not Otherwise Specified

Bertine Enrica Lahuis

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Neurobiological parameters in Multiple Complex Developmental Disorder, a subtype of the Pervasive Developmental Disorder-Not Otherwise Specified

Onderzoek naar het labyrint van het brein

Neurobiologische parameters in MCDD, een subtype van PDD-NOS
(met een samenvatting in het Nederlands)

Proefschrift

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Aan mijn ouders
Aan Jord, Jeppe & Maaike

Table of content

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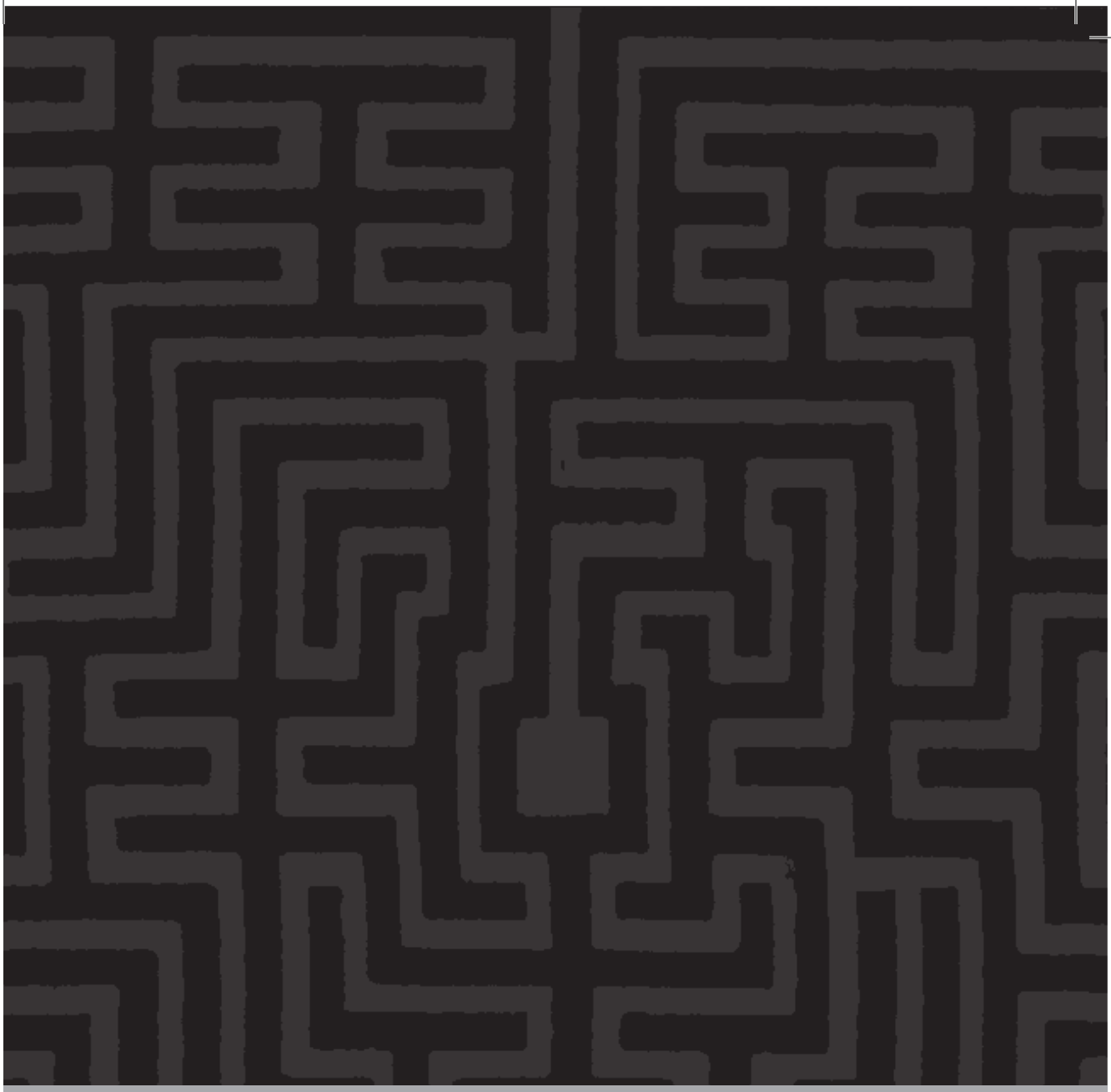


Introduction

In 1943 Leo Kanner was the first who reported on children with autism (Kanner, 1943). He described eleven children with "autistic disturbances of affective contact". Kanner suggested that early infantile autism was an inborn, constitutional disorder; children were born lacking the usual motivation for social interaction (Kanner, 1943). The word autism he used was borrowed from the field of schizophrenia where Bleuler (1950) used autism to describe idiosyncratic, self-centered thinking that led to autistic withdrawal into a private fantasy world (Volkmar et al., 1997). The sharing of the term increased early confusion about the relationship between the two conditions. The severity of the autistic syndrome, the assumed psychosis of afflicted children, and the confusion entailed by the use of the word autism led some clinicians in the 1950s to speculate that autism was the earliest form of schizophrenia (Bender, 1947; Kanner, 1949). In the first and second editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 1952, 1968), only the term childhood schizophrenia was officially available to describe autistic children. Research on this issue was hampered by the lack of consensus on the classification of severe childhood disorders. In the seventies the studies of Rutter and Kolvin gave support to distinghuish autism from schizophrenia (e.g. on organic co-morbidity, symptomatology, age of onset, IQ scores and family history of schizophrenia) and since that time both were seen as two distinct disorders (Rutter et al., 1967a&b; Rutter, 1972; Kolvin et al., 1971a&b).

In 1980 the term autism was officially recognized by including it in the third edition of the DSM (American Psychiatric Association, 1980), as infantile autism under the pervasive developmental disorders. Autism is now defined as a developmental disability with onset in infancy. Its clinical presentation is characterised by impairments in reciprocal social interaction and in communication with others, and by a preference for repetitive, stereotyped behaviours (Szatmari, 2003). It's a life-long illness, with mental retardation in many cases. In the DSM-III the term atypical Pervasive Developmental Disorder could be used if the child did not meet all the criteria for infantile autism. In the DSM-III-R the term Pervasive Developmental Disorder Not Otherwise Specified was introduced to diagnose patients who did not full fill all the criteria for autistic disorder, next to Rett's disorder and Childhood Desintegrative Disorder. In the DSM-IV the classification Asperger's disorder was added (American Psychiatric Association, 1994).

Schizophrenia is a clinical syndrome with peak onset in late adolescence / young adulthood or in rare cases in (very) early childhood, whose symptoms are manifest in multiple domains of behaviour, language, thought, and affect (Cannon et al., 2002). For a reliable diagnosis of schizophrenia in children, the criteria of schizophrenia for adults were (and still are) used (Eggers et al., 2000). Central are the psychotic symptoms (delusions and hallucinations), disorganized speech and behaviour, and / or the negative symptoms (affective flattening, alogia, or avolition). In general it

is a chronic and disabling disease, frequently leading to deterioration. Childhood-onset schizophrenia (onset of psychosis by age 12) is a severe illness that is clinically and neurobiologicaly continuous with the adult disorder (Jacobsen and Rapoport, 1998; Nicolson and Rapoport, 1999).

Although from the seventies on autism and schizophrenia are seen as different psychiatric disorders, the debate on a possible relationship is continuing. There have been reports on autistic features as premorbid characteristics in (childhood-onset) schizophrenia (COS) (Asarnow et al., 1988, 1995; Done et al., 1994; Hollis, 1994, 1995; Jones et al., 1994; Olin and Mednick, 1996; Olin et al.,1998; Cannon et al., 1999, 2002; Eggers et al., 2000; Nicolson et al., 2000 a&b), a co-morbid Pervasive Developmental Disorder (PDD) diagnosis in COS patients (Sporn et al., 2004), a (co-morbid) diagnosis of schizophrenia in (the follow-up) of PDD patients (Konstantareas and Hewitt, 2001; Stahlberg et al., 2004; Bölte and Bosch, 2005; Mouridsen et al., 2007), and a higher risk of autism in patients with a parental psychiatric history of schizophrenia (Larsson et al., 2005). From these studies it can be concluded that a possible relationship between autism and schizophrenia, which was denied earlier (Volkmar and Cohen, 1991), should be reconsidered. Simultaneously it has become clear that both disorders are neurobiological from origin (although the aetiology is still lacking) and manifest themselves with very heterogeneous clinical phenotypes which is also partly reflected in the DSM by the different subtypes for autism and schizophrenia (Volkmar and Pauls, 2003; Mueser and McGurk, 2004).
Research on the overlap between Schizophrenia Spectrum Disorders and Autism Spectrum Disorders (ASD) has been hampered due to different reasons. First there was the conceptual discussion on autism and schizophrenia (as described above), whereby for research strictly classified and distinguishable groups are needed. Second, there is a hierarchical approach in making the diagnosis of PDD and schizophrenia or adult personality disorders: a diagnosis of PDD pre-empting a diagnosis of the last. And the same problem arises for schizophrenia: although a diagnosis of schizophrenia is possible in case of prominent delusions or hallucinations, schizophrenia pre-empts a diagnosis of autism or PDD-NOS (Clarke et al., 1989; American Psychiatric Association 2000). Third, adult psychiatrists in general are less familiar with autistic spectrum disorders and will focus more, within this group of patients, on a diagnosis within the schizophrenia spectrum. Fourth, making a correct diagnosis of hallucinations and/or delusions in young children is difficult, especially in low-functioning children who hardly verbalize (which is the case for many autistic children) (Petty et al., 1984; Bettes and Walker, 1987; Konstantareas and Hewitt, 2001).

Regarding the issue of a possible overlap between autism and schizophrenia, the Multiple Complex Developmental Disorders (MCDD) and Multi Dimensionally Impaired (MDI) patient groups are of interest. Both are more or less diagnostic homeless groups (many MCDD patients are given the Pervasive Developmental Disorder -Not Otherwise Specified [PDD-NOS] label, MDI patients do formally have the Psychotic Disorder- Not Otherwise Specified [PD-NOS] label) (Towbin et al., 1993; Van der Gaag et al., 1995; Kumra et al., 1998). There is an overlap in diagnostic criteria for both disorders, both revealing characteristics of social (autistic) and cognitive (schizophrenia) deficits (Paul et al., 1999). This thesis will focus on the MCDD group of patients.

Multiple Complex Developmental Disorder (MCDD)

Individuals diagnosed with Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) are characterized by the same set of impairments as for autistic disorder, but fail to meet the full criteria for autism and are therefore, often considered to have a milder variant of the disorder. The boundaries between PDD-NOS and other developmental disorders are poorly defined and unarticulated. PDD-NOS refers to a very heterogenous group of patients, as has recently been illustrated by De Bruin et al. (De Bruin et al., 2007a). Although PDD-NOS is supposedly a residual category of autism, epidemiological studies have shown that the prevalence of PDD-NOS has risen and outnumbers autism by up to three times (Wing and Could 1979; Fombonne 2003, 2005; MMWR Surveill Summ 2007) supporting the need for defining subtypes. Perhaps the best defined and validated PDD-NOS subgroup to date is Multiple Complex Developmental Disorder (MCDD) (Towbin et al., 1993; Van der Gaag et al., 1995; Buitelaar and Van der Gaag, 1998; Ad-Dab'bagh and Greenfield, 2001). The MCDD child is having difficulties in regulating affects: outbursts of aggression and anger, panic attacks and bizarre anxiety reactions and showing huge problems in social interactions, and frequently revealing ambivalent reactions to their care givers. They have difficulties to keep their thoughts straight, and confuse reality and fantasy. Of importance is the fluctuation of the described abnormal behaviour, with moments of regression which can last from minutes to days. Most of these children are severely impaired and frequently require inpatient, day-hospital, or residential care in a child psychiatric setting (Ad-Dab'bagh and Greenfield 2001). Numbers up to 25% of the hospitalised childpsychiatric population, in for example the Netherlands, have been mentioned (Van der Gaag 1993). Different diagnostic or descriptive terms were used for this patient group (see for an overview thesis of Van der Gaag 1993). This category includes children previously diagnosed as: A-typical personality development (Rank 1949, 1955; Brown 1960), symbiotic psychosis (Mahler 1952), borderline disorders (Robson 1983), childhood schizophrenia (Bender 1942; Fish 1968), schizoid personality

(Wolff and Barlow 1979) and within the DSM-III-R, schizotypal personality, childhood onset PDD or atypical PDD (Geller 1981) (See also thesis of Van der Gaag 1993). It was left open whether all cases with a proposed MCDD should be placed within the PDD category and considered as nonautistic PDDs. The following criteria were proposed (Cohen et al 1987; Cohen et al., 1991 revised version; Towbin et al., 1993 modified criteria):

Diagnostic Criteria for Multiple Complex Developmental Disorder (according to Cohen et al., 1987):

MCDD is a serious, early onset and persistent disturbance affecting several major domains of functioning, including the following three major areas:

1. Regulation of affective state and anxiety is impaired beyond that seen in children of comparable age, as exemplified by several of the following: (at least two of the following)
   a) intense generalized anxiety or tension
   b) fears and phobias (often unusual and peculiar)
   c) recurrent panic episodes or 'flooding' with anxiety
   d) episodes of behavioral disorganization punctuated by markedly immature, primitive or violent behaviors
   e) significant and wide emotional variability with or without environmental precipitants.
   f) frequent idiosyncratic or bizarre anxiety reactions
2. Consistently impaired social behavior/sensitivity, as exemplified by the following types of disturbances: (at least two of the following)
   a) social disinterest, detachment, avoidence or withdrawal despite evident competence
   b) severely impaired peer relationships
   c) markedly disturbed attachments; high degrees of ambivalence to adults (esp.parents/ caretakers)
   d) profound limitations in the capacity for empathy or understanding others affects accurately
3. Impaired cognitive processing (thinking disorder), as exemplified by some of the following difficulties: (at least two of the following)
   a) irrationality, sudden intrusions on normal thought process, magical thinking, neologism or repetitions of nonsense words, desultory thinking, blatantly illogical, bizarre ideas
   b) confusion between reality and inner fantasy life
   c) perplexity and easy confusability (trouble with understanding ongoing social processes or keeping one's thoughts 'straight')
   d) 'delusions', over valued ideas including fantasies of omnipotence, paranoid preoccupations, overengagement with fantasyfigures, grandiose fantasy of special powers, and referential ideation
4. The syndrome appears during the first several years of life
5. The child is not suffering from autism or schizophrenia

These children all exhibit multiple, serious, early-onset disturbances in development. Compared to autism more psychotic thinking / anxiety, more aggression, more suspiciousness / odd interaction, less deficient interaction / communication, less stereotyped and rigid behavior, more fluctuations in level of functioning and disturbed attachments were found (Van der Gaag, 1993). This was underlined by a more recent study of De Bruin et al. (2007b), although in this study also MCDD, non-PDD patients were included. Beside the 2 studies on the definition and validity of the criteria of MCDD, which gave support for a separate subcategory of MCDD within the DSM (Towbin et al., 1993; Van der Gaag et al., 1995), interesting results came out of the follow-up study carried out by Van der Gaag (Van der Gaag, 1993; Van Engeland and Van Der Gaag, 1994), giving support to the discussion on a possible relationship between autism and schizophrenia.
In this follow-up study (44 adolescents with identified MCDD, 15 young adults diagnosed MCDD, respectively 43 and 12 participants for follow-up), a remarkable large percentage of schizophrenia spectrum disorders at follow-up, especially in the adult group (66%) was found (Van Engeland and Van der Gaag 1994).

Diagnosis at follow-up	Adolescent group (43 subjects)	Adult group (12 subjects)
Schizophrenia	0	2 (positive symptoms)
Schizotypal Personality Disorder	5	2
Schizoid Personality Disorder	5	4

The main focus of interest for this thesis is:
- if MCDD as an ASD subtype can be differentiated from other ASD subtypes on neurobiological parameters, and
- if these neurobiological parameters in MCDD are similar as found in schizophrenia, supporting MCDD as a represententive of a more close relationship between ASD and schizophrenia than earlier suggested, or if these parameters are more like what has been found in autism.

Biological research on MCDD

Studies on biological aspects of MCDD (defined as a subtype PDD-NOS) were carried out on event-related-potential (ERP) (Kemner et al., 1999), and on psychosocial stress (Jansen et al., 2000, 2003). Both studies revealed differences between MCDD and autism (Kemner et al., 1999, Jansen et al., 2003), and MCDD and typical controls (Jansen et al., 2000), supporting the concept of MCDD as a subtype within the ASD. In patients with schizophrenia, a similar decrease in response to psychosocial stress

was found (Jansen et al., 1998). Two other neurobiological studies were carried out, however they used a broader and different definition of MCDD (Lincoln et al., 1998; Herba et al., 2007).
In conclusion, the amount of research on MCDD is limited.

In furthering understanding of the PDD-NOS, MCDD subtype within the ASD group and the search for similarities with schizophrenia spectrum disorders three fields of research have been chosen to be of interest, namely (1) structural magnetic resonance imaging (sMRI), (2) neuropsychology, and (3) psychophysiology.

Structural Imaging

In the past years significant progress has been made in structural imaging studies of different psychiatric diagnosis, especially autism and schizophrenia. The main question in all these studies is whether the clinical features of the psychiatric syndrome are reflected in structural brain abnormalities. Evidence for structural abnormalities does help to evaluate different hypotheses on where and possibly when in the brain abnormal development occurs. For both (childhood-onset) schizophrenia and for autism many studies have been carried out.

For autism most studies show enlargements of the cerebral hemispheres, intracranial volume, cerebellum and (lateral) ventricles (reviews Palmen and Van Engeland 2004; Stanfield et al., 2007 and see chapter 2). The finding of enlargement is in line with the earlier results from post-mortem studies reporting megalencephaly, cortical thickening and an increase in cerebral neuronal density (Bailey et al., 1998).

For childhood-onset schizophrenia the most consistent findings are ventricular enlargement and reduced total brain volume (Sowell et al., 2000; Mehler and Warnke, 2002 and see chapter 2). In general, the differences were more marked in childhood-onset schizophrenia than in adolescence- or adult onset schizophrenia. For adult-onset schizophrenia similar deficits in gray matter volume, especially in frontal and temporal regions, along with increases in ventricular and sulcal size are found. Progressive degenerative changes (as in autism) – ventricular enlargement and atrophy of the total brain- seem to occur (Pearlson and Marsh 1999). These findings are in line with the post-mortem findings of reduced cerebral volume as a result of reduced neuropil and neuronal size (rather than a loss of neurons) and a lack of gliosis (Nasrallah et al., 1993; Weinberger et al., 1995).
As such, sMRI seems to be a useful method to investigate whether patients with MCDD show abnormalities similar to those found in schizophrenia or autism.

To date, there are no sMRI studies on directly comparing subjects with autism and subjects with schizophrenia.

Aim of the present sMRI study

It is hypothesized that if the MCDD patients will show changes similar to children with autism, in particular larger total brain volume and larger ventricles are expected. However, if MCDD does truly represent a neurobiologically distinct subtype of PDD, with an increased risk of psychosis, a decrease in total brain volume and larger ventricles would be expected (as are found in schizophrenia). An enlargement of ventricle volumes would be expected in both cases.

(Neuro)psychology:

For schizophrenia as well as for autism there is a broad agreement that both disorders produce impairments on a wide range of neuropsychological functions. Because of the heterogeneity of the clinical behavioural expressions of the illnesses ASD and Schizophrenia (Spectrum Disorders), the different methodologies used in all studies (age, IQ, instruments) and the lacking of sensitive neuropsychological tests across the range of functional domains, the results from the literature are complex and sometimes inconsistent.

For ASD neuropsychological problems in a wide range of domains are found: intelligence, attention, memory, language and executive functioning (EF). It has been suggested that severely affected patients tend to have lower IQ's, severely impaired language and memory impairments (Dawson, 1996).
Wechsler intelligence quotient scales show spiky profiles, with most subjects with autism showing peak performance on block design subtests (performance scales) and digit-span (verbal test) and worst performance on comprehension (subtest of the verbal measures) and picture arrangement (nonverbal subtest) (Happé and Frith, 1996). Special interest has arisen for EF. EF refers to higher order cognitive control processes, such as working memory, inhibition, planning, sustained attention, and attentional flexibility (Hughes et al., 1994; Akshoomoff, 2005). Although EF deficits have been asserted to be prominent in ASD (Penninton and Ozonoff 1996), the results are inconsistent (Pennington and Ozonoff, 1996; Geurts et al., 2004; Goldberg et al., 2005; Happé et al., 2006; Verté et al., 2006; Johnson et al., 2007) and are also characteristic of many other neurodevelopmental disorders (Pennington and Ozonoff, 1996). Research on differentiating within the spectrum on the basis of EF characteristics is limited (Verté et al., 2006).

For schizophrenia verbal memory functions, attention regulation and executive functioning have been reported as markedly impaired (Asarnow et al., 1994; Elliott and Sahakian, 1995; Heinrichs and Zakzanis, 1998; Hoff et al., 1999; Aleman et al.,

1999; Bilder et al., 2000; Goldstein et al., 2002). A review of findings reveals that the greatest mean effect sizes have been found for measures of global verbal memory, performance and full scale IQ, word fluency and Continuous Performance (Heinrichs and Zakzanis, 1998). Several studies pointed out that neurocognitive deficits (including deficits in general intellectual functioning, gross motor skills, attention, memory functions and executive functioning) are already present, and even sometimes identified as phenotypic indicator of a psychosis-proneness trait (especially the attentional problems) in preschizophrenic subjects and high-risk populations (Erlenmeyer-Kimling et al., 2000; Davalos et al., 2004; Yung et al., 2004; Mason and Beavon-Pearson, 2005).

In light of the prominent presence of disruptive behaviors and thought regulation problems observed in MCDD the reported signs of EF deficits in MCDD - such as extreme fluctuations in level of functioning, reduced attentional resource allocation, restricted ability to respond adequately to the environment or feedback, and impaired flexibility - likely candidate markers to delineate MCDD from PDD-NOS are neuropsychological measures of executive control and attention, i.e. inhibition, sustained attention, behavioral adaptation, and working memory (capacity).

To date, there are no neuropsychology studies on directly comparing subjects with autism and subjects with schizophrenia.

Aim of the present neuropsychology study

It is hypothesized that children with MCDD differ from children with PDD-NOS on executive functioning (tasks of inhibition, attention regulation, adaptive strategies to cope with informational feedback, and memory capacity). If substantial differences in these abilities would be revealed, there is further evidence for recognizing a PDD subcategory of MCDD. In addition it is expected that especially problems will be found on aspects of attention, which is known to be a vulnerability factor in schizophrenia.

Psychophysiology

Psychophysiology is another method for trying to discriminate between different psychiatric illnesses by a biological parameter. In psychophysiological research on schizophrenia three methods are regularly being used: smooth pursuit, startle (PPI) and P50 measurements.

Smooth Pursuit

During a smooth pursuit task eye tracking is recorded while subjects follow a target moving horizontally across a screen at a constant velocity. Smooth pursuit eye movement (SPEM), or smooth pursuit, is necessary to keep a moving stimulus projected onto the fovea. If an object is moving slowly, smooth pursuit is accurate. If the velocity of the object increases, smooth pursuit cannot compensate completely for the movement of the target. SPEM is roughly divided in two aspects: gain and frequency of saccades. Velocity gain is defined as mean eye velocity divided by target velocity. Saccades in general function to significantly reduce error between foveal gaze and target location and by that compensate for poor smooth-pursuit system performance.

For many years now SPEM abnormalities have been associated with (adult) onset schizophrenia. Reduced gain and increased frequency of saccades, are among the most consistent and reproducible abnormalities (Jacobsen et al., 1996; Ross et al., 1999, 2002, 2003; Kumra et al., 2001; Trillenberg et al., 2004). Even unaffected relatives of patients with schizophrenia show abnormalities in their smooth pursuit (Ross 2003). Patients with childhood-onset schizophrenia (COS) reveal the same and even a higher frequency of abnormalities which has been related to a higher genetic loading for COS (Ross et al., 1999).
For autism the amount of studies is limited. There have been two studies of SPEM in children with autism and in neither study abnormalities of pursuit gain were found (Kemner et al. 2004; Takarea et al. 2004).
Thereby SPEM seems to be a useful method to find out if patients with MCDD reveal abnomalities known to be associated with schizophrenia or no abnormalities as was found in children with autism.

To date, there are no SPEM studies on directly comparing subjects with autism and subjects with schizophrenia.

Aim of the present SPEM study

It is hypothesized that children with MCDD differ from children with autism on SPEM. If abnormalities as in schizophrenia (reduced gain and an increased frequency of saccades) are found in patients with MCDD, in contrast to no abnormalities for patients with autism and typical controls there is further evidence for recognizing a PDD subcategory of MCDD.

Startle

The startle reflex consists of a contraction of the skeletal and facial muscles in response to a sudden, relatively intense stimulus that may be presented across multiple modalities (visual, auditory, or tactile) (Braff et al., 2001). Prepulse inhibition (PPI) of the startle response refers to an attenuation in response to a strong stimulus (pulse) if this is preceded shortly (30-500 ms) by a weak non-startling response (prepulse). This weak prestimulus evokes inhibitory mechanisms, which presumably gate further stimulation until the processing of the prepulse has been achieved. The hypothesis is that this results in disrupted processing and reduced impact of the pulse, and hence the PPI effect. PPI thus serves the function of avoiding behavioural interference that might otherwise arise from the simultaneous processing of discrete stimuli. Excess or trivial stimuli are screened or "gated out" of awareness, so that an individual can focus attention on the most salient aspects of the stimulus-laden environment (Braff et al., 2001). Deficits in the ability to avoid such interference are thought to lead to sensory over-stimulation and behavioural confusion.

For autism spectrum disorders and PPI (auditory stimulus) the number of studies is limited. Three studies on startle response, including PPI, have been published (Ornitz et al., 1993; McAlonan et al., 2002, Perry et al., 2007). In adults with Asperger Syndrome and Autistic Disorder a reduced PPI compared to healthy controls, was found (McAlonan et al., 2002, Perry et al., 2007). Ornitz et al. (1993) reported no consistent significant differences between diverse groups of autism including children and adolescents, and a healthy control group.
For patients with schizophrenia, schizophrenia related disorders and unaffected relatives of patients with schizophrenia different studies have demonstrated impaired PPI (Braff et al., 2001; Kumari and Sharma, 2002; Swerdlow et al., 2006).

Advantage of startle research is that no tasks are involved, and so neither motivation nor significant cooperation is required. PPI occurs in all mammals, and it is not a form of conditioning, because it occurs on the first exposure to the combination of prepulse and pulse stimuli, and does not exhibit habituation or extinction over multiple trials (Braff et al., 2001).
Thereby PPI seems to be a useful method in children to find out if patients with MCDD reveal abnormalities known to be associated with schizophrenia or no abnormalities as was found in children with autism.

To date, there are no startle studies on directly comparing subjects with autism and subjects with schizophrenia.

Aim of the present PPI study

It is hypothesized that children with MCDD differ from children with autism on PPI. If abnormalities as in schizophrenia (impaired PPI) are found in patients with MCDD, in contrast to no abnormalities for patients with autism and typical controls there is further evidence for recognizing a PDD subcategory of MCDD.

P50

Next to prepulse inhibition (PPI) of the acoustic startle response, the gating of the auditory evoked (P50) potential is a paradigm that is thought to measure aspects of stimulus filtering related to inhibitory mechanisms.

In the P50 sensory gating paradigm, subjects listen to two identical auditory stimuli presented 500 milliseconds apart. Normal subjects have an auditory evoked positive deflection 50 milliseconds after the first sound (P50), but a much smaller response to the second sound. In the P50 condition a first stimulus, the conditioning stimulus, causes a neuronal response, the P50 potential, but at the same time activates inhibitory pathways. These inhibitory pathways are still active when a second stimulus is presented shortly thereafter (after about 500 ms). Although both paradigms (PPI and P50) involve the inhibitory effect of an initial stimulus on the response to a second stimulus, there are differences in the variables and probably differences in the basic circuitry between the 2 paradigms.
It has been suggested that patients with autism do have a problem in the filtering of sensory input (Kootz 1982). Some of the symptoms of autism, such as withdrawal from social contact, serve to minimize sensory input and to prevent overloading of central processing systems. Research on the suppression of the P50 potential in autistic patients however, (including children) is lacking. The only study that reports on this reveals normal P50 suppression for children with autism (Kemner et al., 2002).
Abnormalities for P50 suppression have been clearly demonstrated across the schizophrenia spectrum (adults and children), including probands, their unaffected relatives, and schizotypal patients (see for references Ross et al., 1993, 1996,1999; Braff et al., 2001 and Swerdlow et al., 2006). For the P50 suppression paradigm, a deficit in the inhibition of the P50 evoked response (less amplitude reduction to the second stimulus) was found for both medicated and unmedicated patients with schizophrenia (Freedman et al., 1983).

P50 auditory sensory gating changes little during normal childhood and adolescent development (Ross et al., 1999) and is therefore useful in comparing the results of the different diagnostic and different age groups in patients with autism and MCDD.

Thereby P50 seems to be a useful method in children to find out if patients with MCDD reveal abnormalities known to be associated with schizophrenia or no abnormalities as was found in children with autism.

To date, there are no P50 studies on directly comparing subjects with autism and subjects with schizophrenia.

Aim of the present P50 study

It is hypothesized that children with MCDD differ from children with autism on P50. If abnormalities as in schizophrenia (abnormal P50 suppression) are found in patients with MCDD, in contrast to no abnormalities for patients with autism and typical controls there is further evidence for recognizing a PDD subcategory of MCDD.

Aim and outline of this thesis

The overall aim of this study is to find (1) support for the subtype MCDD within the ASD spectrum from a neurobiological point of view, and to find (2) if these neurobiological parameters are similar for MCDD and schizophrenia supporting a more close relationship between ASD and schizophrenia than earlier suggested. Patients with MCDD are described in direct comparison to patients with autism, PDD-NOS and / or typical controls and indirect to what is known in the literature of patients with schizophrenia. In chapter 2 structural imaging on autism spectrum disorders and (childhood-onset) schizophrenia is reviewed. In chapter 3 the data of a structural imaging study are described. In chapter 4 neuropsychology data are presented. Chapter 5 and 6 cover the data of psychophysiology studies, namely SPEM, PPI and P50. The thesis concludes (chapter 7) with a summary and general conclusion, including strenghts, weaknesses and suggestions for future research.

References

Ad-Dab'Bagh Y & Greenfield B (2001). Multiple Complex Developmental Disorder: The "Multiple and Complex" evolution of the "Childhood Borderline Syndrome" construct. J Am Acad Child Adolesc Psychiatry 40(8):954-964.

Akshoomoff N (2005). The neuropsychology of autistic spectrum disorders. Dev Neuropsychol 27(3), 307-310.

Aleman A, Hijman R, de Haan EH, Kahn RS (1999). Memory impairment in schizophrenia: a meta-analysis. Am J Psychiatry 156(9):1358-66.

American Psychiatric Association (1952). Diagnostic and Statistical Manual of Mental Disorders (1rd ed.). Washington, DC: American Psychiatric Association Press.

American Psychiatric Association (1968). Diagnostic and Statistical Manual of Mental Disorders (2rd ed.). Washington, DC: American Psychiatric Association Press.

American Psychiatric Association (1980). Diagnostic and Statistical Manual of Mental Disorders (3rd ed.). Washington, DC: American Psychiatric Association Press .

American Psychiatric Association (1994). Diagnostic and Statistical Manual of Mental Disorders (4th ed). Washington, DC: American Psychiatric Association Press .

American Psychiatric Association (2000). Diagnostic and Statistical Manual of Mental Disorders (4th TR ed). Washington, DC: American Psychiatric Association Press .

Asarnow JR, Ben-Meir S (1988). Children with schizophrenia spectrum and depressive disorders: a comparative study of premorbid adjustment, onset pattern and severity of impairment. J Child Psychol Psychiatry 29: 477-488.

Asarnow RF, Asamen J, Granholm E, Sherman T, Watkins JM, Williams ME (1994). Cognitive / neuropsychological studies of children with a schizophrenic disorder. Schizophr Bull 20: 647-669.

Asarnow RF, Brown W. & Stranburg R (1995). Children with a schizophrenic disorder: neurobehavioural studies. Eur Arch Psychiatry Clin Neurosc 245: 70-79.

Autism and Developmental Disabilities Monitoring Network Surveillance Year 2002 Principal Investigators; Centers for Disease Control and Prevention (2007). Prevalence of autism spectrum disorders--autism and developmental disabilities monitoring network, 14 sites, United States, 2002. MMWR Surveill Summ 9; 56(1):12-28

Bailey A, Luthert P, Dean A, Harding B, Janota I and Montgomery M et al., (1998). A clinicopathological study of autism, Brain 121 (Pt 5), pp. 889–905.

Bender L (1942). Childhood Schizophrenia. Nervous Child, 1, 138-154.

Bender L (1947). Childhood schizophrenia: Clinical study of one hundred schizophrenic children. Am J of Orthopsychiatry, 17, 40-56.

Bettes B, Walker E (1987). Positive and negative symptoms in psychotic and other psychiatrically disturbed children. J Child Psychol Psychiatry 28: 555-68.

Bilder RM, Goldman RS, Robinson D, Reiter , Bell L, Bates JA, Pappadopulos E, Willson DF, Alvir JMJ, Woerner MG, Geisler S, Kane JM, Lieberman JA. (2000). Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. Am J Psychiatry 157: 549-559.

Bleuler E (1950). Dementia Praecox or the Group of Schizophrenias. International Universities Press, New York.

Bölte S, Bosch G (2005). The long-term outcome in two females with autism spectrum disorder. Psychopathology 38(3):151-4

Braff DL, Geyer MA, Swerdlow NR (2001). Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. Psychopharmacology 156(2-3): 234-258.

Brown J (1960). Prognosis from presenting symptoms of pre-school children with atypical development. Am J Orthopsychiatry, 30, 382-390.

Buitelaar JK, Van der Gaag RJ (1998). Diagnostic rules for children with PDD-NOS and Multiple Complex Developmental Disorder. J Child Psychol Psychiatry 39 (6): 911-918.

Cannon M, Caspi A, Moffitt TE, Harrington H, Taylor A, Murray RM, Poulton R (2002). Evidence for early childhood, pan-developmental impairment specific to schizophreniform disorder. Arch Gen Psychiatry 59:449-456.

Cannon M, Jones P, Huttunen MO, Tanskanen A, Huttunen T, Rabe-Hesketh S, Murray RM (1999). School performance in Finnish children and later development of schizophrenia: a population-based longitudinal study. Arch Gen Psychiatry 56: 457-463.

Clarke DJ, Littlejohns CS, Corbett JA, Joseph S (1989). Pervasive developmental disorders and psychoses in adult life. Br J Psychiatry 115: 692-699.

Cohen DJ, Paul R, Volkmar F (1987). Issues in the classification of Pervasive Developmental Disorders and Associated Conditions. In D.J. Cohen & A. M. Donnellan & P. Rhea (eds.). Handbook of Autism and Pervasive Developmental Disorders (pp.20-39). New York: Wiley & Sons.

Cohen DJ, Towbin KE, Mayes L, Volkmar F (1991). Developmantal Psychopathology of Multiplex Developmental Disorder. In S.L.Friedman & H.C. Haywood (Eds.). Developmental Follow-up: Concepts, Genres, Domains and Methods.

Davalos DB, Compagnon N, Heinlein S, Ross RG (2004). Neuropsychological deficits in children associated with increased familial risk for schizophrenia. Schizophr Res 67(2-3):123-30.

Dawson G (1996). Brief report: Neuropsychology of autism : a report on the state of the science. J Autism Dev Disord 26(2): 179-184.

De Bruin EI, Ferdinand RF, Meester S, De Nijs PFA,Verheij F (2007a). High rates of psychiatric co-morbidity in PDD-NOS. J Autism Dev Disord 37, 877-886.

De Bruin EI, De Nijs PFA, Verheij F, Hartman CA, Ferdinand RF (2007b). Multiple complex developmental disorder delineated from PDD-NOS. J Autism Dev Disord 37, 1181-1191.

Done DJ, Crow TJ, Johnstone EC, Sacker A (1994). Childhood antecedents of schizophrenia and affective illness: social adjustment at ages 7 and 11. Br Med J 309: 699-703.

Eggers C, Bunk, D, Krause D (2000). Schizophrenia with onset before the age of eleven: Clinical Characteristics of the onset and course. J Autism Dev Disord 30(1), 29-38.

Elliott R, Sahakian BJ (1995). The neuropsychology of schizophrenia: relations with clinical and neurobiological dimensions. Psychol Med 25: 581-594.

Erlenmeyer-Kimling L, Rock D, Roberts SA, Janal M, Kestenbaum C, Cornblatt B, Adamo UH, Gottesman II (2000). Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: the New York High-Risk Project. Am J Psychiatry 157(9):1416-22.

Fish B, Shapiro T, Campbell M, Wile R (1968). A classification of Schizophrenic children under five years. Am J Psychiatry 124, 1415-1423.

Fombonne E (2003). Epidemiological surveys of autism and other pervasive developmental disorders: an update. J Autism Dev Disord; 33(4):365-82

Fombonne E (2005). Epidemiology of autistic disorder and other developmental disorders. J Clin Psychiatry 66, 10:3-8.

Freedman R, Adler LE, Waldo MC, Pachtman E, Franks, RD (1983). Neurophysiological evidence for a defect in inhibitory pathways in schizophrenia: comparison of medicated and drug-free patients. Biol Psychiatry 18(5):537-51.

Geurts HM, Verté S, Oosterlaan J, Roeyers H, Sergeant JA (2004). How specific are executive functioning deficits in attention deficit hyperactivity disorder and autism? J Child Psychol Psychiatry, 45, 836-854.

Goldberg MC, Mostofsky SH, Cutting LE, Mahone EM, Astor BC, Denckla MB, Landa RJ (2005). Subtle executive impairment in children with autism and children with ADHD. J Autism Dev Disord, 35, 279-93.

Geller B, Guttmacher L, Bleeg M (1981). Coexistence of childhood onset pervasive developmental disorder and attention deficit disorder with hyperactivity. Am J Psychiatry 138, 388-389.

Goldstein G, Minshew NJ, Allen DN, Seaton E (2002). High-functioning autism and schizophrenia; A comparison of an early and late onset neurodevelopmental disorder. Arch Clin Neuropsychol 17(5): 461-475.

Happé F, Frith U (1996). The neuropsychology of autism. Brain 119: 1377-1400.

Happé F, Booth R, Charlton R, Hughes C (2006). Executive function deficits in autism spectrum disorders and attention-deficit/hyperactivity disorder: examining profiles across domains and ages. Brain and Cognition, 61, 25-39.

Heinrichs RW, Zakzanis KK (1998). Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 12(3): 426-445.

Herba CM, De Bruin E, Althaus M, Verheij F, Ferdinand RF (2007). Face and Emotion Recognition in MCDD Versus PDD-NOS. J Autism Dev Disord, 25; [Epub ahead of print].

Hoff AL, Sakuma M, Wieneke M, Horon R, Kushner M, DeLisi LE (1999). Longitudinal Neuropsychological follow-up study of patients with first-episode schizophrenia. Am J Psychiatry 156: 1336-1341.

Hollis CP (1994). Developmental language impairment in child and adolescent-onset schizophrenia. Schizophr Res 11: 183-184.

Hollis C (1995). Child and adolescent (juvenile onset) schizophrenia: a case control study of premorbid development impairments. Br J Psychiatry 166:489-495.

Hughes C, Russell J, Robbins TW (1994). Evidence for executive dysfunction in autism. Neuropsychol 32, p 477

Jacobsen LK, Rapoport JL (1998). Research update: childhood-onset schizophrenia: implications of clinical and neurobiological research. J Child Psychol Psychiatry 39:101-113.

Jacobsen LK, Hong WL, Hommer DW, Hamburger SD, Castellanos FX, Frazier JA, Giedd JN, Gordon CT, Karp BI, McKenna K, Rapoport JL (1996). Smooth pursuit eye movements in childhood-onset schizophrenia: comparison with attention-deficit hyperactivity disorder and normal controls. Biol Psychiatry 1; 40(11): 1144-1154.

Jansen LMC, Gispen-de Wied CC, Gademan PJ, De Jonge RCJ, Van der Linden JA, Kahn RS (1998). Blunted cortisol response to a psychosocial stressor in schizophrenia. Schizophr Res 33: 87-94.

Jansen LMC, Gispen-de Wied CC, Van der Gaag RJ, ten Hove F, Willemsen-Swinkels SWM, Harteveld E, Van Engeland H (2000). Unresponsiveness to psychosocial stress in a subgroup of autistic-like children, Multiple Complex Developmental Disorder. Psychoneuroendocrinology 25: 753-764.

Jansen LM, Gispen-de Wied CC, Van de Gaag RJ, Van Engeland H (2003). Differentiation between autism and multiple complex developmental disorder in response to psychosocial stress. Neuropsychopharmacology 28(3): 582-590.

Johnson KA, Robertson IH, Kelly SP, Silk TJ, Barry E, Dáibhis A, Watchorn A, Keavey M, Fitzgerald M, Gallagher L, Gill M,Bellgrove MA (2007). Dissociation in performance of children with ADHD and high-functioning autism on a task of sustained attention. Neuropsychologia, 45: 2234-2245.

Jones P, Rodgers B, Murray R, Marmot M (1994). Child development risk factors for adult schizophrenia in the British 1946 birth cohort. Lancet 344: 1398-1402.

Kanner L (1943). Early infantile autism. J Pediatrics, 25(3), 211-217.

Kanner L (1949). Problems of nosology and psychodynamics of early infantile autism. Am J Orthopsychiatry 19:416-26.

Kemner C, van der Gaag RJ, Verbaten M, van Engeland H (1999). ERP differences among subtypes of pervasive developmental disorders. Biol Psychiatry 46: 781-789.

Kemner C, Oranje B, Verbaten MN, Engeland van H (2002). Normal P50 gating in children with autism. J Clin Psychiatry 63(3): 214-217.

Kemner C, van der Geest JN, Verbaten MN, van Engeland H (2004). In search of neurophysiological markers of pervasive developmental disorders: smooth pursuit eye movements? J Neural Transm 111(12):1617-26. Epub 2004 Jul 14.

Kolvin I (1971a). Studies in the childhood psychoses. I. Diagnostic criteria and classification. Br J Psychiatry 118(545):381-4.

Kolvin I, Ounstad C, Humphrey M, McNay A (1971b). Studies in the childhood psychoses, II: the phenomenology of childhood psychoses. Br J Psychiatry 118(545):385-395.

Konstantareas MM, Hewitt T (2001). Autistic disorder and schizophrenia: Diagnostic overlaps. J Autism Dev Disord 31 (1): 19-28.

Kootz JP, Marinelli B, Cohen DJ (1982). Modulation of response to environmental stimulation in autistic children. J Autism Dev Disord 12(2):185-93.

Kumari V, Sharma T (2002). Effects of typical and atypical antipsychtics on preplse inhibition in schizophrenia: a critical evaluation of current evidence and directions for future research. Psychopharmacology 162(2): 97-101.

Kumra S, Jacobsen LK, Lenane M, Zahn TP, Wiggs E, Alaghband-Rad J, Castellanos FX, Frazier JA, McKenna K, Gordon CT, Smith A, Hambur ger S, Rapoport JL (1998)."Multidimensionally impaired disorder": is it a variant of very early-onset schizophrenia? J Am Acad Child Adolesc Psychiatry 37: 91-99.

Kumra S, Sporn A, Hommer DW, Nicolson R, Thaker G, Israel E, Lenane M, Bedwell J, Jacobsen LK, Gochman P, Rapoport JL (2001). Smooth pursuit eye-tracking impairment in childhood-onset psychotic disorders. Am J Psychiatry 158: 1291-1298.

Larsson HJ, Eaton WW, Madsen KM, Vestergaard M, Olesen AV, Agerbo E, Schendel D, Thorsen P, Mortensen PB (2005). Risk factors for autism: Perinatal factors, parental psychiatric history, and socioeconomic status. Am J Epidemiol 161:916-925.

Lincoln AJ, Bloom D, Katz M, Boksenbaum N (1998). Neuropsychological and neurophysiological indices of auditory processing impairment in children with multiple complex developmental disorder. J Am Acad Child Adolesc Psychiatry 37(1): 100-112.

Mahler M (1952). On child psychoses and schizophrenia: Autistic and symbiotic infantile psychoses. Psychoanalytic Study of the Child 7, 286-305.

Mason OJ, Beavan-Pearson J (2005). Understanding the genesis of psychotic disorder: Issues in the prediction and prophylaxis of those at 'ultra-high' risk. Br J Clin Psychol 44, 383-404.

McAlonan GM, Daly E, Kumari V, Critchley HD, van Amelsvoort T, Suckling J, Simmons A, Sigmundsson T, Greenwood K, Russell A, Schmitz N, Happe F, Howlin P, Murphy DG (2002). Brain anatomy and sensorimotor gating in Asperger's syndrome. Brain 125: 1594-1606.

Mehler C, Warnke A (2002). Structural brain abnormalities specific to childhood-onset schizophrenia identified by neuroimaging techniques. J Neural Transm 109:219-234.

Mouridsen SE, Rich B, Isager T (2007). Psychoiatric disorders in adults diagnosed as children with atypical autism. A case control study. J Neural Transm Epub ahead sept 2007.

Mueser KT, McGurk SR (2004). Schizophrenia Lancet 19;363(9426):2063-72

Nasrallah HA (1993). Neurodevelopmental pathogenesis of schizophrenia. Psychiatr Clin North Am 16(2):269-80.

Nicolson R, Lenane M, Singaracharlu S, Malaspina D, Giedd JN, Hamburger SD, Gochman P, Bedwell J, Thaker GK, Fernandez T, Wudarsky M, Hommer DW, Rapoport JL (2000a). Premorbid speech and language impairments in childhood-onset schizophrenia: association with risk factors. Am J Psychiatry 157:794-800.

Nicolson R, Lenane M, Hamburger SD, Fernandez T, Bedwell J, Rapoport JL (2000b). Lessons from childhood-onset schizophrenia. Brain Res Rev 3: 147-156.

Nicolson R, Rapoport JL (1999). Childhood-onset schizophrenia: rare but worth studying. Biol Psychiatry 46: 1418-1428.

Olin SS, Mednick SA (1996). Risk-factors of psychosis: Identifying vulnerable populations premorbidly. Schizophr Bull 22: 223-240.

Olin SS, Mednick SA, Cannon T, Jacobsen B, Parnas J, Schulsinger F, Schulsinger H (1998). School teacher ratings predictive of psychiatric outcome 25 years later. Br J Psychiatry 173: 536-539.

Ornitz EM, Lane SJ, Sugiyama T, de Traversay J (1993). Startle modulation studies in autism. J Autism Dev Disord 23(4): 619-37.

Palmen JMC, Van Engeland H (2004). Review on structural neuroimaging findings in autism. J Neural Transm 111:903-929

Paul R, Cohen D, Klin A, Volkmar F (1999). Multiplex developmental disorders – the role of communication in the construction of a self-.Child Adolesc Psychiatric Clin North Am 8, 189-202.

Pearlson GD, Marsh L (1999). Structural brain imaging in schizophrenia: a selective review. Biol Psychiatry 1; 46(5):627-49.

Pennington BF, Ozonoff S (1996). Executive functions and developmental psychopathology. J Child Psychol Psychiatry 37(1): 51-87.

Perry W, Minassian A, Lopez B, Maron L, Lincoln A (2007). Sensorimotor Gating Deficits in Adults with Autism. Biol Psychiatry 15:61(4):482-6.

Petty LK, Ornitz EM, Michelman JD, Zimmerman EG (1984). Autistic children who become schizophrenic. Arch Gen Psychiatry 41: 129-135.

Rank B (1949). Adaptation of the psychoanalytic Technique for the treatment of Young Children with Atypical Development. Am J of Orthopsychiatry 19, 130-139.

Rank B (1955). Intensive study and treatment of preschool children who show marked personality deviations or "atypical development"and their parents. In G.Caplan (Ed.). Emotional problems of early childhood (pp. 491-501). New York: Basic Books.

Ross RG, Olincy A, Harris JG, Radant A, Hawkins, Adler LE, Freedman R (1999). Evidence for bilineal inheritence of physiological indicators of risk in childhood-onset schizophrenia. Am J Med Genet 16; 88(2): 188-199.

Ross RG, Olincy A, Mikulich SK, Radant AD, Harris JG, Waldo M, Compagnon N, Heinlein S, Leonard S, Zerbe GO, Adler L, Freedman R (2002). Admixture analysis of smooth pursuit eye movements in probands with schizophrenia and their relatives suggests gain and leading saccades are potential phenotypes. Psychophysiology 39 (6): 809-819.

Ross RG (2003). Early expression of a psychophysiological feature of schizophrenia: saccadic intrusions into smooth-pursuit eye movements in school-age children vulnerable to schizophrenia. J Am Acad Child Adolesc Psychiatry 42(4): 468-476.

Ross RG, Radant AD, Hommer DW (1993). A developmental study of smooth pursuit eye movements in normal children from 7 to 15 years of age. J Am Acad Child Adolesc Psychiatry 32: 783-791.

Ross RG, Hommer D, Radant AD, Roath M, Freedman R (1996). Early expression of smooth-pursuit eye movement abnormalities in children of schizophrenic parents. J Am Acad Child Adolesc Psychiatry 35: 941-949.

Rutter M, Lockyer L (1967a). A fifteen year follow-up study of infantile psychosis. I. Description of the sample. Br J Psychiatry 113(504): 1169-82.

Rutter M, Greenfeld D, Lockyer L (1967b). A fifteen year follow-up study of infantile psychosis. II. Social and behavioural outcome. Br J Psychiatry 113(504): 1183-99.

Rutter M (1972). Childhood schizophrenia reconsidered. J Autism Child Schizophr 2 : 315-337.

Satzmari P (2003). The causes of autism spectrum disorders. Br Med J 326: 173-174.

Siever LJ, Coursey RD (1985). Biological markers for schizophrenia and the biological high-risk approach. J Nerv Ment Dis 173: 4-16.

Smeraldi E, Gambini O, Bellodi L, et al. (1987). Combined measure of smooth pursuit eye movements and ventricle-brain ratio in schizophrenic disorders. Psychiatry Res 21: 293-301.

Sowell ER, Toga AW, Asarnow R (2000). Brain abnormalities observed in childhood-onset schizophrenia: a review of the structural magnetic resonance imaging litarture. MRDD Res Reviews 6:180-185.

Spohn HE, Coyne L, Spray J (1988). The effects of neuroleptics and tardive dyskinesia on smooth pursuit eye movements in chronic schizophrenics. Arch Gen Psychiatry 45: 833-840.

Sporn AL, Addington AM, Gogtay N, Ordoňez AE, Gornick M, Clasen L, Greensyein D, Tossell JW, Gochman P, Lenane M, Sharp WS, Straub RE, Rapoport JL (2004). Pervasive developmental disorder and childhood-onset schizophrenia: comorbid disorder or a phenotypic variant of a very early onset illness? Biol Psychiatry 55(10): 989-994.

Stahberg O, Soderstrom H, Ratam M, Gillberg C (2004). Bipolar disorder, schizophrenia, and other psychotic disorders in adults with childhood onset AD/HD and / or autism spectrum dsiorders. J Neural Transm 111: 891-902.

Stanfield AC, McIntosh AM, Spencer MD, Philip R, Gaur S,,Lawrie SM (2007). Towards a neuroanatomy of autism: A systematic review and meta-analysis of structural magnetic resonance imaging studies. Eur Psychiatry Epub aug 2007

Swerdlow NR, Geyer MA, Shoemaker,JM, Light GA, Braff DL, Stevens KE, Sharp R, Breier M, Neary A, Auerbach PP (2006). Covergence and divergence in the neurochemical regulation of prepulse inhibition of startle and N40 suppresion in rats. Neuropsychopharmacology 31:506-515.

Takarea Y, Minshew NJ, Luna B, Krisky CM, Sweeney JA (2004). Pursuit eye movement deficits in autism. Brain 127: 2584-2594.

Towbin KE, Duykens EM, Pearson GS, Cohen DJ (1993). Conceptualizing "borderline syndrome of childhood" and "childhood schizophrenia" as a developmental disorder. J Am Acad Child Adolesc Psychiatry 32(4), 775-82.

Trillenberg P, Lencer R, Heide W (2004). Eye movements and psychiatric disease. Curr Opin Neurol 17(1):43-7.

Van der Gaag R.J (1993). Multiplex Developmental Disorder, an exploration of borderlines on the autistic spectrum. Thesis, University of Utrecht.

Van der Gaag RJ, Buitelaar J, Ban van den E, Bezemer M, Njio L, Van Engeland H (1995). A controlled multivariate chart review of multiple complex developmental disorder. J Am Acad Child Adolesc Psychiatry 34(8): 109-106.

Van Engeland H, Van der Gaag RJ (1994). MCDD in childhood - a precursor of schizophrenia spectrum disorders. Schizophr Res, 11, 197-197.

Verté S, Geurts HM, Roeyers H, Oosterlaan J, Sergeant JA (2006). Executive functioning in children with an autism spectrum disorder: can we differentiate within the spectrum? J Autism Dev Disord, 36, 351-372.

Volkmar FR, Cohen DJ (1991). Comorbid association of autism and schizophrenia. Am J Psychiatry, 148:1705-1707.

Volkmar FR, Klin A, Cohen DJ (1997). Diagnosis and classification of Autism and Related Conditions: Consensus and Issues. In: D.J. Cohen & F.R. Volkmar (eds.). Handbook of Autism and Pervasive Developmental disorders. 2nd edition. (pp.5-40).Wiley & Sons, inc.

Volkmar FR and Pauls D (2003). Autism. Lancet 362:1133-41

Weinberger DR (1995). From neuropathology to neurodevelopment. Lancet 26; 346(8974):552-7.

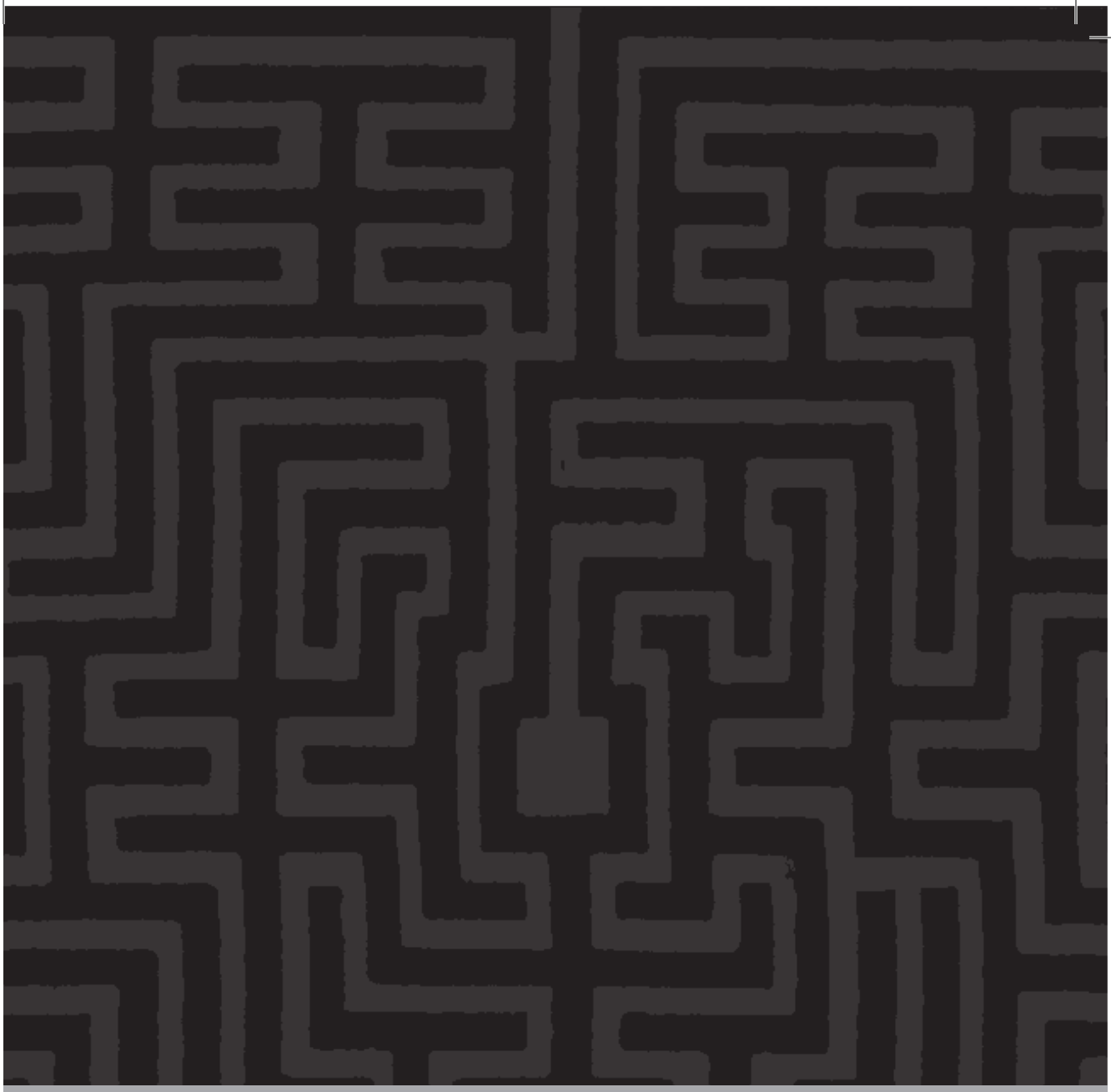
Wing L & Gould J (1979). Severe impairments of social interaction and associated abnormalities in children: Epidemiology and classification. J Autism Dev Disord 9, 11-29.

Wolff S, Barlow A (1979). Schizoid personality in childhood: A comparative study of schizoid, autistic, and normal children. J Child Psychol, Psychiatry, 20, 29-46.

Yung AR, Phillips LJ, Yuen HP, McGorry PD (2004). Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. Schizophr Res 67(2

[2]

Lahuis BE, Kemner C, Van Engeland H (2003).
Acta Neuropsychiatrica, 15:140-147.



Magnetic Resonance Imaging studies on Autism and Childhood-Onset Schizophrenia in children and adolescents; a review

Abstract

Objective

To find out whether the neurodevelopmental disorders autism and childhood-onset schizophrenia have a common developmental pathway and whether the abnormalities detected are 'disorder-specific', by reviewing magnetic resonance imaging (MRI) studies.

Method

As a result of a Medline search, we were able to access 28 studies on autism and 12 studies on childhood-onset schizophrenia, which focused on children and adolescents.

Results

Larger lateral ventricles were found to be a common abnormality in both disorders. 'Disorder-specific' abnormalities in patients with autism were larger brains, a larger thalamic area, and a smaller right cingulate gyrus. Subjects with childhood-onset schizophrenia were found to have smaller brains, a smaller amygdala and thalamus, and a larger nucleus caudatus. In subjects with childhood-onset schizophrenia, abnormalities appeared to progress over a limited period of time.

Conclusions

Because the study designs varied so much, the results should be interpreted cautiously. Before abnormalities found in the disorders can be designated as equal or 'disorder-specific', it will be essential to perform large longitudinal and cross-sectional follow-up studies.

Introduction

Of all the Pervasive Developmental Disorders (PDDs) autism is the prototype that has been studied most extensively. It is characterised by sustained impairments in reciprocal social interactions, communication deviance, and restricted, stereotypical behavioural patterns. According to DSM-IV, one of the main criteria for the diagnosis of autism is abnormal functioning in the above areas by the time a child reaches the age of 3 years (American Psychiatric Association, 1994). DSM-IV criteria for childhood-onset schizophrenia (COS) (onset of psychosis by age 12) are similar to those for schizophrenia that begins in adulthood (American Psychiatric Association, 1994). Multiple signs and symptoms involving thought, perception, emotion, movement and behaviour mark both types of schizophrenia. Autism and schizophrenia are regarded as two distinct disorders (Rutter, 1970; Kolvin, 1971). MRI studies on both disorders demonstrate structural abnormalities.

However, several authors have reported on subjects with early onset schizophrenia who (retrospectively) were characterised by premorbid autistic features (poor social adjustment, motor stereotypes, language development delay) (Watkins et al., 1988; Alaghband-Rad et al., 1995; Hollis, 1995; Chua and Murray, 1996; Olin and Mednick, 1996). Negative symptoms have also been described in patients with autism (Rumsey et al., 1985, 1986). Thus, two distinct psychiatric disorders (autism and schizophrenia), although showing differences in their course of development, family history and clinical features (Rutter, 1970; Kolvin, 1971), reveal overlapping symptoms (premorbid autistic features and negative symptoms). MRI on both disorders reveals abnormalities: it might be questioned whether there is also overlap in these abnormalities indicating a (partly) common pathway.

So far, there have been no comparative MRI studies of patients with COS and patients with autism. In this review of structural MRI studies we present the similarities and dissimilarities of the aberrant brain structures in children and adolescents with autism and COS. ADHD and dyslexia will be mentioned as well as comparative neurodevelopmental disorders, to define whether and which cerebral abnormalities are also present in other developmental psychiatric disorders of childhood.

Methods

Medline was searched for MRI studies on autism and COS since 1987. Keywords autism, COS and MRI were used. We found 28 studies on autism and 12 studies on COS; all these studies focused on children and adolescents. Special attention was given to the study designs; diagnostic variability's, variables between and within groups and the MRI protocols (methodological comments). The studies that we consider being the best are marked with an asterisk in the tables.

Autism in MRI studies

Cerebrum

Larger total brain (Piven et al., 1992, 1995, 1996, 1997), larger white matter and cortex (Filipek et al., 1992), and especially larger temporal, parietal and occipital lobes (Piven et al., 1996), and smaller parietal volumes (Courchesne et al., 1993) were found.

Ventricles

MRI studies revealed larger volumes (Gafney et al., 1987a&b) and no differences (Garber et al., 1989; Holtthum et al., 1992; Kleiman et al., 1992; Piven et al., 1992) for the 4th ventricle. Enlarged lateral ventricles were identified by Gaffney et al. (1989) (especially anterior horns) and Piven et al. (1995) but Filipek et al. (1992) found no differences in the ventricular system.

Cerebellum

A smaller cerebellum (Gaffney et al., 1987; Murakami et al., 1989; Hashimoto et al., 1995) and no cerebellar differences (Ritvo et al., 1986; Hashimoto et al., 1992 a&b; Holtthum et al., 1992; Kleiman et al., 1992) were found. Piven et al. (1997) found a larger cerebellum which disappeared when an adjustment was made for total brain volume (TBV). Smaller (Hashimoto et al., 1995), and larger (Filipek et al., 1992) lobules I-V, and smaller lobules VI-VII (Courchesne et al., 1988; Murakami et al., 1989; Piven et al., 1992; Hashimoto et al., 1995) and VIII-X (Hashimoto et al., 1993,1995) were detected. Courchesne et al. (1994) and Saitoh et al. (1995) suggested a bimodal distribution to explain the contradictory findings.

Corpus Callosum

In most studies the structure appeared to be smaller (Courchesne et al., 1994; Egaas et al., 1995; Saitoh et al., 1995; Piven et al., 1997) (esp. in the posterior subregions) but Filipek et al. (1992) found no differences.

Hippocampus and Amygdala

No differences were visible in the hippocampus (Saitoh et al., 1995; Piven et al., 1998), total hippocampus and amygdala (Filipek et al., 1992) or the limbic system (Courchesne et al., 1993).

Corpus striatum

A smaller R nucleus lenticularis (Gaffney et al., 1989), a larger nucleus lenticularis (Filipek et al., 1992), and an unchanged caudatus (Filipek et al., 1992) were reported.

Brainstem

Larger (Filipek et al., 1992), smaller (Gaffney et al., 1988; Hashimoto et al., 1992 a&b, 1993, 1995) and no differences (Hsu et al., 1991; Courchesne et al., 1993, 1994; Hashimoto et al., 1993) were found. The study by Hashimoto et al. (1993) revealed a smaller midbrain and medulla oblongata. However, the patients in the studies by Gaffney et al. (1988) and Hashimoto et al. (1992 a&b, 1993,1995) had low IQ's and the results resembled those for retarded control groups.

A smaller **R anterior cingulate gyrus** (Haznedar et al., 1997) and a larger **thalamic** area (Filipek et al., 1997) were demonstrated, although this last result was not noted specifically in the original report (Filipek et al., 1992). **Table 1** summarizes the results of the MRI studies on autism.

Childhood-onset Schizophrenia in MRI studies

Cerebrum

Smaller (Frazier et al., 1996; Gordon et al., 1994; Jacobsen et al., 1996, 1997 a&b) (only in females) (Rapoport et al., 1997; Jacobsen et al., 1998) or no significant smaller (Woody et al., 1987; Hendren et al., 1995; Jacobsen et al., 1997; Yeo et al., 1997) total cerebral volume was found. Hendren et al. (1995) and Yeo et al. (1997) demonstrated enhanced overall asymmetry. Smaller (Hendren et al., 1995) and larger (Jacobsen et al., 1996) volumes were found for the temporal lobe. However, in the follow-up study of Jacobsen et al. (1998) they demonstrated a larger decrease than healthy subjects in the right temporal lobe, bilateral superior temporal gyrus, posterior temporal gyrus and right anterior superior temporal gyrus.

Ventricles

For the 3rd and 4th ventricle, larger ventricles (Woody et al., 1987) and no differences (Hendren et al., 1995; Jacobsen et al., 1997c) were reported. Larger (Woody et al., 1987; Hendren et al., 1991; Rapoport et al., 1997), a trend to larger (Gordon et al., 1994; Frazier et al., 1996) and no differences (Hendren et al., 1995; Yeo et al., 1997) were found for lateral ventricles.

Table1 Summary of major MRI findings in Autism in children and adolescents

Study	Patients / Controls	Results compared to control group
Gaffney et al., 1987a	13 / 35	larger 4th ventricle, trend towards smaller cerebellum
Gaffney et al., 1987b	14 / 28	4th ventricle -to-post fossa twice as large, smaller cerebellum, trend to larger 4th ventricle, larger cerebellar-pontine complex
Courchesne et al., 1988	18 /12	smaller vermal lobules VI and VII
Ritvo et al., 1988	15 / 15	no differences
Gaffney et al., 1988	13 /35	smaller total brainstem, smaller pons
Murakami et al., 1989	10 / 8	12% smaller cerebellar volume, 20% smaller sup post vermis size
Garber et al., 1989	15 /15	no differences
Gaffney et al., 1989	13 / 33	larger ventricular size esp. ant horns of lat ventricles, smaller R lent nuclei, smaller VBR
Hsu et al., 1991	34 / 44	no differences
Filipek et al., 1992	9 HAD / 13 LOW / 15 DLD / 10 NAMD	volume hierarchy: HAD>LAD>DLD>C>NAMD esp. in pericallosal regions
Piven et al., 1992	15 / 15 + 15 (2 C groups)	larger MSBA, smaller cerebellar lobules VI-VII
Hashimoto et al., 1992	12 / 15 + 14 (2 C groups)	smaller brainstem ,esp. midbrain and medulla oblongata in retarded (autistic and non-autistic) pt, smaller ratio midbrain to post fossa area and no cerebellum changes in (retarded) autistic pt
Hashimoto et al., 1992	29 / 15	smaller brainstem
Holtthun et al., 1992	18 / 18	no differences
Kleiman et al., 1992	13 / 28	no differences
Hashimoto et al., 1993a	21 / 21	smaller midbrain, smaller pons, smaller medulla oblongata, smaller vermal lobules VIII-X
Hashimoto et al., 1993b	12 / 24	smaller midbrain, smaller medulla oblongata, no difference in whole brain stem area and pons and lobules I-X, no ratio differences in brain areas to post fossa area
Courchesne et al., 1993	21 / 12 + 23 + 17 (3 C groups)	smaller parietal volumes
Courchesne et al., 1994	50 / 53	no differences vermal lobules I-V, 16% smaller VI and VII area in 86% of the patients, 34% larger VI and VII in 12% of the patients, no differences in ventral pons and corpus callosum (smaller in hyperplasia group)

Note: post= posterior; sup= superior; ant= anterior; lat= lateral; TBV= total brain volume; MSBA= midsagittal brain area, LAD= low functioning autistic disorder, HAD= high functioning autistic disorder, DLD= developmental language disorder, c=control, *= best studies in the opinion of the authors.

Table 1 Continued

Study	Patients / Controls	Results compared to control group
Hashimoto et al., 1995	102 / 112	smaller posterior fossa structures (midbrain, pons, medulla oblongata, vermian lobules I-X)
Egaas et al., 1995	51 /51	smaller cross sectional area corpus callosum (4th and 5th subregion size reduction), trend for smaller corpus callosum in 1st subregion
*Piven et al., 1995	22 / 20	larger total brain, larger lateral ventricles, larger total tissue
Saitoh et al., 1995	33 / 23	no differences for hippocampus, vermian lobules VI and VII smaller in nearly all pt, no differences in VIII-X, post area of corpus callosum smaller, no differences in ant regions of corpus callosum
*Piven et al., 1996	35 / 36	larger total brain volume (only in M), larger temporal (8%), larger parietal (13.5%), larger occipital (21.3%) lobes
*Piven et al., 1997a	35 / 36	smaller body and post subregions in corpus callosum
Haznedar et al., 1997	7 / 7	smaller R ant cingulate area 24'
*Piven et al., 1997b	35 / 36	larger cerebellar volume, unchanged lobules VI, VII
*Piven et al., 1998	35 / 36	no differences in hippocampal volume

Note: post= posterior; sup= superior; ant= anterior; lat= lateral; TBV= total brain volume; MSBA= midsagittal brain area, LAD= low functioning autistic disorder, HAD= high functioning autistic disorder, DLD= developmental language disorder, c=control, *= best studies in the opinion of the authors.

Cerebellum

Smaller (Woody et al., 1987), only smaller in females (Jacobsen et al., 1997c), and no differences (Hendren et al., 1995) were found.

Thalamus

A smaller thalamus was demonstrated in one study of Frazier et al. (1996).

Corpus striatum

Larger caudate volume was demonstrated (Gordon et al., 1994; Frazier et al., 1996). The caudate asymmetry was decreased, and a larger putamen and globus pallidus were demonstrated as well (Frazier et al., 1996).

Amygdala

The amygdala was shown to be smaller (Hendren et al., 1995; Yeo et al., 1997) and asymmetric volumes (R > L) were demonstrated in patients (Jacobsen et al., 1996).

Hippocampus

No differences in volume were found (Hendren et al., 1995; Jacobsen et al., 1996, 1998; Yeo et al., 1997) but Jacobsen et al. (1996) reported a lack of (R > L) asymmetry.

Corpus callosum

The results of the MRI studies were inconsistent: a smaller callosum except for the anterior midbody and splenium (Hendren et al., 1995; Yeo et al., 1997), a larger splenium (Gordon et al., 1994) and larger total, anterior and posterior areas (Jacobsen et al., 1997b).

The two follow-up studies (Rapoport et al., 1997; Jacobsen et al., 1998) (with both an interval of 2 years) reported a decrease in cerebral volume (both studies), progressive ventricular enlargement (Rapoport et al., 1997), and a reduced right temporal lobe, total, right-anterior, and -posterior superior temporal gyrus, left hippocampal volume (Jacobsen et al., 1998) and thalamus (Rapoport et al., 1997) compared with healthy controls. In the follow-up study of Jacobsen et al. (1998) they did not reveal any significant decrease in the size of the amygdala over time.
In the initial scan in the study of Rapoport et al. (1997), globus pallidus, caudate and putamen volumes tended to be larger, but there were greater decreases in globus pallidus and caudate in the rescan (2 years later). Thus, the rescan did not reveal significant differences between patients and controls. **Table 2** summarizes the results of the MRI studies on COS

Methodological comments

Summarising, we have identified three main problems which hinder the inter alia comparison of these studies. *First*, the diagnostic variability: different versions of the DSM (III or III-R) were used as well as different additional diagnostic tools [e.g. Autism Diagnostic Interview for autism (Holtthum et al., 1992; Egaas et al., 1995; Piven et al., 1995, 1996, 1997a&b, 1998; Saitoh et al., 1995) and Schedule for Affective Disorders and Schizophrenia for school-age children for COS (Hendren et al., 1995; Frazier et al., 1996; Gordon et al., 1994; Jacobsen et al., 1996, 1997 a&b&c;

Table 2 Summary of major MRI findings in Childhood-onset-Schizophrenia in children and adolescents

Study	Patients / Controls	Results compared to control group
Woody et al., 1987	1 / 0	larger lat,-3rd,- and 4th ventricle, larger cisterna magna, smaller L cerebellum
Hendren et al., 1991	37 / 0 (8 PDD, 6 Sx-related, 15 DBD., 3 MD, 5 'other')	50% of PDD and Sx-related had abnormal scans, 50% of Sx-related : L larger than R frontal horns of the lat ventricle
*Gordon et al., 1994	19 / 37	8% smaller TBV, trend for larger L frontal ventricular volume, larger caudate volume (esp L), lack of normal caudate symmetry, larger splenium CC
Hendren et al., 1995	12 / 13	smaller amygdala volume, smaller temp cortex volume, smaller callosal area, smaller temp lobe asymmetry, larger absolute linear asymmetry, hippocampus unchanged
*Jacobsen et al., 1996	21/ 41	smaller cerebral volumes (8%), larger volumes of the sup temporal gyrus and its post segment, trend towards larger temporal lobe volume, lacking normal (R > L) hippocampal asymmetry, amygdala asymmetry (R > L)
*Frazier et al., 1996	21/ 33	smaller TCV (9.2%) and mid sagittal area, larger caudate (esp L), putamen and globus pallidus, smaller (R > L) caudate asymmetry, lat ventricles tended to be larger, larger VBR, smaller midsagittal area thalamus (17.2%)
*Jacobsen et al., 1997	16 / 16	smaller total cerebral volume (9.3%), no difference for planum temporale
*Rapoport et al., 1997	16 / 24	1st scan: trend towards smaller TBV and larger lat ventricles, globus pallidus, caudate, and putamen volumes. Rescan: larger ventricular volume, smaller midthalamic area
*Jacobsen et al., 1997c	24 / 52	smaller vermis volume (11.7%), smaller midsagittal inf post lobe area (10.9%), smaller midsagittal inf post lobe volume (8.9%)
*Jacobsen et al., 1997b	25 / 55	larger corpus callosum area (total, ant and post), smaller TBV (significant in F, trend in M)
Yeo et al., 1997	20 / 20	smaller amygdala, trend to smaller temporal cortex volumes, smaller callosal areas (overall, esp. ant midbody and post), changed absolute linear asymmetry TBV, no differences for ventricles, hippocampus, and frontal area.
*Jacobsen et al., 1998	10 / 17	in 2 years a decrease in: R temporal lobe volume (8.3%), total and post sup temporal gyrus (8.6%), R ant sup temporal gyrus (7.4%), L hippocampus (14.3%), amygdala (trend) and smaller TBV.

Note: F= female; M= male; inf= inferior; sup= superior; ant= anterior; post= posterior; lat= lateral; PDD= Pervasive Developmental Disorder; DBD= Disruptive Behaviour Disorder; MD= Mood Disorder; TBV= Total Brain Volume; *= best studies in the opinion of the authors.

Yeo et al., 1997). Some patient groups with comorbidity (Jacobsen et al., 1998; Rapoport et al., 1997) and some control groups with a medical (Courchesne et al., 1988, 1993, 1994; Gaffney et al., 1987 a&b, 1988; Murakami et al., 1989; Hsu et al., 1991; Kleiman et al., 1992; Hashimoto et al., 1992, 1993a&b, 1995) or psychiatric (Hendren et al., 1991) history were studied, causing heterogeneity in the presumed similar diagnostic groups. *Second*, there are variations within and between the subject groups. In the last few years more has become known about factors that influence the size of several brain structures. It has become clear that the following factors are important in this connection: age (Zipursky et al., 1992; Giedd et al., 1996), IQ (Bauman et al., 1986; Willerman et al., 1991; Andreassen et al., 1993), gender (Andreassen et al., 1986; Jacobsen et al., 1997; Giedd et al., 1996), weight, height (Ritvo et al., 1986), socio-economic status (SES) (Pearlson et al., 1989, 1991; Andreasen et al., 1990), alcohol consumption (Jernigan et al., 1991; Pfefferbaum et al., 1992) and probably drug abuse, neuroleptica (Chakos et al., 1994; Saitoh et al., 1995), handedness (Andreasen et al., 1986; Wittelson et al., 1991), puberty stage and some medical and neurological illnesses.

Authors have pointed to the influence of adjustments of TBV both in subjects with autism (Courchesne et al., 1993; Hashimoto et al., 1993a; Haznedar et al., 1997; Piven et al., 1997, 1998), and in subjects with COS (Hendren et al., 1995; Frazier et al., 1996; Jacobsen et al., 1996, 1997 b&c, 1998; Yeo et al., 1997). It is remarkable that all the patients with COS had a lower IQ than their control groups. Also many studies, both on autism [the studies of Courchesne et al. (1988, 1993, 1994) , Murakami et al. (1989) and Hsu et al. (1991), the studies of Hashimoto et al. (1992 a&b, 1993 a&b, 1995) and the studies of Piven et al. (1996, 1997 a&b, 1998)] and on COS [the studies of the NIMH-group (Frazier et al., 1996; Jacobsen et al., 1996, 1997 a&b&c, 1998; Rapoport et al., 1997)] are based on the same, or slightly changed group of patients. Although different structures of the brain are measured, these in fact are not independent observations.

Third, the various quantitative and qualitative MRI methods (slice thickness and gap, orientation and position), used in the studies possibly have led to different results (Filipek et al., 1995). Gaffney et al. (1987, 1989) drew attention to the different results for axial and coronal scanning and for spin echo versus inversion recovery techniques.

Although the studies are difficult to compare, we believe that the studies by Piven (1995, 1996, 1997 a&b, 1998) are the most accurate as far as autism is concerned. This is concluded because of the following aspects. Piven et al. used the ADI to confirm their DSM-III-R diagnosis, used small slices in their MRI technique (1.5 mm), had large enough groups without comorbidity (35 patients and 36 healthy controls), and controlled for gender, height and PIQ. Also in some studies they made adjustments for TBV. The studies by the NIMH-group (Gordon et al., 1994; Frazier et al., 1996; Jacobsen et al., 1996, 1997 a&b&c, 1998; Rapoport et al., 1997) are probably the most accurate studies of COS. This conclusion is based on the

combination of the used additional diagnostic tools (K-SADS, DICA-R [Diagnostic Interview for Children and Adolescents-Revised]) for confirming their DSM-III-R diagnosis, their MRI techniques, number of patients (10-25), and known variabilities of patients and controls (age, gender, height, weight, Tanner, handedness). Also, in most studies, adjustments for TBV were made. Unfortunately not all patients could be tested with the total WISC-R.

Discussion

In this review of structural MRI studies of children and adolescents with autism or COS, we wanted to focus particularly on common as well as on 'disorder-specific' brain abnormalities.

The only abnormalities found in both autistic and COS patients were enlarged lateral ventricles. Larger lateral ventricles, as compared with healthy control groups, were found in one study of autism (Piven et al., 1995), and in three studies of COS (Gordon et al., 1994[trend]; Frazier et al., 1996[trend]; Rapoport et al., 1997). Furthermore, one study on autism with medical controls (Gaffney et al., 1989) and one study on COS (Woody et al., 1987) (case-report) reported larger lateral ventricles. Further support for enlarged ventricles in autism was found in a post mortem study by Bauman and Kemper (Bauman and Kemper, 1985). Furthermore, in none of the MRI studies on subjects with ADHD were larger lateral ventricles demonstrated (Castellanos et al., 1996; Filipek et al., 1997) and in none of the dyslexia studies it was measured.

Although a conclusion is premature, this finding of enlarged ventricles is particularly interesting with regard to the question of overlapping symptoms and a common pathway in COS and autism. Andreasen et al. (1990) found that patients with schizophrenia with prominently negative symptoms had significantly larger ventricular size. Rapoport et al. (1997) suggested that there was more ventricle enlargement in COS patients with higher premorbid adjustment scale scores, including early transient autistic features. However, it has to be noted that Frazier et al. (1996) measured negative symptoms (with the Schedule for the Assessment of Negative Symptoms), but found no correlation with larger ventricles. The reviewed literature might suggest that the two disorders, autism and COS, do have shared negative symptoms and have common structural abnormalities (larger ventricles) as well as that there is a relation between larger ventricles and negative symptoms. Significant ventricular enlargement proved to be a disease-specific marker in (adult) patients with schizophrenia, since it was not seen in siblings without schizophrenia and healthy controls (Cannon et al., 1998). It would be interesting to know whether ventricular enlargement is also unique to the clinical phenotype in autism. However, all these hypotheses are limited because of the restricted number of MRI studies and their methodological limitations as mentioned above.

The 'disorder-specific' abnormalities revealed in subjects with autism were: larger

brains, a smaller R anterior cingulate gyrus and a larger thalamic area. A post mortem study on autism (adults) endorsed this result for the cerebrum (Bailey et al., 1993). Patients with COS were found to have smaller brains, especially the temporal lobe over time (although patients with ADHD also turned out to have smaller brains), a larger nucleus caudatus (propably due to the influence of neuroleptics), a smaller amygdala, a smaller thalamus and changed asymmetry of several structures. For schizophrenia (adults), post mortem studies confirmed the results of the cerebrum (Altshuler et al., 1990; Bogarts et al., 1990), corpus striatum (Heckers et al., 1991), amygdala (Altshuler et al., 1990; Bogarts et al., 1990) and thalamus (Bogarts et al., 1993). These results differ from the results of the MRI studies on subjects with ADHD (Hynd et al., 1990, 1991, 1993; Giedd et al., 1994; Semrud-Clikeman et al., 1994; Baumgardner et al., 1996; Castellanos et al., 1994, 1996; Filipek et al., 1997; Mataro et al., 1997; Berquin et al., 1998) and dyslexia (Hynd et al., 1990, 1995; Larsen et al., 1990, 1992; Duara et al., 1991; Kushch et al., 1993; Leonard et al., 1993; Schultz et al., 1994).

The most striking 'disorder-specific' feature in patients with autism was the enlargement of the brain and its separate structures, whereas in subjects with COS it was the attenuated brain and its separate structures. The biological processes underlying these abnormalities are still unsolved (Weickert and Weinberger, 1998). At least two follow-up studies (Rapoport et al., 1997; Jacobsen et al., 1998) lend support to a progressive rather than a static neurodevelopmental interpretation (Woods, 1998).

There are indications that the aforementioned abnormalities are already present at a young age. Bailey et al. (1993) found enlarged brains in patients with autism before the age of 16. Jacobsen et al. (1998) and Rapoport et al. (1997) revealed abnormal changes in the brains of COS around the time of puberty. Therefore, if these changes are related to a progressive process, the processes of interest will be competitive elimination, myelination and arborization (Tamminga, 1999). These processes persist throughout childhood and adolescence and might therefore be responsible for the enlargement or attenuation in the cerebrum of, respectively, patients with autism or COS.

In view of the difficulty of interpreting the results mentioned in this article and the MRI results obtained so far, we need to be cautious about drawing conclusions. However, there seems to be a common structural brain abnormality (the enlarged ventricles) as well as shared symptomatology (the negative symptoms) in autism and COS. Also, there are indications that the enlarged ventricles and negative symptomatology are correlated. This could be an indication for a partly common pathway in autism and COS. Further research with well designed studies is needed to affirm these conclusions.

References

Alaghband-Rad J, McKenna K, Gordon CT et al.(1995). Childhood-onset schizophrenia: The severity of premorbid course. J Am Acad Child Adolesc Psychiatry 34(10):1273-1283.

Altshuler LL, Casanova MF, Goldberg TE et al. (1990). The hippocampus and parahippocampus in schizophrenic, suicide, and control brains. Arch Gen Psychiatry 47:1029-1034.

American Psychiatric Association (1994). Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. American Psychiatric Association: Washington DC.

Andreasen NC, Nasrallah HA, Dunn V et al. (1986). Structural abnormalities in the frontal system in schizophrenia. Arch Gen Psychiatry 43:137-144.

Andreasen NC, Ehrhardt JC, Swayze V et al. (1990). Magnetic resonance imaging of the brain in schizophrenia: The pathophysiologic significance of structural abnormalities. Arch Gen Psychiatry 47:35-44.

Andreasen NC, Flaum M, Swayze et al. (1993). Intelligence and brain structure in normal individuals. Am J Psychiatry 150(1):130-134.

Bailey A, Luthert P, Bolton P et al. (1993). Autism and megalencephaly. Lancet 341,854:1225-1226.

Bauman M, Kemper TL (1985), Histoanatomic observations of the brain in early infantile autism. Neurology 35:866-874.

Bauman ML, Kemper TL (1986). Developmental cerebellar abnormalities: a consistent finding in early infantile autism. Neurology 36(1):190.

Baumgardner TL, Singer HS, Denckla MB et al. (1996). Corpus callosum morphology in children with Tourette syndrome and attention deficit hyperactivity disorder. Neurology 47:477-482.

Berquin PC, Giedd JN, Jacobsen LK et al. (1998). Cerebellum in attention-deficit hyperactivity disorder. Neurology 50:1087-1093.

Bogarts B, Falkai P, Haupts M et al. (1990). Post-mortem volume measurements of limbic systems and basal ganglia structures in chronic schizophrenics: initial results from a new brain collection. Schizophr Res 3:295-301.

Bogarts B, Falkai P, Greve B et al. (1993). Volumes of thalamic, limbic structures and basalganglia in chronic schizophrenia. A controlled post-mortem study from the New Düsseldorf Brain Collection. Schizophr Res 9(2-3), 146-147.

Cannon TD, van Erp TGM, Huttunen M et al. (1998). Regional gray matter, white matter, and cerebrospinal fluid distributions in schizophrenic patients, their siblings, and controls. Arch Gen Psychiatry 55:1084-1091.

Castellanos FX, Giedd JN, Eckburg P et al. (1994). Quantitative morphology of the caudate nucleus in attention deficit hyperactivity disorder. Am J Psychiatry 151:1791-1796.

Castellanos FX, Giedd JN, Marsh WL et al. (1996). Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. Arch Gen Psychiatry 53:607-616.

Chakos MH, Leiberman JA, Bilder RM (1994). Caudate volume increases in first episode schizophrenia after treatment. Am J Psychiatry 151:1430-1436.

Chua SE, Murray RM (1996), De ontwikkelingsneurologische theorie van Schizofrenie: bewijsmateriaal betreffende structuur en neuropsychologie. Acta Neuropsychiatrica 8:25-34.

Courchesne E, Yeung-Courchesne R, Press BA et al. (1988). Hypoplasia of cerebellar vermal lobules VI and VII in autism. N Engl J Med 318:1349-1354.

Courchesne E, Press GA, Yeung-Courchesne R (1993). Parietal lobe abnormalities detected with MR in patients with infantile autism. Am J Roentgenol 160:387-393.

Courchesne E, Saitoh O, Yeung-Courchesne R et al. (1994). Abnormality of cerebellar vermian lobules VI and VII in patients with infantile autism: Identification of hypoplastic and hyperplastic subgroups with MR Imaging. Am J Roentgenol 162:123-130.

Duara R, Kushch A, Gross-Glenn K et al. (1991). Neuroanatomic differences between dyslexic and normal readers on magnetic resonance imaging scans. Arch Neurol 48:410-416.

Egaas B, Courchesne E, Saitoh O (1995). Reduced size of the corpus callosum in autism. Arch Neurol 52:794-801.

Filipek PA, Richelme C, Kennedy DN et al. (1992). Morphometric analysis of the brain in developmental language disorders and Autism (abstract). Ann of Neurology 32:475.

Filipek PA (1995), Brief report: Neuroimaging in Autism: The state of the science 1995. J Autism Dev Disord 26:211-215.

Filipek PA, Semrud-Clikeman M, Steingard RJ et al. (1997). Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. Neurology 48:589-601.

Frazier JA, Giedd JN, Hamburger SD et al. (1996). Brain anatomic magnetic resonance imaging in childhood-onset schizophrenia. Arch Gen Psychiatry 53:617-624.

Gaffney GR, Kuperman S, Tsai LY et al. (1987a). Midsagittal magnetic resonance imaging of autism. Br J Psychiatry 151:831-833.

Gaffney GR, Tsai LY, Kuperman S et al. (1987b). Cerebellar structure in Autism. Am J Dis Child 141:1330-1332.

Gaffney GR, Kuperman S, Tsai LY et al. (1988). Morphological evidence for brainstem involvement in infantile autism. Biol Psychiatry 24:578-586.

Gaffney GR, Kuperman S, Tsai LY et al. (1989). Forebrain structure in infantile autism. J Am Acad Child Adolesc Psychiatry 28 (4):534-537.

Garber HJ, Ritvo ER, Chiu LC et al. (1989). A magnetic imaging study of autism: normal fourth ventricle size and absence of pathology. Am J Psychiatry 146:532-534.

Giedd JN, Castellanos FX, Casey BJ et al. (1994). Quantitative morphology of the corpus callosum in attention deficit hyperactivity disorder. Am J Psychiatry 151:665-669.

Giedd JN, Snell JW, Lange N et al. (1996). Quantitative magnetic resonance imaging of human brain development: ages 4-18. Cereb cortex 6:551-560.

Gordon CT, Frazier JA, McKenna K et al. (1994). Childhood-onset schizophrenia: An NIMH study in progress. Schizophr Bull 20(4), 697-712.

Hashimoto T, Murakawa K, Miyazaki M et al. (1992a). Magnetic resonance imaging of the brain structures in the posterior fossa in retarded autistic children. Acta Paediatr 81:1030-1034.

Hashimoto T, Tayama M, Miyazaki M et al. (1992b). Reduced brainstem size in children with autism. Brain Dev 14:94-97.

Hashimoto T, Tayama M, Miyazaki M et al. (1993a). Brainstem and cerebellar vermis involvement in autistic children. J Child Neurol 8:149-153.

Hashimoto T, Tayama M, Miyazaki M et al. (1993b). Brainstem involvement in high functioning autistic children. Acta Neurol Scand 88:123-128.

Hashimoto T, Tayama M, Murakawa K et al. (1995). Development of the brainstem and cerebellum in autistic patients. J Autism Dev Disord 25:1-18.

Haznedar MM, Buchsbaum MS, Metzger et al. (1997). Anterior cingulate gyrus volume and glucose metabolism in autistic disorder. Am J Psychiatry 154:1047-1050.

Heckers S, Heinsen H, Heinsen Y et al. (1991). Cortex, white matter, and basal ganglia in schizophrenia: a volumetric post mortem study. Biol Psychiatry 29:556-566.

Hendren RL, Hodde-Vargas JE, Vargas LA et al. (1991). Magnetic resonance imaging of severely disturbed children- A preliminary study. J Am Acad Child Adolesc Psychiatry 30(3):466-470.

Hendren RL, Hodde-Vargas J, Yeo RA et al. (1995). Neuropsychophysiological study of children at risk for schizophrenia: A preliminary report J Am Acad Child Adolesc Psychiatry 34(10):1284-1291.

Hollis C (1995). Child and adolescent (juvenile onset) schizophrenia. A case control study of premorbid developmental impairments. Br J Psychiatry 166:489-495.

Holtthum JR, Minshew NJ, Sanders RS et al. (1992). Magnetic resonance imaging of the posterior fossa in autism. Biol Psychiatry 32:1091-1101.

Hsu M, Yeung-Courchesne R, Courchesne E et al. (1991). Absence of magnetic resonance imaging evidence of pontine abnormality in infantile autism. Arch Neurol 48:1160-1163.

Hynd GW, Semrud-Clikeman M, Lorys AR et al. (1990). Brain morphology in developmental dyslexia and attention deficit disorder/hyperactivity. Arch Neurol 47:919-926.

Hynd GW, Semrud-Clikeman M, Lorys AR et al. (1991). Corpus callosum morphology in attention deficit-hyperactivity disorder: morphometric analysis of MRI. J Learn Disabil 24(3):141-146.

Hynd GW, Hern KL, Novey ES et al. (1993). Attention deficit-hyperactivity disorder and asymmetry of the caudate nucleus. J Child Neurol 8:339-347.

Hynd GW, Hall J, Novey ES et al. (1995). Dyslexia and the corpus callosum morphology. Arch Neurol 52:32-38.

Jacobsen LK, Giedd JN, Vaituzis AC (1996). Temporal lobe morphology in childhood-onset schizophrenia. Am J Psychiatry 153(3):355-360.

Jacobsen LK, Giedd JN, Cigcem Tanrikut BA et al. (1997a). Three-dimensional cortical morphometry of the planum temporale in childhood-onset schizophrenia. Am J Psychiatry 154(5):685-687.

Jacobsen LK, Giedd JN, Rajapakse JC (1997b). Quantitative magnetic resonance imaging of the corpus callosum in childhood-onset schizophrenia. Psychiatry Res 68:77-86.

Jacobsen LK, Giedd JN, Berquin PC et al. (1997c). Quantitative morphology of the cerebellum and fourth ventricle in childhood-onset schizophrenia. Am J Psychiatry 154(12):1663-1669.

Jacobsen LK, Giedd JN, Castellanos FX et al. (1998). Progressive reduction of temporal lobe structures in childhood-onset schizophrenia. Am J Psychiatry 155:678-685.

Jernigan TL, Butters N, DiTraglia G et al. (1991). Reduced cerebral grey matter observed in alcoholics using magnetic resonance imaging. Alcohol Clin Exp Res 15(3):418-427.

Kleiman MD, Neff S, Rosman NP. (1992). The brain in infantile autism: are posterior structures abnormal? Neurology 42:753-760.

Kolvin I (1971). Studies in the Childhood Psychoses, I: Diagnostic criteria and classification. Br J Psychiatry 118:381-384.

Kushch A, Gross-Glenn K, Jallad B et al. (1993). Temporal lobe surface area measurements on the MRI in normal and dyslexic readers. Neuropsychologia 31(8):811-821.

Larsen JP, Hoien T, Lundberg I et al. (1990). MRI Evaluation of the size of the planum temporale in adolescents with developmental dyslexia. Brain Lang 39:289-301.

Larsen JP, Hoien T, Odegaard H (1992). Magnetic resonance imaging of the corpus callosum in developmental dyslexia. Cogn Neuropsychol 9(2):123-134.

Leonard CM, Voeller KKS, Lombardino LJ et al. (1993). Anomalous cerebral structure in dyslexia revealed with magnetic resonance imaging. Arch Neurol 50:461-469.

Mataro M, Garcia-Sanchez C, Junque C et al. (1997). Magnetic resonance imaging measurement of the caudate nucleus in adolescents with attention-deficit hyperactivity disorder and its relationship with neuropsychological and behavioral measures. Arch Neurol 54:963-968.

Murakami JW, Courchesne E, Press GA et al. (1989). Reduced cerebellar hemisphere size and its relationship to vermal hypoplasia in autism. Arch Neurol 46:689-694.

Olin SS, Mednick SA (1996). Risk factors of psychosis: Identifying vulnerable populations premorbidly. Schizophr Bull 22:223-240.

Pearlson GD, Kim WS, Kubos KL et al. (1989). Ventricle-brain ratio, computed tomographic density and brain area in 50 schizophrenics. Arch Gen Psychiatry 46:690-697.

Pearlson GD, Batra PE, Schraml FV et al. (1991). Brain size in schizophrenia. Arch Gen Psychiatry 48:180-181.

Piven J, Nehme E, Simon J et al. (1992). Magnetic resonance imaging in autism: measurement of the cerebellum, pons, and fourth ventricle. Biol Psychiatry 31:491-504.

Piven J, Arndt S, Bailey J et al. (1995). An MRI study of brain size in autism. Am J Psychiatry 152:1145-1149.

Piven J, Arndt S, Bailey J et al. (1996). Regional enlargement in autism: a magnetic resonance imaging study. J Am Acad Child Adolesc Psychiatry 35(4):530-536.

Piven J, Saliba K, Bailey J et al. (1997a). An MRI study of autism: The cerebellum revisited. Neurology 49:546-551.

Piven J, Bailey J, Ranson BJ et al. (1997b). An MRI study of the corpus callosum in autism. Am J Psychiatry 154:1051-1056.

Piven J, Bailey J, Ranson BJ et al. (1998). No difference in hippocampus volume detected on magnetic resonance imaging in autistic individuals. J Autism Dev Disord 28 (2):105-110.

Pfefferbaum A, Lim KO, Zipursky RB et al. (1992). Brain grey and white matter volume loss accelerates with aging in chronic alcoholics: a quantitative MRI study. Alcohol Clin Exp Res 16(6):1078-1089.

Rapoport JL, Giedd J, Kumra S (1997). Childhood-onset schizophrenia. Arch Gen Psychiatry 54:897-903.

Ritvo ER, Freeman BJ, Scheibel AB et al. (1986). Lower Purkinje cell counts in the cerebella of four autistic subjects: initial findings of the UCLA-NSAC autopsy research report. Am J Psychiatry 143:862-866.

Rumsey JM, Rapoport JL, Sceery WR (1985). Autistic children as adults: Psychiatric, social, and behavioral outcomes. J Am Acad Child Psychiatry 24(4):465-473.

Rumsey JM, Andreasen NC, Rapoport JL (1986). Thought, language, communication, and affective flattening in autistic adults. Arch Gen Psychiatry 43:771-777.

Rutter M (1970). Autistic children: infancy to adulthood. Seminars in Psychiatry 2:435-450.

Saitoh O, Courchesne E, Egaas B et al. (1995). Cross-sectional area of the posterior hippocampus in autistic patients with cerebellar and corpus callosum abnormalities. Neurology 45:317-324.

Schultz RT, Cho NK, Staib LH et al. (1994). Brain morphology in normal and dyslexic children: the influence of sex and age. Ann Neurol 35:732-742.

Semrud-Clikeman M, Filipek PA, Biederman J et al. (1994). Attention-deficit hyperactivity disorder: Magnetic resonance imaging morphometric analysis of the corpus callosum. J Am Acad Child Adolesc Psychiatry 33(6):875-881.

Tamminga CA (1999). Images in neuroscience. Am J of Psychiatry 156:1.

Watkins JM, Asarnow RF, Tanguay PE (1988). Symptom development in childhood-onset schizophrenia. J Child Psychol Psychiatry 29(6):865-878.

Weickert CS, Weinberger DR (1998). A candidate molecule approach to defining developmental pathology in schizophrenia. Schizophr Bull 24(2):303-316.

Willerman L, Schultz R, Rutledge JN et al. (1991). In vivo brain size and intelligence. Intelligence 15:223-228.

Witelson SF, Goldtsmidth CH (1991). The relationship of hand preference to anatomy of the corpus callosum in man. Brain Res 545:175-182.

Woody RC, Bolyard BS, Eisenhauer G et al. (1987). CT scan and MRI findings in a child with schizophrenia. J Child Neurol 2:105-110.

Woods BT (1998). Is schizophrenia a progressive neurodevelopmental disorder? Toward a unitary pathogenetic mechanism. Am J Psychiatry 155:1661-1670.

Yeo RA, Hodde-Vargas J, Hendren et al. (1997). Brain abnormalities in schizophrenia-spectrum children: implications for a neurodevelopmental perspective. Psychiatry Res 76:1-13.

Zipursky RB, Lim KO, Sullivan EV (1992). Widespread cerebral grey matter volume in schizophrenia. Arch Gen Psychiatry 49(3):195-205.

Added Note

In Chapter 1 we compared structural MRI studies (sMRI) from 1987 till 1998, on autism and (childhood-onset) schizophrenia (COS) at the age of childhood to find out if the suggestions of overlap in the literature could be underlined by neurobiological research, especially in structural imaging, and by that indicating a (partly) common pathway. Main conclusion was that for subjects with autism there was an enlargement of the brain and its separate structures, whereas for subjects with COS the brain and its separate structures were smaller. Larger lateral ventricles were found for both groups. The aim of this additional paragraph is to review the more recent sMRI literature from 1998 onward, on autism and schizophrenia in studies including children and adolescents, and find out if the earlier conclusion from the publication in 2003 is still accurate or if new insights can be found in the sMRI literature.

Methods

Medline was searched for MRI studies on autism and COS since 1998. The keywords autism, COS and (structural) MRI were used. Sixteen new studies on COS, and 35 studies on autism were found.

Autism in sMRI studies

Cerebrum

No differences in total brain volume were reported by Herbert et al. (2003), Kates et al. (2004), Schumann et al. (2004) and Harden et al. (2006, 2008). Howard et al. (2000) found no differences in overall temporal lobe volume but larger intra-cranial volumes.

Increased volumes were reported by Courchesne et al. (2001 [2-3 years], 2003), Carper et al. (2002), Aylward et al. (2002 [< 12 years]), Sparks et al. (2002), Akshoomoff et al. (2004 [LFA]), Herbert et al. (2004), Lotspeich et al. (2004), Hazlett et al. (2005, 2006), Palmen et al. (2005), and Bloss and Courchesne (2007). Most reports were on gray matter (Courchesne et al., 2001 [cortical]; Carper et al., 2002[2-3 years old, frontal and temporal]; Akshoomhoff et al., 2004; Lotspeich et al., 2004; Palmen et al., 2005 [frontal, parietal and temporal]; Hazlett et al., 2006 [frontal and temporal]); Bloss and Courchesne 2007 [temporal]; Brieber et al. (2007) [inferior parietal cortex]. Some white matter enlargement was reported (Courchesne et al., 2001[cerebral]; Carper et al., 2002 [frontal, parietal, temporal]; Herbert et al., 2003 [trend, no enlarged TBV]; Herbert et al., 2004 [WM enlargement for outer zones of all lobes but not for the inner lobes]; Bloss and Courchesne 2007 [temporal]).

Some reported a decrease in volume (Herbert et al., 2003 [cerebral cortex]; Kates et al., 2004 [white matter frontal, temporal, occipital]; Girgis et al., 2007 [gray matter right lateral orbito frontal cortex]). Harden et al. (2006b) reported on increases in total cerebral sulcul and gyral thickness (parietal and temporal).

Ventricles

Howard et al. (2000 [lateral]), Kates et al. (2004), Hazlett et al. (2005) and Palmen et al. (2005 [lateral and 3rd]) found a ventricular volume which was enlarged. Harden et al. (2006) and Brieber et al. (2007) found no enlarged ventricular volume.

Cerebellum

Larger volumes (cerebellar white matter, midsagittal area vermis lobules I-V), and smaller volumes for vermis lobules VI-VII for LFA group were reported by Akshoomoff et al. (2004). Sparks et al. (2002), Herbert et al. (2003) and Palmen et al. (2005) also reported on increased volumes. Kates et al. (2004) and Hazlett et al. (2005) found no differences in gray or white matter. Manes et al. (1999) found no differences in the cerebellum regions I-V, VI-VII, VIII-X. Courchesne et al. (2001) reported less gray matter in cerebellum and smaller vermis lobules VI-VII for autistic boys. Bloss and Courchesne (2007) found reduced gray matter.

Corpus Callosum

No differences were reported by Elia et al. (2000), Herbert et al. (2004) and Boger-Megiddo et al. [although smaller after TBV adjustment](2006), decreases were reported by Manes et al. (1999) (most marked in the body of CC) and Vidal et al. (2006) (anterior third).

Hippocampus and Amygdala

Inconsistent results were found by Nacewicz et al. (2006) (smaller amygdala in one group, no differences in another group). Howard et al. (2000), Sparks et al. (2002) and Schumann et al. (2004 [only in children not in adolescents]) reported on an increase of the amygdala bilaterally. Schumann et al. (2004) found a larger right hippocampal volume and without mental retardation an increased left hippocampal volume.
Sparks et al. (2002) also found an enlarged hippocampal R and L volume. Howard et al. (2000) reported a trend towards decreased hippocampus and parahippocampal gyrus, Saitoh et al. (2001) reported on a decreased area dentata (dentate gyrus + CA4) and no significant differences in CAS (subiculum and CA1 – CA3). Brieber et al. (2007) reported on GM reduction in the hippocampus-amygdala complex. Palmen et al. (2006) reported on no enlargement on hippocampus [after TBV adjustment] and amygdala.

Table 1 Summary of major MRI findings in Autism in children and adolescents

Study	Patients / Controls Mean age (or range) of ASD patients	Results compared to control group
Manes et al., 1999	27/17 (mean 14.3 ± 6.8)	Decreased CC, most marked in body of CC; no differences in the CB regions I-V, VI-VII, VIII-X.
Howard et al., 2000	10/10 (15.8-40.3 yr)	Increased AMYG bilaterally; trend towards decreased hippocampus and parahippocampal gyrus; no differences in overall temp lobe volume; larger lat ventricle and ic volumes
Elia et al., 2000	22/11 (mean 10.9 yr)	No differences in CC
Saitoh et al., 2001	59/51 (29 mnth-43 yr, mean 11.2 sd 9.2 yr)	Decreased area dentata (dentate gyrus + CA4); no significant differences in CAS (subiculum and CA1 – CA3).
Courchesne et al., 2001	60/52 (2-16 yr, mean 6.2 ± 3.5 yr)	Increased cortical GM and cerebral and CB WM in 2-3 yr; less GM in CB, smaller vermis lobules VI-VII for autistic boys.
Nieminen-von Wendt et al., 2002	28/28 (17 adolesc 6-19 yr, mean 12.4 yr; 11 adults 20-60 yr, mean 37.9 yr)	No focal abnormalities; anterior-posterior diameter mesencephalon shorter
Carper et al., 2002	38/39 (2-11 yr, mean 5.7 ± 2.2 yr)	Enlarged frontal, parietal, and temp WM; frontal and temp GM enlargement only in 2-3 yr
Sparks et al., 2002	45/26 (38-54 mnths, mean 47.4 ± 4.2 mnths)	Increased TBV; increased CB volume, hippocampal R and L volume, AMYG R and L volume [not significant after adjustment TBV] (AD and PDD-NOS)
Aylward et al., 2002	67/ 83 (8-46 yr, mean 18.8 yr)	Increased brain volume < 12 years; increased head circumference all ages
Hardan et al., 2003	40/41	No volume differences for basal ganglia (after adjustment TBV)
Herbert et al., 2003	17/15 (7-11 yr)	Diencephalon, cerebral white matter, CB, globus pallidus-putamen larger (without adjustment TBV); cerebral cortex and HIPP-AMYG showed a trend of being smaller (adjusted).
Bigler et al., 2003	38/27, (7-13 yr, mean 5.24 yr)	No volumetric temp lobe differences.
Levitt et al., 2003 3-D mapping	21/20 (mean 10.7 ± 3.1 yr)	Ant and sup shifting of the sup frontal sulci bilaterally; ant shifting of the R Sylvian fissure, the sup temp sulcus and the L inf frontal sulcus.
Courchesne et al., 2003	48/normative data (2-5 yr)	Smaller head circumference at birth; sudden and excessive increase at 1-2 and 6-14 months.

Table 1 Continued I

Study	Patients / Controls Mean age (or range) of ASD patients	Results compared to control group
Akshoomoff et al., 2004	52/15 (1.9-5.2 yr)	TBV and cerebral volume, especially GM, larger for LFA; no WM differences; larger CB WM volume and larger midsagittal area CB vermis lobules I-V for all ASS subjects (AD and PDD-NOS), vermis lobules VI-VII smaller for LFA group.
Herbert et al., 2004	13/14 (5.7-11.3 yr, mean 9.0 ± 0.9 yr)	Enlargement of WM outer zone of alle lobes; no difference for inner lobes; cerebral cortex, CC, internal capsule volume no differences.
Lotspeich et al., 2004	52/24 (7.8-17.9 yr)	Increased cerebral GM for LFA and HFA
Kates et al., 2004	18/16, (5.3-13.8 yr, mean 8.4 yr)	Decrease of WM volume frontal, temp & occipital (for the AD and broad-phenotype of the discordant twin pairs). No CB differences. Enlarged VV for the autistic group.
Schumann et al., 2004	63/22 (7.5-18.5 yr)	No differences for TBV. Larger R and LAMYG in children not in adolescents; larger R HIPP volume; increased L HIPP volume without MR
Palmen et al., 2005	21/21 (6.9-14.6 yr, mean 11.12 ± 2.2 yr)	Overall brain enlargement: ic, TBV, cerebral GM (frontal, parietal, temp) and CB volume enlarged; VV disproportionally enlarged (lat and 3rd)
Hazlett et al., 2005	51/25 (mean 2.7 ± 0.3 yr) 113/189 (longitudinal study)	Larger TBV, VV, WM and GM); no enlarged CB volume Normal head circumference at birth, growth beginning around 12 mnths of age.
Rojas et al., 2005	12/12 (mean 11.7 ± 3.3 yr)	Smaller L PT, lack of PT asymmetry, no differences in Heschl's gyrus.
Voebel et al., 2006	38/13 (7-13 yr, mean 10.16 ± 1.92)	Larger R and L caudate volumes (autism and Asperger), after controlling for ic volume
Nacewicz et al., 2006	28/26 (8-25 yr)	Smaller AMYG L and R in one group (16/14, mean 19 yr), no differences in other group (12/12) (AD, Asp, PDD-NOS)
Hazlett et al., 2006	23/15 (13-29 yr, mean 19.1 ± 4.6)	TBV enlarged; Increased GM volume; frontal and temp lobe enlarged; no enlargement for parietal and occipital lobes
Harden et al., 2006	40/41 (8-45 yr, mean 19.3 ± 9.9 yr)	No enlarged thalamus (no TBV adjustment); no linear relationship TBV and thalamic volume in AD
Harden et al., 2006	17/14 (mean 10.5 ± 1.5 yr)	No differences in TBV, VV, ic volume; Increases in total cerebral sulcul and gyral thickness (parietal and temporal)
Boger-Megiddo et al., 2006	45/26 (mean 47.4 ± 4.2 mnths)	No differences in CC, smaller after TBV adjustment
Palmen et al., 2006	42/42 (mean 15.6 ± 5.25 yr)	AMYG not enlarged, no enlarged HIPP afterTBV adjustment

Table 1 Continued II

Study	Patients / Controls Mean age (or range) of ASD patients	Results compared to control group
Vidal et al., 2006 (Including 3D)	24/26 (mean 10.0 ± 3.3 yr)	Smaller CC (and ant third of CC); in 3D smaller splenium and genu.
Girgis et al., 2007	11/18 (8.1-12.7 yr)	Decreased GM in R lat orbitofrontal cortex (also after adjustment TBV); no WM differences
Langen et al., 2007	21/21 (mean 11.12 ± 2.2 yr) and 21/21 (mean 20.1 ± 3.1 yr)	Enlarged nucleus caudatus and putamen, also after adjustment TBV; enlarged putamen in young AD
Bloss et al., 2007	36/27 (1.96-5.33 yr)	Enlarged temporal WM an GM; smaller CB GM
Brieber et al., 2007 sMRI and voxel-based	15/15 (& 15 ADHD) (10-16 yr)	Compared to controls: No total volume (GM, WM), CSF differences; GM reduction in L medial temp lobe, HIPP-AMYG complex, L middle occipital gyrus, L premotor gyrus; increased GM in L inf parietal cortex; increased GM in R supramarginal gyrus, L postcentral gyrus.
Hardan et al., 2008	12/12 (10-35 yr, mean 16.4 ± 8.0 yr))	No thalamic differences; no TBV differences
Voxel-based studies		
Kwon et al., 2004	20 (AD and Asp) /13 (mean 13.6 ± 3.4 yr/ 13.6 ± 2.5yr)	Decreased GM density in ventromedial aspects of the temp cortex
Waiter et al., 2004	16/16 (mean 15.4 ±2.24 yr)	Total GM increased; local volume increase in R fusiform gyrus, R temp-occiptal region and L frontal pole.; local GM decrease in R thalamus. No WM differences.
Chung et al., 2004	16/12 (mean 16.1 ± 4.5 yr)	Less WM concentration in the genu, rostrum, splenium-not midbody- of the CC; increase (2.5%) over time was found for the genu.
Boddaert et al., 2004	21/12 (mean 9.3 ± 2.2 yr)	Decreases in GM concentration in the sup temp sulcus and in the WM concentration in the R temp pole and CB
McAlonan et al., 2005	17/17 (mean 12 ± 1.8 yr)	Decreased GM total volume; increased CSF; no difference in TBV or total WM volume; GM reduction in R orbital, inf & middle frontal gyri, caudate nucleus, ventral temp lobe, medial parietal lobe; L orbital, middle & medial frontal gyri, middle & sup temp gyri, caudate nucleus, medial parietal lobe; WM reduction in CB (19%), L internal capsule & bilaterally fornices (21%)

Table 1 Continued III

Study	Patients / Controls Mean age (or range) of ASD patients	Results compared to control group
Salmond et al., 2005	14/13 (mean 12.9 ± 0.7 yr)	Increase of GM density bilaterally fusiform gyrus, inf CB, dorsolateral prefrontal cortex, peri-HIPP cortex, lat occipitotemp sulcus
Rojas et al., 2006	24/23 (7.8-44 yr, mean 20.8 ± 10.6 yr)	No differences for TBV, GM, WM; enlarged medial frontal gyri, L pre-frontal gyrus, R post central gyrus, R fusiform gyrus, nucleus caudatus L and R, L HIPP

AMYG= amygdala; AD=Autistic Disorder; ant=anterior; Asp=Asperger Disorder; CC= Corpus Callosum; CB= Cerebellum; CSF= Central System Fluid; GM= Gray Matter; HIPP= Hippocampus; HFA= High-Functioning Autism; inf= inferior; ic= intra-cranial; L= Left; lat= lateral; LFA= Low-Functioning Autism; MR= Mental Retardation; PDD-NOS= Pervasive Developmental Disorder Not Otherwise Specified; post= posterior; PT= Planum Temporale; R= Right; sup= superior; TBV= Total Brain Volume; temp= temporal; VV= Ventricle volume

Corpus Striatum

Larger left and right caudate volumes were reported by Voebel et al. (2006). Larger globus pallidus-putamen volumes were found by Herbert et al. (2003). Langen et al. (2007) found an enlarged caudatus and putamen [also after TBV adjustment].

Additional

A shorter anterior-posterior diameter of the mesencephalon was reported by Nieminen-von Wendt et al. (2002), and an enlarged diencephalon was found by Herbert et al. (2003). No volume differences were found for the internal capsule (Herbert et al., 2004). A smaller left Planum Temporale (PT) and lack of asymmetry in PT, and no differences in Heschl's gyrus was found by Rojas et al. (2005). No enlarged thalamus was found by Harden et al. (2006a, 2008).

Very early onset of schizophrenia (VEOS) and COS in sMRI studies

Cerebrum

Smaller cerebral volume (Giedd et al., 1999; Kumra et al., 2000 [not for the anterior frontal and temporal lobe]; Badura et al., 2001; Sporn et al., 2003 [only frontal and parietal gray matter]; Ballmaier et al., 2004; Marquardt et al., 2005), and smaller cortical thickness (Greenstein et al., 2006) was reported. Also a progressive loss over time was repeatedly found (Gied et al., 1999 [total cerebrum]; Rapoport et al., 1999 [frontal, parietal, temporal gray matter]; Keller et al., 2003 [total cerebrum]; Sporn et al., 2003 [total cerebrum, frontal, parietal, temporal gray matter]; Gogtay et al., 2004 [total, frontal, temporal & parietal gray matter]; Greenstein et al., 2006 [prefrontal and

temporal cortex; Vidal et al., 2006 [superior medial frontal and right medial frontal cortex gray matter). Levitt et al. 2001 found no differences for the total brain volume, Kumra et al. (2000) found no differences for the superior temporal gyrus. Taylor et al. (2005) found a bilaterally enlargement of the posterior superior temporal gyrus (white matter) and an increase of white matter in the right Heschl's gyrus.

Ventricles

Larger ventricles were reported by Giedd et al. (1999[lateral]), Kumra et al. (2000[lateral]), Badura et al. (2001[esp. frontal horns and 3rd ventricle]). Also increases over time were reported (Giedd et al., 1999; Sporn et al., 2003).

Cerebellum

No differences for the cerebellum were found on an initial scan by Keller et al. (2003), but they did find a progressive loss of cerebellar volume during adolescence (except for the vermal area and posterior-inferior volume).

Corpus Callosum

Kumra et al. (2000) found no differences.

Hippocampus and Amygdala

Giedd et al. (1999) found no differences at initial scan, and a decreased volume for the amygdala but not for the hippocampus at follow-up. Kumra et al. (2000) found no differences for hippocampus or amygdala. Levitt et al. (2001) found a larger amygdala (esp. on the left side) but no differences for the hippocampus. Nugent et al. (2006) found smaller hippocampal volumes bilaterally, which remained significant over time.

Corpus Striatum

Kumra et al. (2000) found an enlarged volume of the basal ganglia.

Cingulate gyrus

Vidal et al. (2006) reported gray matter loss in the left cingulate gyrus. Marquardt et al. (2005) found a larger right anterior cingulated gyrus, but decreases of the volume with age.

Additional

No differences for the nucleus accumbens were reported (Ballmaiar et al., 2004). Nopoulos et al. (1998) found an enlarged and more anomalies in the cavum septi pellucidi.

Table 2 Summary of major MRI findings in COS / VEOS

Study	Patients / Controls / Mean age (or range) of COS patients	Results compared to control group
Nopoulos et al., 1998	24/95 (9-19 yr, mean 14.6 ± 2.1 yr)	Enlarged and more anomaly in the cavum septi pellucidi
Rapoport et al., 1999	15/34 (initial scan: 9.2-17.9, mean 13.9 ± 2.3 yr, at follow-up 13.3-23.3, mean 18.1 ± 2.7 yr)	Decrease in cerebral GM (frontal, parietal, and temp , but not occipital region).; no WM change differences.
Giedd et al., 1999	42/74 (initial scan: mean 14.8 ± 2.5 yr, at follow-up 16.2 ± 3.1 yr)	Initial scan: smaller TBV, larger lat ventricle, no differences for AMYG and HIPP volumes. Decreased volume of total cerebrum and HIPP and increased volume lat VV but not for the AMYG at follow-up; no asymmetry effects for any of the structures
Kumra et al., 2000	44/64 (14.4 ± 2.3 yr)	Smaller TBV, smaller midsagittal thalamic area, enlarged volume basal ganglia, enlarged lateral VV (adjusted TBV); no differences for CC, anterior frontal, temp lobe, HIPP, sup temp gyrus, AMYG.
Badura et al., 2001	19/19 (7-16 yr, mean 12.6 ± 3.3 yr)	(CAT- scans) TBV reduced (9%); Increased VV, for VEOS group; more pronounced liquor spaces (frontal horns and 3rd ventricle) in pt with longer history of illness.
Levitt et al., 2001	13/20 (8.6- 20.0 yr, mean 14.2 ± 3.8 yr)	Larger AMYG especially L (adjustment for TBV). No differences for the HIPP no differences in TBV
Keller et al., 2003	50/101 (initial scan 14.8 ± 2.5 yr, mean interval between scans 2.4 yr))	Initial scan: no differences for total cerebrum, CB or vermis. Progressive loss of total cerebrum and CB volume during adolescence; no age related changes for vermal area and post-inf volume. (no differences at initial scan)
Sporn et al., 2003	60-39/64-43 (mean 14.5 ± 2.5 yr, 2 yr interval)	Larger lat ventricles and decreased frontal and parietal GM; at follow-up progressive reduction of GM (19.4%) and increased lateral VV (41.3%)
Vidal et al., 2006	12/12 (mean 14.1 ± 2.7 yr; mean at follow-up 18.7 ± 3.1 yr)	(3D-MRI) GM loss in sup medial frontal regions (sup frontal and precentral gyri), L cingulated gyrus, L and R medial frontal cortex
Sporn et al., 2003	60/64 (mean 14.5 ±2.5 yr); 39/43 at follow-up (mean 18.4 ± 2.1 yr)	At initial scan less frontal, parietal GM and larger VV. Nonlinear decline for total cerebral volume, total, frontal, parietal and temp GM volumes, linear increase for lat VV
Gogtay et al., 2004	23/38 (mean 13.9 ± 2.5 yr; at follow-up mean 16.4 ±2.5 yr)	Greater total, frontal, temp, and parietal GM loss over time, but not occipital

Table 2 Continued

Study	Patients / Controls / Mean age (or range) of COS patients	Results compared to control group
Ballmaier et al., 2004	12/15 (mean 11.4 ±3.0 yr)	No differences for the nucleus accumbens (adjusted for TBV); smaller TBV;
Taylor et al., 2005	18/16 (mean 11.8, ± 3.2 yr)	Bilaterally enlargement of post sup temp gyrus (WM) volume; increase of WM in R Heschl's gyrus
Marquardt et al., 2005	13/18 (8-17 yr, mean 12.0 ±3.0 yr)	Larger R ant cingulated gyrus (ACG); reduced L ward skew of double cingulate sulcal pattern; absence of normal L>R ant cingulated gyrus volume asymmetry; decreases ant cingulated gyrus volumes with age; smaller TBV (TBV adjustment).
Greenstein et al., 2006	70/72 (7-26 yr, mean 16.9 ± 3.6 yr)	Smaller mean cortical thickness; cortical thickness loss in prefrontal and temp regions throughout the age range (also after TBV adjustment)
Nugent et al., 2006	29/31 (9-26 yr, mean age over 5 scans: 17.6 yr)	Consistent over time smaller total HIPP volume bilateral (progressive loss in ant and post ends, modest gain in the body) (adjusted for TBV)
Voxel-based studies		
Sowell et al., 2000	10/9 (14.4 ± 3.6 yr)	Larger volumes in the post horns of the lat ventricles; midcallosal, post cingulated, caudate, and thalamus abnormalities.

AMYG= amygdala; AD=Autistic Disorder; ant=anterior; Asp=Asperger Disorder; CC= Corpus Callosum; CB= Cerebellum; CSF= Central System Fluid; GM= Gray Matter; HIPP= Hippocampus; HFA= High-Functioning Autism; inf= inferior; ic= intra-cranial; L= Left; lat= lateral; LFA= Low-Functioning Autism;

Discussion

For none of the structures all studies revealed the same conclusions. This could be due to the heterogeneity of the illness or due to the differences in methods that have been used. Although a comparison between all the above described studies is hindered by the differences in groups and techniques, some conclusions can be made.

For autism in most studies a larger cerebrum and its separate structures, cerebellum and ventricles are found (see **table 1**). Interesting are the longitudinal studies which suggest an enlargement of the brain during a time-limited period and normalization after that. However, the literature is not consistent about this item. For the smaller structures the number of studies is limited and by that conclusions can not be made. Newer techniques as voxel-based studies are not very helpful for a more uniform outcome (Kwon et al., 2004; Waiter et al., 2004; Chung et al.,

2004; Boddaert et al., 2004; McAlonan et al., 2005: Salmond et al., 2005, Rojas et al., 2006, see **table 1**). For childhood-onset schizophrenia (and veos) in most studies a (progressive) smaller cerebrum and its separate structures is found (see **table 2**). A (progressive) enlargement of the ventricles is another replicated finding. For the cerebellum and other smaller structures the number of studies is too limited to draw any conclusions. The only consistent abnormality found in autism as well as in VEOS / COS is a larger ventricle volume (Howard et al., 2000; Palmen et al., 2005; Kates et al., 2004; Giedd et al., 1999; Kumra et al., 2000; Badura et al., 2001; Hazlett et al., 2005).
It can be concluded that more recent sMRI research confirmes the earlier reports (Lahuis et al., 2003). As mentioned before, correlations on ventricular enlargement and symptoms are described (Andreassen et al., 1990; Young et al., 1991; Rapoport et al., 1997). However, there is a lack of studies which consequently used standardized (symptoms) scoring scales for the included patients and made correlations with the results of the sMRI findings.

In the earlier report different methodological problems are mentioned. For example diagnostic variability, variations within and between subjects, and the various quantitative and qualitative methods which hinder the inter alia comparison of the sMRI studies (see Lahuis et al., 2003). Although more studies have been published in the past years with larger and better identified groups, the above mentioned methodological problems are still an issue. For example the problem of diagnostic variability: some studies included only patients with autism, others included autism and asperger patients and others also included pdd-nos patients.
On the other hand there is more uniformity in the sMRI technique and uniformity in the diagnosis (using the ADI-R and /or ADOS) than before. Although there is more uniformity in the sMRI technique, the limitations of the structural techniques have led to the introduction of new techniques as 3D and voxel-by-voxel based techniques.
For getting more insights in these illnesses large samples and longitudinal follow-up studies are needed. A proposal for more uniform research approaches and cooperation between institutes is given by Belmonte and colleagues (Belmonte et al., 2007). To get more insight in the possible overlap between autism spectrum and schizophrenia spectrum disorders, different research instruments (e.g. diagnostic and clinical correlates, imaging, psychophysiological tools) need to be combined in large samples of both groups.

References

Akshoomoff N, Lord C, Lincoln AJ, Courchesne RY, Carper RA, Townsend J, Courchesne E (2004). Outcome classification of preschool children with autism spectrum disorders using MRI brain measures. J Am Acad Child Adolesc Psychiatry 43(3):349-57.

Andreasen NC, Ehrhardt JC, Swayze V et al. (1990). Magnetic resonance imaging of the brain in schizophrenia: The pathophysiologic significance of structural abnormalities. Arch Gen Psychiatry 47:35-44.

Aylward EH, Minshew NJ, Field K, Sparks BF, Singh N (2002). Effects of age on brain volume and head circumference in autism. Neurology 23;59(2):175-83.

Badura F, Trott GE, Mehler-Wex C, Scheuerpflug P, Hofmann E, Warmuth-Metz M, Nadjmi M, Solymosi L, Warnke A (2001). A study of cranial computer tomograms in very early and early onset schizophrenia. J Neural Transm108(11):1335-44.

Ballmaier M, Toga AW, Siddarth P, Blanton RE, Levitt JG, Lee M, Caplan R (2004). Thought disorder and nucleus accumbens in childhood: a structural MRI study. Psychiatry Res 15;130(1):43-55.

Belmonte MK, Mazziotta JC, Minshew NJ, Evans AC, Courchesne E, Dager SR, Bookheimer SY, Aylward EH, Amaral DG, Cantor RM, Chugani DC, Dale AM, Davatzikos C, Gerig G, Herbert MR, Lainhart JE, Murphy DG, Piven J, Reiss AL, Schultz RT, Zeffiro TA, Levi-Pearl S, Lajonchere C, Colamarino SA (2007). Offering to Share: How to Put Heads Together in Autism Neuroimaging. J Autism Dev Disord Mar 9; [Epub ahead of print]

Bigler ED, Tate DF, Neeley ES, Wolfson LJ, Miller MJ, Rice SA, Cleavinger H, Anderson C, Coon H, Ozonoff S, Johnson M, Dinh E, Lu J, Mc Mahon W, Lainhart JE (2003). Temporal lobe, autism, and macrocephaly. Am J Neuroradiol 24(10):2066-76.

Bloss CS, Courchesne E (2007). MRI neuroanatomy in young girls with autism: a preliminary study. J Am Acad Child Adolesc Psychiatry 46(4):515-23.

Boddaert N, Chabane N, Gervais H, Good CD, Bourgeois M, Plumet MH, Barthelemy C, Mouren MC, Artiges E, Samson Y, Brunelle F, Frackowiak RS, Zilbovicius M (2004). Superior temporal sulcus anatomical abnormalities in childhood autism: a voxel-based morphometry MRI study. Neuroimage 23(1):364-9.

Boger-Megiddo I, Shaw DW, Friedman SD, Sparks BF, Artru AA, Giedd JN, Dawson G, Dager SR (2006). Corpus callosum morphometrics in young children with autism spectrum disorder. J Autism Dev Disord 36(6):733-9.

Brieber S, Neufang S, Bruning N, Kamp-Becker I, Remschmidt H, Herpertz-Dahlmann B, Fink GR, Konrad K (2007). Structural brain abnormalities in adolescents with autism spectrum disorder and patients with attention deficit/hyperactivity disorder. J Child Psychol Psychiatry 48(12):1251-8.

Carper RA, Moses P, Tigue ZD, Courchesne E (2002). Cerebral lobes in autism: early hyperplasia and abnormal age effects. Neuroimage 16(4):1038-51.

Chung MK, Dalton KM, Alexander AL, Davidson RJ (2004). Less white matter concentration in autism: 2D voxel-based morphometry. Neuroimage 23(1):242-51.

Courchesne E, Carper R, Akshoomoff N (2003). Evidence of brain overgrowth in the first year of life in autism. JAMA 16; 290(3):337-44.

Courchesne E, Karns CM, Davis HR, Ziccardi R, Carper RA, Tigue ZD, Chisum HJ, Moses P, Pierce K, Lord C, Lincoln AJ, Pizzo S, Schreibman L, Haas RH, Akshoomoff NA, Courchesne RY (2001). Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study. Neurology 24;57(2):245-54.

Elia M, Ferri R, Musumeci SA, Panerai S, Bottitta M, Scuderi C (2000). Clinical correlates of brain morphometric features of subjects with low-functioning autistic disorder. J Child Neurol 15(8):504-8.

Giedd JN, Jeffries NO, Blumenthal J, Castellanos FX, Vaituzis AC, Fernandez T, Hamburger SD, Liu H, Nelson J, Bedwell J, Tran L, Lenane M, Nicolson R, Rapoport JL (1999). Childhood-onset schizophrenia: progressive brain changes during adolescence. Biol Psychiatry 1; 46(7):892-8.

Girgis RR, Minshew NJ, Melhem NM, Nutche JJ, Keshavan MS, Hardan AY (2007). Volumetric alterations of the orbitofrontal cortex in autism. Prog Neuropsychopharmacol Biol Psychiatry 30;31(1):41-5.

Gogtay N, Sporn A, Clasen LS, Nugent TF 3rd, Greenstein D, Nicolson R, Giedd JN, Lenane M, Gochman P, Evans A, Rapoport JL (2004). Comparison of progressive cortical gray matter loss in childhood-onset schizophrenia with that in childhood-onset atypical psychoses. Arch Gen Psychiatry 61(1):17-22.

Greenstein D, Lerch J, Shaw P, Clasen L, Giedd J, Gochman P, Rapoport J, Gogtay N (2006). Childhood onset schizophrenia: cortical brain abnormalities as young adults. J Child Psychol Psychiatry 47(10):1003-12.

Hardan AY, Kilpatrick M, Keshavan MS, Minshew NJ (2003). Motor performance and anatomic magnetic resonance imaging (MRI) of the basal ganglia in autism. J Child Neurol 18(5):317-24.

Hardan AY, Girgis RR, Adams J, Gilbert AR, Keshavan MS, Minshew NJ (2006a). Abnormal brain size effect on the thalamus in autism. Psychiatry Res 30;147(2-3):145-51.

Hardan AY, Muddasani S, Vemulapalli M, Keshavan MS, Minshew NJ (2006b). An MRI study of increased cortical thickness in autism. Am J Psychiatry 163(7):1290-2.

Hazlett HC, Poe M, Gerig G, Smith RG, Provenzale J, Ross A, Gilmore J, Piven J (2005). Magnetic resonance imaging and head circumference study of brain size in autism: birth through age 2 years. Arch Gen Psychiatry 62(12):1366-76.

Hardan AY, Girgis RR, Adams J, Gilbert AR, Melhem NM, Keshavan MS, Minshew NJ (2008). Brief Report: Abnormal Association Between the Thalamus and Brain Size in Asperger's Disorder. J Autism Dev Disord 38(2):390-4.

Hazlett HC, Poe MD, Gerig G, Smith RG, Piven J (2006). Cortical gray and white brain tissue volume in adolescents and adults with autism. Biol Psychiatry 1; 59(1):1-6. Herbert MR, Ziegler DA, Makris N, Filipek PA, Kemper TL, Normandin JJ, Sanders HA, Kennedy DN, Caviness VS Jr (2004). Localization of white matter volume increase in autism and developmental language disorder. Ann Neurol 55(4):530-40.

Herbert MR, Ziegler DA, Deutsch CK, O'Brien LM, Lange N, Bakardjiev A, Hodgson J, Adrien KT, Steele S, Makris N, Kennedy D, Harris GJ, Caviness VS Jr (2003). Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys. Brain 126 (Pt 5):1182-92.

Howard MA, Cowell PE, Boucher J, Broks P, Mayes A, Farrant A, Roberts N (2000). Convergent

neuroanatomical and behavioural evidence of an amygdala hypothesis of autism. Neuroreport 11;11(13):2931-5.

Kates WR, Burnette CP, Eliez S, Strunge LA, Kaplan D, Landa R, Reiss AL, Pearlson GD (2004). Neuroanatomic variation in monozygotic twin pairs discordant for the narrow phenotype for autism. Am J Psychiatry 161(3):539-46.

Keller A, Castellanos FX, Vaituzis AC, Jeffries NO, Giedd JN, Rapoport JL(2003). Progressive loss of cerebellar volume in childhood-onset schizophrenia. Am J Psychiatry 160(1):128-33.

Kumra S, Giedd JN, Vaituzis AC, Jacobsen LK, McKenna K, Bedwell J, Hamburger S, Nelson JE, Lenane M, Rapoport JL (2000). Childhood-onset psychotic disorders: magnetic resonance imaging of volumetric differences in brain structure. Am J Psychiatry 157(9):1467-74.

Kwon H, Ow AW, Pedatella KE, Lotspeich LJ, Reiss AL (2004). Voxel-based morphometry elucidates structural neuroanatomy of high-functioning autism and Asperger syndrome. Dev Med Child Neurol 46(11):760-4.

Lahuis BE, Kemner C, Engeland Van H(2003). Magnetic Resonance Imaging studies on autism and childhood-onset schizophrenia in children and adolescents; a review. Acta Neuropsychiatrica 15 (3): 140-147.

Langen M, Durston S, Staal WG, Palmen SJ, van Engeland H (2007). Caudate nucleus is enlarged in high-functioning medication-naive subjects with autism. Biol Psychiatry 1;62(3):262-6.

Levitt JG, Blanton RE, Caplan R, Asarnow R, Guthrie D, Toga AW, Capetillo-Cunliffe L, McCracken JT (2001). Medial temporal lobe in childhood-onset schizophrenia. Psychiatry Res 108(1):17-27.

Levitt JG, Blanton RE, Smalley S, Thompson PM, Guthrie D, McCracken JT, Sadoun T, Heinichen L, Toga AW (2003). Cortical sulcal maps in autism. Cereb Cortex 13(7):728-35.

Lotspeich LJ, Kwon H, Schumann CM, Fryer SL, Goodlin-Jones BL, Buonocore MH, Lammers CR, Amaral DG, Reiss AL (2004). Investigation of neuroanatomical differences between autism and Asperger syndrome. Arch Gen Psychiatry 61(3):291-8. Erratum in: Arch Gen Psychiatry 61(6):606.

Manes F, Piven J, Vrancic D, Nanclares V, Plebst C, Starkstein SE (1999). An MRI study of the corpus callosum and cerebellum in mentally retarded autistic individuals. J Neuropsychiatry Clin Neurosci 11(4):470-4.

Marquardt RK, Levitt JG, Blanton RE, Caplan R, Asarnow R, Siddarth P, Fadale D, McCracken JT, Toga AW (2005). Abnormal development of the anterior cingulate in childhood-onset schizophrenia: a preliminary quantitative MRI study. Psychiatry Res 30;138(3):221-33.

McAlonan GM, Cheung V, Cheung C, Suckling J, Lam GY, Tai KS, Yip L, Murphy DG, Chua SE (2005). Mapping the brain in autism. A voxel-based MRI study of volumetric differences and intercorrelations in autism. Brain 128(Pt 2):268-76.

Nacewitz BM, Dalton KM, Johnstone T, Long MT, McAuliff EM, Oakes TR, Alexander AL, Davidson RJ (2006). Amygdala volume and nonverbal social impairment in adolescent and adult males with autism.

Arch Gen Psychiatry 63:1417-1428.

Nieminen-von Wendt T, Salonen O, Vanhala R, Kulomaki T, von Wendt L, Autti T (2002). A quantitative controlled MRI study of the brain in 28 persons with Asperger syndrome. Int J Circumpolar Health 61 Suppl 2:22-35.

Nopoulos PC, Giedd JN, Andreasen NC, Rapoport JL (1998). Frequency and severity of enlarged cavum septi pellucidi in childhood-onset schizophrenia. Am J Psychiatry 155(8):1074-9.

Nugent TF 3rd, Herman DH, Ordonez A, Greenstein D, Hayashi KM, Lenane M, Clasen L, Jung D, Toga AW, Giedd JN, Rapoport JL, Thompson PM, Gogtay N (2007). Dynamic mapping of hippocampal development in childhood onset schizophrenia. Schizophr Res 90(1-3):62-70.

Palmen SJ, Hulshoff Pol HE, Kemner C, Schnack HG, Durston S, Lahuis BE, Kahn RS, Van Engeland H (2005). Increased gray-matter volume in medication-naive high-functioning children with autism spectrum disorder. Psychol Med 35(4):561-70.

Palmen SJ, Durston S, Nederveen H, Van Engeland H (2006). No evidence for preferential involvement of medial temporal lobe structures in high-functioning autism. Psychol Med 36(6):827-34.

Rapoport JL, Giedd J, Kumra S (1997). Childhood-onset schizophrenia. Arch Gen Psychiatry 54:897-903.

Rapoport JL, Giedd JN, Blumenthal J, Hamburger S, Jeffries N, Fernandez T, Nicolson R, Bedwell J, Lenane M, Zijdenbos A, Paus T, Evans A (1999). Progressive cortical change during adolescence in childhood-onset schizophrenia. A longitudinal magnetic resonance imaging study. Arch Gen Psychiatry 56(7):649-54.

Rojas DC, Peterson E, Winterrowd E, Reite ML, Rogers SJ, Tregellas JR (2006). Regional gray matter volumetric changes in autism associated with social and repetitive behavior symptoms. BMC Psychiatry 13;6:56.

Rojas DC, Camou SL, Reite ML, Rogers SJ (2005). Planum temporale volume in children and adolescents with autism. J Autism Dev Disord 35(4):479-86.

Saitoh O, Karns CM & Courchesne E (2001). Development of the hippocampal formation from 2 to 42 years: MRI evidence of smaller area dentate in autism. Brain 124:1317-24.

Salmond CH, Ashburner J, Connelly A, Friston KJ, Gadian DG, Vargha-Khadem F (2005). The role of the medial temporal lobe in autistic spectrum disorders. Eur J Neurosci 22(3):764-72.

Schumann CM, Hamstra J, Goodlin-Jones BL, Lotspeich LJ, Kwon H, Buonocore MH, Lammers CR, Reiss AL, Amaral DG (2004). The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages. J Neurosci 14;24(28):6392-401.

Sowell ER, Levitt J, Thompson PM, Holmes CJ, Blanton RE, Kornsand DS, Caplan R, McCracken J, Asarnow R, Toga AW (2000). Brain abnormalities in early-onset schizophrenia spectrum disorder observed with statistical parametric mapping of structural magnetic resonance images. Am J Psychiatry 157(9):1475-84.

Sparks BF, Friedman SD, Shaw DW, Aylward EH, Echelard D, Artru AA, Maravilla KR, Giedd JN, Munson J, Dawson G, Dager SR (2002). Brain structural abnormalities in young children with autism spectrum disorder. Neurology 23;59(2):184-92.

Sporn AL, Greenstein DK, Gogtay N, Jeffries NO, Lenane M, Gochman P, Clasen LS, Blumenthal J, Giedd JN, Rapoport JL (2003). Progressive brain volume loss during adolescence in childhood-onset schizophrenia. Am J Psychiatry 160(12):2181-9.

Taylor JL, Blanton RE, Levitt JG, Caplan R, Nobel D, Toga AW (2005). Superior temporal gyrus differences in childhood-onset schizophrenia. Schizophr Res 1;73(2-3):235-41.

Vidal CN, Nicolson R, DeVito TJ, Hayashi KM, Geaga JA, Drost DJ, Williamson PC, Rajakumar N, Sui Y, Dutton RA, Toga AW, Thompson PM (2006). Mapping corpus callosum deficits in autism: an index of aberrant cortical connectivity. Biol Psychiatry 1;60(3):218-25.

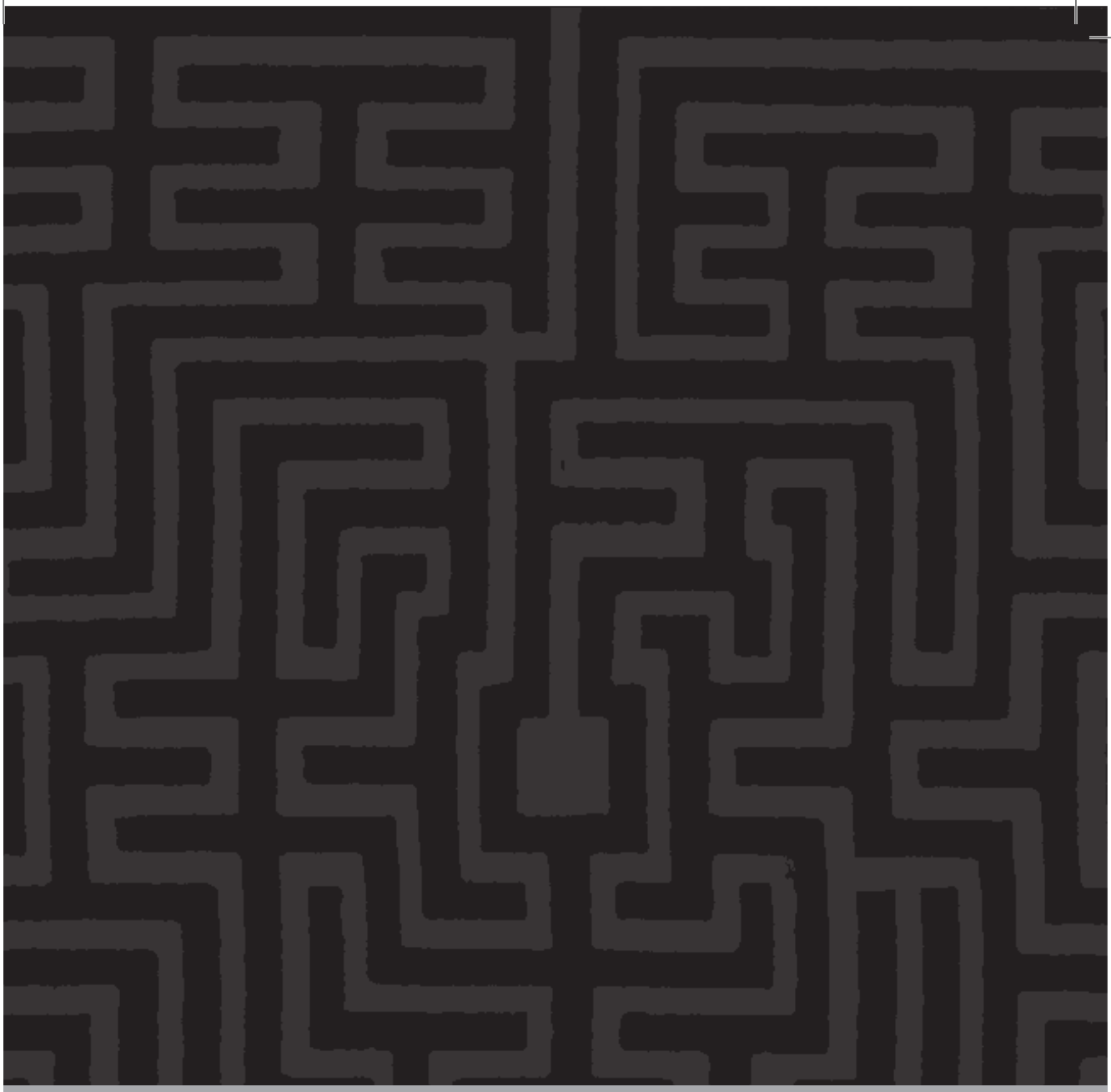
Voelbel GT, Bates ME, Buckman JF, Pandina G, Hendren RL (2006). Caudate nucleus volume and cognitive performance: Are they related in childhood psychopathology? Biol Psychiatry 1;60(9):942-50.

Waiter GD, Williams JH, Murray AD, Gilchrist A, Perrett DI, Whiten A (2004). A voxel-based investigation of brain structure in male adolescents with autistic spectrum disorder. Neuroimage 22(2):619-25.

Young AH, Blackwood DHR, Roxborough H, Mcqueen JK, Martin MJ, Kean D (1991). A magnetic resonance imaging study of schizophrenia: brainstructure and clinical symptoms. Br J Psychiatry 158:158-164.

[3]

Lahuis BE, Durston S, Nederveen H, Zeegers M, Palmen SJMC, Van Engeland H (2007).
Psychological Medicine, Epub 10:1-7



MRI-based morphometry in children with Multiple Complex Developmental Disorder, a phenotypically defined subtype of Pervasive Developmental Disorder Not Otherwise Specified

Abstract

Background

The DSM-IV-R classification Pervasive Developmental Disorder – Not otherwise Specified (PDD-NOS) is based on the symptoms for autism and includes a wide variety of phenotypes that do not meet full criteria for autism. As such, PDD-NOS is a broad and poorly defined residual category of the autism spectrum disorders. In order to address the heterogeneity in this residual category it may be helpful to define clinical and neurobiological subtypes. Multiple Complex Developmental Disorder (MCDD) may constitute such a subtype. In order to study the neurobiological specificity of MCDD in comparison to other autism spectrum disorders, we investigated brain morphology in children (age 7-15 years) with MCDD compared to children with autism and typically developing controls.

Methods

Structural MRI-measures were compared between 22 high-functioning subjects with MCDD and 21 high-functioning subjects with autism and 21 matched controls.

Results

Subjects with MCDD showed an enlarged cerebellum and a trend towards larger grey-matter volume compared to control subjects. Compared to subjects with autism, subjects with MCDD had a smaller intracranial volume.

Conclusions

We report a pattern of volumetric changes in the brains of subjects with MCDD, similar to that seen in autism. However, no enlargement in head size was found. This suggests that although some of the neurobiological changes associated with MCDD overlap with those in autism, others do not. These neurobiological changes may reflect differences in the developmental trajectories associated with these two subtypes of autism spectrum disorders.

Introduction

Autism is a well-defined and validated child psychiatric disorder. It is characterized by impairments in social interaction and communication, restricted repetitive and stereotyped patterns of behaviour, interests and activities, and an onset prior to age three years (American Psychiatric Association, 1994). Individuals diagnosed with Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) are characterized by the same set of impairments, but fail to meet the full criteria for autism and are therefore, often considered to have a milder variant of the disorder. However, the boundaries between PDD-NOS and other developmental disorders are poorly defined and unarticulated. Although PDD-NOS is supposedly a residual category of autism, epidemiological studies have shown that the prevalence of PDD-NOS outnumbers autism by up to three times (Wing and Could, 1979; Fombonne, 2003, 2005) and many children with PDD-NOS occupy beds in child psychiatric wards and have treatment needs similar to those of children with autism. The lack of explicit and positive diagnostic criteria for PDD-NOS hampers neurobiological and epidemiological research of its etiology. Although there is discussion in the literature on different subtypes, there seems to be consensus on the necessity of the issue on differentiating within the PDD group for different reasons such as getting more insight in the neurobiology, developmental trajectories and predictive issues. To address this issue, Cohen and colleagues have attempted to formulate criteria that would define subgroups of PDD-NOS (Cohen et al., 1986, 1987). Perhaps the best defined and validated PDD-NOS subgroup to date is Multiple Complex Developmental Disorder (MCDD) (Towbin et al., 1993; Van der Gaag et al., 1995; Buitelaar & van der Gaag, 1998; Ad-Dab'bagh & Greenfield, 2001). MCDD is characterized by (1) impaired regulation of affective state and anxiety, (2) impaired social behaviour and sensitivity, and (3) impaired cognitive processing (thought disorder) (Cohen et al., 1986; Towbin et al., 1993; Van der Gaag et al., 1995; Buitelaar and Van der Gaag et al., 1998). Similar to children with autism, children with MCDD are disturbed in their social interactions, communication, and display stereotyped and rigid behaviour (Van der Gaag et al., 1995). However, these behaviours are typically less marked in MCDD than in autism. Children with MCDD are further similar to children with autism in that they show some developmental delays in a number of domains, including language (late speech development), motor development (late walking), as well as physicial development (young skeletal age and more neurological soft signs and clumsiness than in children with other psychiatric diagnoses) (Van der Gaag, 1993). In contrast, children with MCDD are found to be more impaired than children with autism on measures of (pre-) psychotic thinking (e.g., overengagement with fantasy figures; magical thinking; irrationality; marked loosening of association; marked fantasy activity;

bizarre delusions), aggression (e.g, hurting other people; aggressive behaviour 'outside' and within the family; lack of appreciation of danger to others; impulsive behaviour and pervasive hyperactivity), and a 'suspicious' approach (e.g., suspicious or paranoid; odd, one-sided inappropriate approach; feeling of loneliness) (Van der Gaag, 1993; Van der Gaag et al., 1995; Buitelaar & Van der Gaag, 1998). Furthermore, children with MCDD typically have later onset of symptoms than their counterparts with autism (95% of children with autism has onset of symptoms before 30 months of age, versus 43% of children with MCDD), as well as higher verbal IQ scores, more family adversity and a higher incidence of psychiatric problems, a higher incidence of abnormal EEGs, and a higher incidence of schizophrenia spectrum disorders later in life (Van der Gaag, 1993; Van Engeland & Van der Gaag, 1994). Two studies investigating the neurobiological basis of MCDD have suggested that there may be differences between children with MCDD and autism in event-related-potentials to visual odd-balls, as well as in cortisol response to psychosocial stress (Kemner et al., 1999; Jansen et al., 2003). Taken together, these reports suggest that children with MCDD may represent a subtype of PDD-NOS that is neurobiologically and clinically distinct from autism (Buitelaar & Van der Gaag, 1998).

Structural neuroimaging studies in children with autism have demonstrated that this disorder is associated with changes in brain volume compared to typically developing children. The most reliable finding to date is probably that total brain and intracranial volume are increased in children with autism (Courchesne et al., 2001; Cody et al., 2002; Sparks et al., 2002; Palmen & Van Engeland, 2004; Palmen et al., 2005; Lainhart, 2006), although this enlargement may be limited to early childhood (Courchesne et al., 2001; Aylward et al., 2002), or to individuals with high functioning autism (Akshoomoff et al., 2002; Palmen & Van Engeland, 2004; Palmen et al., 2005).

We set out to investigate to what extent children with MCDD show changes in brain volume similar to those found in children with autism and whether there are changes that differentiate between these two forms of PDD. To limit the heterogeneity in the samples investigated and as previous studies of MCDD all investigated high-functioning individuals (Van England & Van der Gaag, 1994; Van der Gaag et al., 1995; Kemner et al., 1999; Jansen et al., 2003), we included only high-functioning individuals. We collected MRI-scans from a group of high-functioning children with MCDD and compared brain volumetric measures to those from (1) typically developing children and (2) high-functioning children with autism, matched for age, IQ, hand preference, socioeconomic status and gender. We hypothesized that children with MCDD would show changes in brain volume similar to those found in the children with autism, but to a lesser extent. Specifically, we hypothesized that they would have larger total brain volume and larger ventricles. However, we reasoned that if MCDD does truly represent a neurobiologically distinct subtype of

PDD, with an increased risk of psychosis, this may be reflected in neurobiological measures and therefore we might also expect differences between brain changes in autism and MCDD. Therefore, we formulated the alternative hypothesis that children with MCDD might display the *opposite* of children with autism and have decreases in the total brain volume. An enlargement of ventricle volumes would be expected in both cases. However, given that none of the children in our sample have a history of psychosis, we focused on the first hypothesis of brain enlargement.

Methods

Subjects

Twenty-two male subjects meeting the criteria for PDD-NOS (American Psychiatric Association, 1994) and MCDD as defined by Cohen et al. (1986, 1987), and 21 subjects meeting the criteria for autism (American Psychiatric Association, 1994) were included. All subjects with autism and MCDD were recruited through the (out)-patient clinic at the Department of Child Psychiatry Unit at the University Medical Centre Utrecht or the National Autism Society in the Netherlands. The diagnosis was established by expert clinical opinion (HvE, BL) and confirmed using the Autism Diagnostic Interview- Revised version (ADI-R) (LeCouteur et al., 1989). Subjects were required to meet ADI-R criteria for autism as they are typically employed in research studies (a score within two points of full criteria) (Cox et al., 1999; Sparks et al., 2002; Palmen et al., 2005). One subject in the autism group did not meet this criterion, but was included in the study, as a panel of experts agreed that the low score on ADI-interview was due to underreporting by the parent. Eighty-one percent (17 patients) of the subjects with autism fulfilled the traditional ADI-R threshold in all three domains (Lord et al., 1994); ninety-five % (20 subjects) fulfilled the modified criteria. Fifty-nine percent (13 patients) of the subjects with MCDD met traditional ADI-R threshold for autism, whereas 95 % (21 subjects) of the MCDD subjects reached criteria when modified research criteria were applied. All subjects with MCDD met Cohen's criteria for MCDD (a minimum of six of 14 criteria, including at least two criteria from each of the three domains, whereas none of the subjects with autism did (see **Table 1**; Cohen et al., 1987). Mean score on the MCDD criteria for the subjects with autism was 3.5, compared to 8.6 for subjects with MCDD ($t=8.6$, $df = 38$, $p< 0.001$). Subjects with MCDD were matched to 21 subjects with autism and 21 controls for gender, age, height, weight , IQ, hand preference and parental socio-economic status, expressed as the highest completed level of education by either parent (see **Table 2**). Results from the sample of subjects with autism and controls have been previously reported (Palmen et al., 2005). Subjects with major physical or neurological illness (e.g. epilepsy) or full-scale IQ < 70 were excluded. All subjects were male and of Caucasian ethnicity. None of the subjects met criteria for any DSM-

Table 1 Diagnostic criteria for MCDD (Cohen et al., 1987)

MCDD is a serious, early onset and persistent disturbance affecting several major domains of functioning, including the following three major areas:
1. Regulation of affective state and anxiety is impaired beyond that seen in children of comparable age, as exemplified by several of the following: (at least two of the following)
a) intense generalized anxiety or tension
b) fears and phobias (often unusual and peculiar)
c) recurrent panic episodes or 'flooding' with anxiety
d) episodes of behavioral disorganization punctuated by markedly immature, primitive or violent behaviors
e) significant and wide emotional variability with or without environmental precipitants.
f) frequent idiosyncratic or bizarre anxiety reactions
2. Consistently impaired social behavior/sensitivity, as exemplified by the following types of disturbances: (at least two of the following)
a) social disinterest, detachment, avoidence or withdrawal despite evident competence
b) severely impaired peer relationships
c) markedly disturbed attachments; high degrees of ambivalence to adults (esp.parents/ caretakers)
d) profound limitations in the capacity for empathy or understanding others affects accurately
3. Impaired cognitive processing (thinking disorder), as exemplified by some of the following difficulties: (at least two of the following)
a) irrationality,sudden intrusions on normal thought process, magical thinking, neologism or repetitions of nonsense words, desultory thinking, blatantly illogical, bizarre ideas
b) confusion between reality and inner fantasy life
c) perplexity and easy confusability (trouble with understanding ongoing social processes or keeping one's thoughts 'straight')
d) 'delusions', over valued ideas including fantasies of omnipotence, paranoid preoccupations, overengagement with fantasyfigures, grandiose fantasy of special powers, and referential ideation
4. The syndrome appears during the first several years of life
5. The child is not suffering from autism or schizophrenia

IV-TR diagnosis other than autism (autism group) or PDD-NOS (MCDD-group). Ten of 22 subjects with MCDD were on medication. All ten were taking risperidone for typical symptoms of MCDD, such as problems with affective regulation, combined with episodes of aggressive behaviour, anxieties, disorganized behaviour and problems separating fantasy from reality. One patient was also taking an SSRI for affective symptoms and one patient was taking methylphenidate for attentional problems. All subjects that met inclusion criteria were asked to participate in a 35-minute MR- scan and neuropsychological assessment in order to estimate

Table 2 Demographic data

	MCDD	Autism	Control
age (years), mean ± sd	10.94 ± 1.95	11.12 ± 2.18	10.37 ± 1.84
total iq, mean ± sd	99 ± 13*	107 ± 14	103 ± 15
handedness, (right/left), no	20/2	20/1	19/2
parental education, mean ± sd	12.95 ± 2.77	14.10 ± 2.45#	12.84 ± 2.63
Height	152 ± 12	149 ± 16	146 ± 16
Weight	45.0 ± 13.7	38.8 ± 11.8	38.6 ± 10.1
Medication	9 risperidone, 1 pipamperon, 2 additional fluoxetine or methylphenidate	none	none
adi-r domain scores			
social interaction	17.73 ± 5.17	16.38 ± 4.61	
communication	13.68 ± 5.52	13.00 ± 4.59	
repetitive & stereotyped behavior	4.14 ± 2.53	4.14 ± 2.31	
score on cohen's mcdd scale mean ± sd	8.62 ± 2.40*	3.26 ± 1.37#	

*1 missing data; # 2 missing data

full-scale IQ [Wechsler Intelligence Scale for Children - Revised (WISC-R)] (Vandersteene et al., 1986). The procedure was approved by the institutional review board at our institute. MRI-scans were evaluated by independent clinical neuroradiologists. No clinically relevant abnormalities were present in any of the subjects included in the study.

MRI scan acquisition and analysis

The same scanner and procedures as in the Palmen et al. (2005) study were used. Magnetic resonance images were acquired on a Philips Gyroscan (Philips Medical Systems, Best, The Netherlands) at 1.5 T. For volumetric measurements T1-weighted 3D fast field echo (FFE) scans with 130-150 1.5 mm contiguous coronal slices of the whole head (TE 4.6 ms, TR 30 ms, flip angle 30º, FOV 256 mm, in plane voxel size 1 mm x 1 mm) and T2-weighted dual echo turbo spin echo scans with 65-75 3.0 mm contiguous coronal slices (TE1 14 ms, TE2 80 ms, TR 6350 ms, flip angle 90º, FOV 256 mm, in plane voxel size 1 mm x 1 mm) were acquired. In addition, T2-weighted dual echo turbo spin echo scans with 17 axial 5 mm slices and a 1.2 mm gap (TE1 9 ms, TE2 100 ms, flip angle 90º, FOV 250 mm, in plane voxel size 0.98 mm x 0.98 mm) were acquired for clinical neurodiagnostic evaluation. The processing pipeline has been described previously and included semi-automated assessment of intracranial volume, total brain volume, lateral ventricles, third ventricle and cerebellum, as well as fully automated assessment of grey and white

matter volumes (Durston et al., 2004; Palmen et al., 2005). Grey-White matter differentiation could not be obtained for two subjects with MCDD. Analyses were performed by two independent raters, blind to subject identity and diagnosis. Half of the scans were randomly flipped over the y-axis to ensure raters were also blind to laterality. Intra-class correlation coefficients were calculated to estimate reliability and were > 0.85 for all measures.

Statistical Analysis

All statistical analyses were conducted using the SPSS statistical package, version 11.5 (SPSS Inc., Chigaco, IL, USA). Analysis of variance (ANOVA) was used to assess differences between the three groups (subjects with MCDD, subjects with autism, and controls), and significant differences were further investigated using post-hoc independent-sample t tests (two-tailed). In order to control for global effects of differences in intracranial volume, analyses that yielded significant results were repeated with intracranial volume as a covariate. All analyses that yielded significant results were repeated excluding subjects on medication.

Results

The overall ANOVA showed significant differences between groups for intracranial, total brain, cerebellum and ventricular volume ($F > 3.15$, $df = 2, 61$, $p < 0.05$), as well as a trend for grey- matter volume ($F=2.71$, $df = 2, 59$, $p= 0.08$). Differences between the autism and control groups have been previously reported (Palmen et al., 2005) and are summarized in **Table 3**. Subjects with MCDD had a significantly larger cerebellum than controls ($t=2.93$, $df = 41$, $p=0.005$). After correction for intracranial volume, the enlargement in cerebellum remained significant ($F= 8.24$, $df = 41$, $p=0.007$) and an increase in total grey-matter volume also reached significance ($F= 7.84$, $df = 39$, $p=0.008$). When subjects on medication were excluded from the analyses, differences remained significant for the cerebellum ($t=2.72$, $df = 31$, $p=0.011$) and at trend level for grey matter ($t=1.69$, $df = 30$, $p=0.10$). When comparing subjects with MCDD to subjects with autism, intracranial and ventricular volumes were significantly larger in subjects with autism than in those with MCDD ($t >2.15$, $df = 41$, $p<0.05$) and an increase in total brain volume reached trend level ($t=1.73$, $df = 41$, $p=0.09$). After correction for intracranial volume, differences were no longer significant. When subjects on medication were excluded from the analyses, differences remained significant for the ventricular volume ($F= 7.231$, $df = 31$, $p= 0.048$), and differences for intracranial and total brain volume were still in the same direction but no longer significant, probably related to reduced power.

Table 3 Brain volumes (ml) in subjects with MCDD, autism and typically developing controls

	Autism	MCDD	Controls
	Mean ± SD	Mean ± SD	Mean ± SD
Total intracranial volume	1542.10* ± 103.02	1475.39 ± 97.87	1475.17 ± 69.45
Total brain	1422.79* ± 92.62	1372.36 ± 98.68	1357.85 ± 70.02
Total cerebellum	155.17* ± 11.76	156.89* ± 9.36	147.35 ± 11.86
Total ventricular volume	13.07* ± 5.47	9.94 ± 4.5	9.01 ± 6.00
Total Grey Matter volume	787.43* ± 67.45	765.77 ± 65.74	743.45 ± 49.11

* Indicates a significant difference from the control group at the $p < 0.05$ level

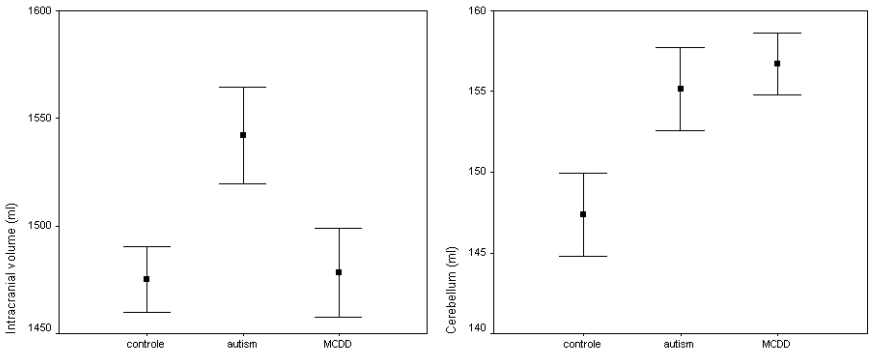
Discussion

We report differences in structural imaging measures of brain volume in both children with MCDD and children with autism compared to typically developing controls. Both groups show increases in grey-matter and cerebellar volume, but we find no evidence of intracranial enlargement in MCDD, contrary to our findings in autism.

Differences between children with autism and control subjects have been previously reported for this sample and are not further discussed here (Palmen et al., 2005). They are reported solely to enable comparisons with differences in the MCDD group. Children with MCDD showed increases in cerebellar and overall grey-matter volume compared to controls, similar to our previous results in children with autism (Palmen & Van Engeland, 2004; Palmen et al., 2005) as well as reports by others (Cody et al., 2002). As such, our first hypothesis that children with MCDD would display changes in brain volume similar to those found in autism was confirmed. This suggests that neurobiological changes in MCDD are similar to those seen in autism,

However, we also found differences between children with MCDD and those with autism: children with autism had larger intracranial and ventricular volumes than children with MCDD and showed a trend towards an increase in total brain volume. These differences were related to an overall difference in head size between subjects with autism and MCDD, as they were no longer significant when corrected for intracranial volume. This finding of an overall difference in head size confirms our second hypothesis that there are also differences between brain changes in these two forms of autism spectrum disorders. These changes are unlikely to be secondary to differences in clinical severity, as ADI scores were similar in both groups (see **Table 2**).

Our main finding is that children with MCDD show no enlargement of intracranial volume, whereas head size is significantly enlarged in children with autism (see **Figure 1**). Intracranial volume increases during the first years of life, under the influence of the growing brain. It continues to grow up until approximately age 5 years and then stabilizes (Durston et al., 2001). The finding of differences in head size between these two forms of autism spectrum disorder is provocative as it suggests that neurobiological differences may map onto clinical differences: If the lack of intracranial enlargement can be confirmed in other studies, it suggest that the onset of MCDD may be later than that of autism. This is in line with clinical evidence, as parents often report later onset of symptoms in children with this form of autism spectrum disorder (Van der Gaag, 1993). As such, these findings suggest that MCDD may represent a form of PDD that is neurobiologically distinct from autism, at least to the extent that it may have a different developmental trajectory with later onset.



Figuur 1 Mean intracranial volume and cerebellum volume [ml (±s.e.)] in controls, subjects with multiple complex developmental disorders (MCDD), and subjects with autism.

In sum, we report a pattern of volumetric changes in the brains of subjects with MCDD, similar to that seen in autism. However, contrary to our results with autism, we find no evidence of intracranial enlargement in MCDD. This suggests that although neurobiological changes associated with MCDD are similar to those in autism, there may be differences in the developmental trajectories associated with these two subtypes of autism spectrum disorders.

These types of observations, although preliminary, can contribute to our understanding of the neurobiology of autism spectrum disorders and eventually facilitate the development of more effective tools for diagnosis and possibly even treatment of these disorders. To date, the number of studies available on the clinical concept and neurobiological background of MCDD are limited. Although the findings of this study should be considered preliminary, it does potentially add

to our biological understanding of this subtype of autism spectrum disorders. As such, if these results can be replicated, they may have implications for considering differences in developmental trajectories within the PDD spectrum disorders. However, at this time MRI remains purely a research tool in the evaluation of autism spectrum disorders. While it is valuable in furthering our understanding of the neurobiological substrates of this disorder, MRI scanning is not appropriate for diagnostic purposes.

Limitations

There are a number of limitations to this study. First, although not atypical of pediatric neuroimaging studies, the sample size of the groups is relatively small. As such, we cannot exclude the possibility that some of our results that did not reach significance are false-negative findings. However, the difference in intracranial volume between subjects with MCDD and controls was negligable (0.23 ml; see **Figure 1** and **Table 3**), making it most unlikely that this particular finding was secondary to limited power. Second, we included only high-functioning individuals in all groups, with average or above average IQ-scores. Therefore it is unclear how well our findings generalize to lower-functioning individuals with diagnoses in the PDD-spectrum. Third, all children with autism were medication-naive. As this is unusual in daily practice, it raises the question of how representative this sample is of children with high-functioning autism. In contrast, half of the subjects with MCDD were using medication at the time of scan. However, all analyses that yielded significant results were repeated without these subjects, and the findings were comparable, although not always significant due to diminished power.

References

Ad-Dab'Bagh Y, Greenfield B (2001). Multiple Complex Developmental Disorder: The "Multiple and Complex" evolution of the "Childhood Borderline Syndrome" construct. J Am Acad Child Adolesc Psychiatry 40:954-964.

Akshoomoff N, Pierce K, Courchesne E (2002). The neurobiological basis of autism from a developmental perspective. Dev Psychopathol 14:613-34.

American Psychiatric Association (1994). Diagnostic and Statistical Manual of Mental Disorders (4th.ed). Washington, DC: Author.

Aylward EH, Minshew NJ, Field K, Sparks BF, Singh N (2002). Effects of age on brain volume and head circumference in autism. Neurology 23; 59(2):175-83.

Buitelaar JK, Van der Gaag RJ (1998). Diagnostic rules for children with PDD-NOS and Multiple Complex Developmental Disorder. J Child Psychol Psychiatry 39 (6): 911-918.

Cody H, Pelphrey K, Piven J (2002). Structural and functional magnetic resonance imaging of autism. Int J Dev Neuroscience : the official journal of the International Society for Developmental Neuroscience 20, 421-438.

Cohen DJ, Paul R, & Volkmar FR (1986). Issues in the classification of pervasive and other developmental disorders: toward DSM-IV. J Am Acad Child Adolesc Psychiatry 25 (2): 213-220.

Cohen DJ, Paul R, & Volkmar FR (1987). Issues in the classification of pervasive and other developmental disorders and associated conditions. In DJ Cohen, AM Donnellan, & R Pauls (Eds), Handbook of autism and pervasive developmental disorders (pp.20-39). New York: Wiley & Sons.

Courchesne E, Karns C, Davis HR, Ziccardi R, Carper RA, Tique ZD, Chisum HJ, Moses P, Pierce K, Lord C, Lincoln AJ, Pizzo S, Schreibman L, Haas RH, Akshoomhoff NA, Courchesne RY (2001). Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study. Neurology 57, 245-254.

Cox A, Klein K, Charman T, Baird G, Baron-Cohen S, Swettenham J, Drew A, Wheelwright S (1999). Autism Spectrum Disorders at 20 and 42 Months of Age: Stability of Clinical and ADI-R Diagnosis. J Child Psychol Psychiatry 40 (5), 719-732.

Durston S, Hulshoff Pol HE, Casey BJ, Giedd JN, Buitelaar JK, van Engeland H (2001). Anatomical MRI of the developing human brain: what have we learned? J Am Acad Child Adolesc Psychiatry 40(9):1012-20.

Durston S, Hulshoff Pol HE, Schnack HG, Buitelaar JK, Steenhuis MP, Minderaa RB, Kahn RS, Van Engeland H (2004), Magnetic Resonance Imaging of boys with Attention Deficit Hyperactivity Disorder and their unaffected siblings. Journal of the American Academy of Child and Adolescent Psychiatry 43(3):332-340

Fombonne E (2003). Epidemiological surveys of autism and other pervasive developmental disorders: an update. J Autism Dev Disord; 33(4):365-82

Fombonne E (2005). Epidemiology of autistic disorder and other developmental disorders. J Clin Psychiatry 66, 10:3-8.

Jansen LM, Gispen-de Wied CC, Van der Gaag RJ, Van Engeland H (2003). Differentiation between autism and multiple complex developmental disorder in response to psychosocial stress. Neuropsychopharmacol 28(3): 582-590.

Kemner C, van der Gaag RJ, Verbaten M, van Engeland H (1999). ERP differences among subtypes of pervasive developmental disorders. Biol Psychiatry 46: 781-789.

Lainhart JE, Bigler ED, Bocian M, Coon H, Dinh E, Dawson G, Deutsch CK, Dunn M, Estes A, Tager-Flusberg H, Folstein S, Hepburn S, Hyman S, McMahon W, Minshew N, Munson J, Osann K, Ozonoff S, Rodier P, Rogers S, Sigman M, Spence MA, Stodgell CJ, Volkmar F (2006). Head circumference and height in autism: a study by the collaborative program of excellence in autism. Am J Med Gen, Part A 140, 2257-2274.

LeCouteur A, Rutter M, Lord C, Rios P, Robertson S, Holdgrafer M, McLennan J (1989). Autism diagnostic interview : A standardized investigator-based instrument. J Autism Dev Disord 19: 363-387.

Lord C, Rutter M, & Le Couteur A (1994). Autism Diagnostic Interview-Revised. J Autism Dev Disord 24, 659-686.

Palmen SJ, Hulshoff Pol HE, Kemner C, Schnack HG, Durston S, Lahuis BE, Kahn RS, Van Engeland H (2005). Increased gray-matter volume in medication-naive high-functioning children with autism spectrum disorder. Psychol Med 35(4):561-70.

Palmen SJ, van Engeland H (2004). Review on structural neuroimaging findings in autism. J Neural Transm 111(7): 903-29.

Sparks BF, Friedman SD,Shaw DW, Aylward EH, Echelard D, Artru AA, Maravilla AR, Giedd JN, Munson J, Dawson G, Dager SR (2002). Brain structural abnormalities in young children with autism spectrum disorder. Neurol 59:184-192

Towbin KE, Duykens EM, Pearson GS, Cohen DJ (1993). Conceptualizing "borderline syndrome of childhood" and "childhood schizophrenia" as a developmental disorder. J Am Acad Child Adolesc Psychiatry 32(4): 775-82.

Van der Gaag RJ (1993). Multiplex development Disorder; an exploration of borderlines on the autistic spectrum. Thesis, University of Utrecht, Netherlands.

Van der Gaag RJ, Buitelaar J, Ban van den E, Bezemer M, Njio, L, Engeland van H (1995). A controlled multivariate chart review of multiple complex developmental disorder. J Am Acad Child Adolesc Psychiatry 34(8): 109-106.

Van Engeland H, Van der Gaag RJ (1994). MCDD in childhood: a precursor of schizophrenic spectrum disorders. Schizophr Res 11, 197.

Vandersteene G, Van Haassen PP, De Bruyn EEJ, Coetsier P, Pijl YL, Poortinga YH, Lutje Spelberg HC, Spoelders-Claes R, Stinissen J (1986). WISC-R, Wechsler Intelligence Scale for Children-Revised, Nederlandstalige uitgave. Lisse: Swets and Zeitlinger.

Wing L & Gould J (1979). Severe impairments of social interaction and associated abnormalities in children: Epidemiology and classification. J Autism Dev Disord 9, 11-29.

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Lahuis BE, de Sonneville LMJ, Pieterse J, Van Engeland H, Swaab H.
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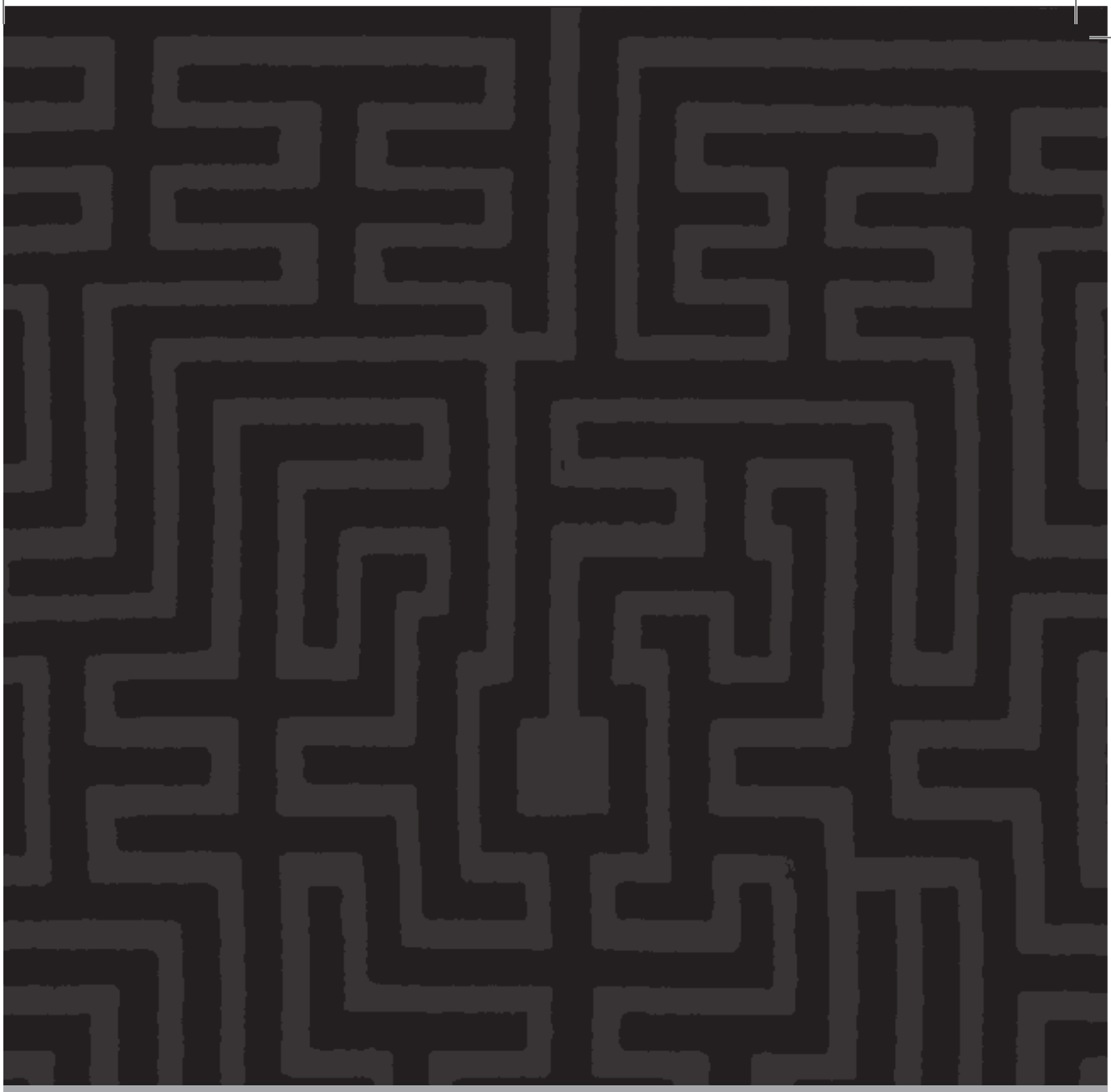

Executive function in MCDD and PDD-NOS: a study of inhibitory control, state regulation and behavioral adaptivity.

Abstract

Children with PDD-NOS, subtype MCDD (n=24) were compared to children with PDD-NOS (n=23) on intelligence and executive function (EF) skills. Significant differences emerged, always to the disadvantage of the children with PDD-NOS, subtype MCDD on various EF measures. The findings suggest compromised state regulation and impaired inhibitory control in perceptual (input) as well as response control (output) processes in children with MCDD. These problems are interpreted as possibly underlying the episodes of loss of emotional control, behavioral disorganization, and thought problems which are frequently observed in these children. The results emphasize the validity for defining the subtype MCDD within the large and ill-defined PDD-NOS group, and may play a role in the search for factors that indicate vulnerability for psychosis.

Introduction

Pervasive developmental disorder-not otherwise specified (PDD-NOS) (American Psychiatric Association, 1994) is an umbrella-type diagnosis, commonly resulting from a failure to meet the criteria for the diagnosis of autistic disorder. Children with PDD-NOS may have problems in communication, motor behavior, emotional, and cognitive behavior, but the combination of symptoms across children may vary widely (Walker et al., 2004). PDD-NOS refers to a very heterogenous group of patients, as has recently been illustrated (De Bruin et al., 2007). In a group of 94 children with PDD-NOS, approximately only 20% of the children were identified having no co-morbid disorders, the remaining group demonstrated internalizing disorders (20%), disruptive behaviors (20%), or both internalizing and disruptive behavior (40%). The existence of both internalizing and externalizing behaviors has earlier been reported (e.g. Lincoln et al., 1998). Practically simultaneously with the introduction of the NOS subcategory of PDD in the DSM-III-R (American Psychiatric Association, 1987), an attempt was initiated (Cohen et al., 1986) to further specify this NOS domain by proposing two new categories, Asperger's disorder, which made it into the DSM-IV (American Psychiatric Association, 1994), and multiplex developmental disorder (MDD), later renamed to multiple complex developmental disorders (MCDD) (Towbin et al., 1993), which category still lacks recognition by the DSM child psychiatric classification system.

Cohen, Paul, and Volkmar (1987) identified three core symptoms in children with MCDD, i.e. impairments in the regulation of affect and anxieties, social behavior problems, and cognitive processing deficiencies (thought problems). MCDD children are also characterized by extreme fluctuations in cognitive, attention, and emotional functioning (Towbin et al., 1993). Validation studies of the criteria for MCDD (Towbin et al., 1993; Van der Gaag et al., 1995) are in support of this construct as a subcategory of PDDs in the upcoming DSM-V (Ad-Dab'bagh & Greenfield, 2001). MCDD children may be at risk for schizophrenic spectrum disorders in adulthood (Van Engeland & Van der Gaag, 1994). In a study on borderline children, who resemble in several ways patients that are nowadays called MCDD, a heightened risk for axis II disorders was reported (Lofgren et al., 1991). In light of the above, surprisingly little research has been done on children with MCDD. More research, relevant to the identification of possible risk factors associated with a psychopathological outcome in adulthood is clearly needed.

To further contribute to the validity of this symptomatology-based construct, the present study attempts to differentiate MCDD from PDD-NOS, focusing on basic neurocognitive functions possibly underlying the regulation of thought and behavior. Symptoms pertaining to deficits in these domains in MCDD (Buitelaar

& Van der Gaag, 1998), include behaviors such as e.g. "recurrent panic episodes", "episodes of behavioral disorganization, punctuated by markedly immature, primitive, or violent behaviors", and "sudden intrusions on normal thought process" that suggest loss of executive control. In contrast, behavioral symptoms associated with PDD, such as "restricted, repetitive, and stereotyped patterns of behavior", reflect a certain behavioral rigidity. Autistic children display more stereotyped and rigid behaviour than MCDD children (Buitelaar & Van der Gaag, 1998).

Many studies set out to identify and describe the salient characteristics of MCDD, in majority by comparing these children with autistic children, and/or with children outside the autistic spectrum, like ADHD, and with normal children (e.g. Kemner et al., 1999; Jansen et al., 2000, 2003; Ad Dab'bagh et al., 2001; Van der Gaag et al., 2005). The outcome in an event-related potential study suggested that children with autism and MCDD differ in attentional resource allocation (Kemner et al., 1999). Children with MCDD were shown to have a reduced cortisol response to psychosocial stress which suggests a restricted ability to respond adequately to their (social) environment (Jansen et al., 2000, 2003). Van der Gaag and colleagues (1995) comparing children with MCDD, autism, ADHD and/or CD, and anxiety and affective disorders, found thought disorders and anxiety to be most characteristic of MCDD. The symptom of "fluctuations in level of functioning" was found to differentiate best, which is interesting as it probably reflects underlying deficits in the behavioral control system.

Controlling one's own behavior constitutes a major aspect of executive functioning (EF). EF refers to higher order cognitive control processes, such as working memory, inhibition, sustained attention, and attentional flexibility. There is ample evidence for the existence of deficits in EF in the autism spectrum disorders (ASD). Recently, a number of studies aimed at differentiating within the spectrum on the basis of EF characteristics (e.g. Geurts et al., 2004; Goldberg et al., 2005; Happé et al., 2006; Johnson et al., 2007; Verté et al., 2006). Lincoln et al. (1998) compared children with comorbid borderline MCDD and ADHD with 'pure' ADHD and non-psychiatric controls. The borderline/MCDD children, note that they did not fulfill the criteria for PDD-NOS, were found to be impaired in areas of executive control, i.e. cognitive flexibility and the ability to adjust responses on the basis of feedback. Under stressful conditions, these types of impairment may induce a greater inclination to disinhibition and/or decompensation (Ad-Dab'bagh & Greenfield, 2001). Happé et al. (2006) assessed response selection/inhibition, flexibility and working memory in children with ASD, ADHD, and controls, and found less severe and persistent EF deficits in ASD than in ADHD. Geurts and colleagues (2004), on the other hand, reported more EF deficits in children with high functioning autism (HFA) compared

to ADHD. Goldberg et al. (2005) compared children with HFA, ADHD and healthy controls and found no group differences on response inhibition, planning, or set-shifting. A similar study, comparing children with HFA, Asperger's syndrome (AS) and PDD-NOS, found the EF profile of the PDD-NOS group to be more disturbed compared to a normal control group, but less disturbed than the profile of the HFA and AS groups, and little differences were found between the three PDD subtypes (Verté et al., 2006). Earlier research demonstrated that children with PDD-NOS show impaired speed and accuracy of processing in sustained and selective attention tasks when compared to normal controls (Althaus et al., 1996a, 1996b; Swaab-Barneveld et al., 2000).
As the quality of executive functions is, above all, dependent on the integrity of functional networks of the brain, it may be hypothesized that EF deficits are associated with disruptions of these networks. Recently, a number of studies have been published that focused on the integrity of brain functional networks in autism spectrum disorders (e.g. Courchesne & Pierce, 2005; Cherkassky et al., 2006; Minshew & Williams, 2007; Murias et al., 2007). Minshew's review (2007) summarizes the evidence supporting autism spectrum disorders as disorders of the association cortex which is known to be involved in higher order processing of information. Lately, studies in autism have identified frontal neural pathology early in development leading to malfunction of frontal microcircuitry (Courchesne et al., 2005). Courchesne postulates that these malfunctions result in local over-connectivity and reduced long-distance connections in the brain that might be associated with impairment of executive function processes.

To date, as may be concluded from the cited literature, there is little research on children with PDD-NOS, and studies that directly compare children with PDD-NOS to those with MCDD, are virtually non-existent, except for a face processing study (Herba et al., 2007) and a study examining symptom differences between those two groups (De Bruin et al., 2007). In these studies children were included who met the MCDD criteria, but not necessarily additional PDD-NOS criteria. The results of the latter study are particularly relevant to our aims. MCDD was reported to be associated with anxiety disorders, psychotic thought problems, and disruptive behavior (i.e. Oppositional Defiant Disorder, and Conduct Disorder – such as aggression, lying, stealing, violence, disobedience and anger) while PDD-NOS was primarily associated with deficits in social contact.

In light of the prominent presence of disruptive behaviors and thought regulation problems observed in MCDD which are notably absent in PDD-NOS, the reported signs of EF deficits in MCDD - such as extreme fluctuations in level of functioning, reduced attentional resource allocation, restricted ability to respond adequately

to the environment or feedback, and impaired flexibility - likely candidate markers to delineate MCDD from PDD-NOS are neuropsychological measures of executive control and attention, i.e. inhibition, sustained attention, behavioral adaptation, and working memory (capacity). If substantial differences in these abilities would be established, there is further evidence for recognizing a PDD subcategory of MCDD. Based on the previous research we predict that children with MCDD differ from children with PDD-NOS on measures of inhibition, attention regulation, adaptive strategies to cope with informational feedback, and memory capacity.

Method

Participants

All patients were recruited in the Department of Child & Adolescent Psychiatry at the University Medical Centre in Utrecht and were classified with a diagnosis of PDD-NOS according to the DSM-IV criteria (American Psychiatric Association, 1994). Children were additionally screened for the criteria for MCDD as formulated by Cohen et al. (1987). Twenty-four children met the criteria for PDD-NOS, subtype MCDD (21 boys and 3 girls), and 23 children were diagnosed having PDD-NOS (17 boys and 6 girls).

Procedure

Psychiatric assessment was performed by means of the Child Behaviour Checklist (CBCL) for parents and the Teacher Report Form (TRF) for teachers (Achenbach, 1991), semi-standardized interviews with the parents regarding problem behavior, developmental history and family history, information from treating physicians and by extensive expert clinical evaluation. Consensus regarding diagnostic classification had to be reached by two, in the field of autism experienced child psychiatrists (HvE, BL) and by a consensus meeting. A set of neurocognitive tasks was administered in a quite room by a certified senior child neuropsychologist.

Instruments

Intelligence

Level of intelligence was assessed with the Wechsler Intelligence Scale for Children-Revised (Wechsler, 1974), adapted for the Dutch population (Vandersteene et al., 1986).

Verbal memory

Verbal memory was measured using the '15-woorden test' (Saan & Deelman, 1986), a Dutch adaptation of the Verbal Learning test. A series of 15 words is presented 5 times and following each presentation the child has to report as many words as possible from memory. Twenty minutes after the 5th learning trial, the child is asked to reproduce the memorized words from long-term memory (active recall score), followed by a passive recognition test in which the child has to identify the target words from a list 30 verbally presented words, among which 15 distracter items, by saying 'yes' or 'no' to each of these presented words. This passive recall score is thought to be affected by interference from distracter items.

Attention and executive function

To measure speed and accuracy of information processing in the executive function domain, three tasks have been selected from the Amsterdam Neuropsychological Tasks (ANT) program, a computerized battery of reaction time tasks (De Sonneville, 1999, 2005). Ample studies have proven the ANT to be a sensitive and valid tool in non-referred samples (e.g. Groot et al., 2004; Brunnekreef et al., 2007), as well as in referred samples of various clinical domains, such as phenylketonuria (e.g., Burgard et al., 1997; Huijbregts et al., 2002), attention deficit disorders (e.g., De Sonneville et al., 1994; Slaats-Willemse et al., 2003; Konrad et al., 2004), and autism-related disorders (e.g., Althaus et al., 1996a, 1996b; Swaab et al. 2000). Several studies have demonstrated satisfactory psychometric properties (validity and test-retest reliability) of ANT task paradigms (Althaus et al., submitted; De Sonneville, 2005; Günther et al., 2005; Polderman et al., 2007).

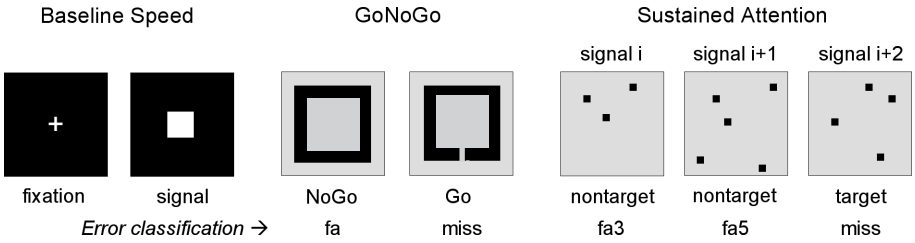

Figure 1 Example of stimuli in the Baseline speed, GoNoGo, and Sustained Attention tasks, and error classification: fa = false alarm, fa3/5 = false alarm on patterns with 3/5 dots.

The Baseline speed task is a simple reaction time task, assessing intensity aspects of attention or alertness. On the screen a (fixation) cross is continuously projected. This cross changes unexpectedly into a square requiring the child to press a mouse key as fast as possible, after which the square turns into a cross again, etc.

The cognitive level of this task is thus limited to the detection of the mere presence of a stimulus. The post response interval (PRI), the time between a response and the onset of the next signal, varies randomly between 500 and 2500 ms to prevent anticipation strategies. A valid response window is set to 150 – 5000 ms post stimulus onset. There are 32 trials to determine the speed of the index finger of the preferred hand.

The GoNoGo task assesses inhibition and inattention. During the task, 24 Go signals and 24 NoGo signals are presented in random order. On a Go signal the child should press a mouse key with the index finger of the preferred hand as fast as possible, while on a NoGo signal it should withhold a response. Misses (no response on Go signal) are taken to reflect inattention, and false alarms (response on NoGo signal) impulsivity. The signal is presented for 800 ms or disappears when a response is given in case RT<800 ms. A valid response window (VRW) is set to 200–2300 ms post stimulus onset. Trials followed by invalid responses (with RT<200 ms) are automatically replaced by trials of the same type. The event rate, the period from stimulus-onset to next stimulus-onset, is 2800 ms.

The Sustained Attention task assesses the ability to sustain attention, i.e. to keep performance at a certain level during a longer period of time. This task was administered to children of seven years and older. Six hundred dot patterns are successively presented in 50 series of 12 trials. Each series consists of four random patterns of three, four, or five dots each, presented in a pseudo random sequence. Children are required to respond to 4-dot patterns by pressing the mouse button with their preferred hand ('yes'-response) and to press the mouse button with their non-preferred hand ('no'-response) whenever 3- or 5-dots patterns are presented. Inaccurate responses, misses ('no'-responses to 4 dots) and false alarms ('yes'-responses to 3 or 5 dots) are followed by auditory feedback (beep) signal. The signals are presented until a key is pressed. The PRI = 250 ms and the VRW = 150 – 5000 ms post stimulus onset. Trials with invalid responses (RT<200 ms, so-called premature responses, or non-responses, i.e. no response within 5000 ms) are automatically replaced by trials of the same type. Task duration is approximately 15-20 minutes. Main outcome parameters are the mean RT to signals, per signal type, number of errors per type, mean completion time per series (tempo), and the within-subject SD of the 50 completion times (fluctuation in tempo).

Verbal task instructions were given before each task emphasizing both speed and accuracy (when relevant) of performance. To ensure that the children understood these instructions, practice trials were performed preceding task assessment.

Statistical Analysis

In principal, general Linear Model (GLM – SPSS 14.0) analyses of (co)variance, with Group (MCDD vs. PDD) as between-subjects factor was used to task performance

differences between groups. As groups differed significantly in age, age was entered as covariate. In case IQ correlated significantly with the dependent variable(s), IQ was also entered as a covariate.

Baseline speed

Speed (mean RT) and speed fluctuation (within-subjects SD of RT of responses) were analyzed in a multivariate analysis of covariance (age, IQ).

GoNoGo

Errors of the GoNoGo task were analyzed in a repeated measures ANCOVA (age, IQ), with Error type (misses vs. false alarms) as within-subjects (WS) factor. Speed of responses to Go-signals was analyzed with an ANCOVA (age, IQ).

Sustained attention

Mean tempo, and fluctuation in tempo were entered as dependent variables in a MANCOVA (age, IQ). 'Responsiveness to Feedback' reflects the ability of the child to adjust its response behavior following feedback on errors. Usually, trials following an error will be processed more carefully and thus more slowly than other trials (Hajcak et al., 2003). This post-error slowing can be analyzed by contrasting the child's mean RT of correct responses to trials directly following an error with the mean RT of the remaining correct (regular) responses. Absence of substantial post-error slowing reflects an inability to adjust behavior following feedback on errors, as has been reported for children with ADHD (De Sonneville et al., 1994), whereas excessive slowing, demonstrated in children with minor neurological dysfunction (De Sonneville et al., 1993), suggests a disruption of the ongoing response process. Post-error slowing will be analyzed in a repeated measure ANCOVA (age, IQ) with Response type (regular responses vs. responses following feedback) as WS-factor. An important marker of sustained attention is the deterioration of performance with time-on-task (TOT). As the target/nontarget ratio is 1:2, on average the 'no'-key has to be pressed twice as frequently as the 'yes'-key, which induces a response bias for the 'no'-key. As a consequence, this paradigm results in an increase of the number of misses relative to the number of false alarms, accompanied with an increase in speed, with time-on-task (De Sonneville et al., 1994). The mean percentage of false alarms and of misses and mean speed has been computed per consecutive block of 10 series of 12 trials (5 blocks in total). We evaluated 'inhibitory control', i.e. the ability to control response bias, in a repeated measure ANCOVA (age, IQ) with Error type (% misses vs. % false alarms) and TOT (period 1-5) as WS-factors, and evaluated changes in speed in a repeated measure ANCOVA (age, IQ) with TOT (period 1-5) as WS factor. Finally, we analyzed another marker of impulsivity. The number of premature responses was recoded in a variable with two levels: 0 vs. 1 or more

premature responses. This variable was entered in a χ^2 test with group (MCDD vs. PDD) to test for differences in distributions.

Verbal learning and memory

The numbers of correctly reproduced words per trial were analyzed by a repeated measure ANCOVA (age, IQ) with Trial (learning trial 1 – 5) as WS-factor to determine whether learning curves were different for the groups. The total, active and passive recall scores were entered in ANCOVAs (age, IQ).

Intelligence

An independent samples T-test was used to test group differences in total IQ. A repeated measure ANOVA with type of IQ (PIQ, VIQ) was performed to evaluate whether group differences were dependent on outcome domain (performance versus verbal IQ).

Comparison to the norm

In order to determine whether performance of the patients differed from the norm, the main outcome parameters (reaction time and error scores of the neuropsychological tasks were transformed to z-scores on the basis of the available means and corresponding standard deviations of age-appropriate norm samples (de Sonneville, 2005). Similarly, the total score and the delayed recall score of the verbal learning task were transformed to age-appropriate decile (d) scores. One-sample T-tests (one-sided) were used to test differences from the norm, testing against 0 for z-scores, 5 for d-scores, and 100 for the IQ scores.

Effect sizes were estimated by means of partial eta squared (η_p^2) or Cohen's d (Cohen, 1988; Stevens, 2002). Large effects correspond with $\eta_p^2 \geq 0.14$ or Cohen's $d = 0.8$, moderate effects with $\eta_p^2 \geq 0.06$ and $\eta_p^2 < 0.14$, or $d = 0.5$, and weak effects with $\eta_p^2 < .06$ or $d = 0.2$ (Stevens, 2002).

Results

The group consisted of 47 children, 38 boys and 9 girls, with a mean age of 9.00 ± 1.85 years, with an age range of 5.44 to 12.36 years. The groups differed significantly in age with the MCDD group being 1.26 years younger on average [$t(45) = -2.63$, $p = 0.012$].

Intelligence

Mean total IQ of children with MCDD (92.83 ± 10.81, range 70-129) did not differ significantly from that of children with PDD (93.96 ± 14.44, range 64-109) [t(45) = -0.30, p = 0.76]. Also differences between groups on performance IQ (92.43 ± 12.28, resp. 93.30 ± 15.39) and verbal IQ (94.24 ± 10.91, resp. 95.39 ± 12.86) were not significant (p> .77).

Learning and verbal memory

The analysis of the learning curves revealed no significant main group or group x trial interaction effect (p > .47). The MCDD group scored lower on total, active recall, and passive recall score but differences were only significant on the passive recall test (26.90, SE = .67; 28.73, SE = .55), [F(1,36) = 3.77, p = 0.05, $\eta_p^2 = 0.11$].

Attention regulation

Forty-seven children completed the baseline speed task, 41 the GoNoGo task and 35 the Sustained Attention task (only for children older than 6 six years). Statistical outliers (performance ≥ 3 SD above the mean) were excluded from analysis. This resulted in 1 outlier (MCDD) for the baseline speed task, 2 outliers for the GoNoGo task (MCDD, PDD), and 3 outliers for the Sustained attention task (2 MCDD, 1 PDD).

Baseline speed

The for age and IQ corrected mean baseline speed of the MCDD and PDD children was respectively 438 ms and 436 ms (SE = 17 ms), and the fluctuation in speed was 190 and 146 ms (SE = 24 ms). The multivariate analysis of these outcome parameters revealed that differences were not significant [F(2,40) = 1.08, p = 0.35, $\eta_p^2 = 0.051$].

GoNoGo

The for age and IQ corrected reaction time to Go-signals was 578 ms (SE = 22 ms) for the children with MCDD, for children with PDD it was 615 ms (SE = 21 ms). This difference was not significant [F(1,34) = 1.37, p = 0.25, $\eta_p^2 = 0.039$]. The MCDD group made more errors than the PDD group [F(1,34) = 10.04, p = 0.003, $\eta_p^2 = 0.23$]. The interaction of Group x Error type revealed that this difference in accuracy could be attributed solely to the measure of impulsivity, i.e. the % of false alarms [F(1,34) = 7.25, p= 0.011, $\eta_p^2 = 0.176$] (see **Figure 2**, left panel).

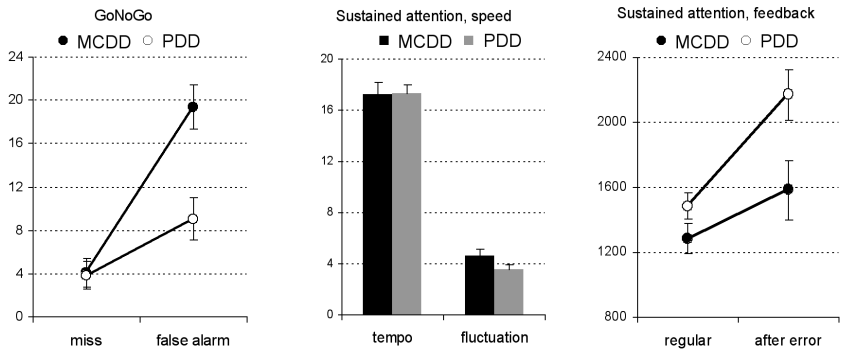

Figure 2 Left panel: accuracy in GoNoGo task, middle panel: tempo and fluctuation in tempo in sustained attention task, right panel: response to feedback in sustained attention task (speed of regular vs. after error responses).

Sustained attention

The MANCOVA of tempo and fluctuation in tempo was significant [$F(2,27) = 5.21$, $p < 0.012$, $\eta_p^2 = 0.278$). Tempo of the MCDD group was about equal to that of the PDD group but the fluctuation in tempo was larger compared to the PDD group (see **Figure 2**, middle panel). As regards post-error slowing, type of response (regular correct responses vs. post-error correct responses) interacted significantly with Group [$F(1,29) = 5.35$, $p = 0.028$, $\eta_p^2 = 0.156$], indicating that feedback on errors slowed down subsequent responses in both groups, but much less so in the MCDD group (see **Figure 3**, right panel). Changes in speed with TOT were different for MCDD and PDD, with the PDD group demonstrating a rather constant level and the MCDD group showing an increase in speed, probably caused by biased (and thus faster) responding. A significant interaction confirmed this observation [$F(4,104 = 3,19$, $p = .016$, $\eta_p^2 = .109$] (see **Figure 3**, left panel). The MCDD group made significantly more errors [$F(1,26) = 13.66$, $p=0.001$, $\eta_p^2 = 0.344$]. The interaction of Error type (false alarms vs. misses) x Group x TOT (period 1 – 5) was significant [$F(4,104 = 2.51$, $p = 0.047$, $\eta_p^2 = 0.088$], indicating that the % of errors increased with time-on-task, but this held only for the misses - reflecting the impact of the growing response bias, and this deterioration was larger in the MCDD group (see **Figure 3**, right panel). Eight out of 11 (73 %) children with MCDD and 9 out of 21 (43%) children with PDD made one or more premature responses during sustained attention task execution, which difference in distribution was significant [χ^2 (1,35) = 4.38, p = 0.036].

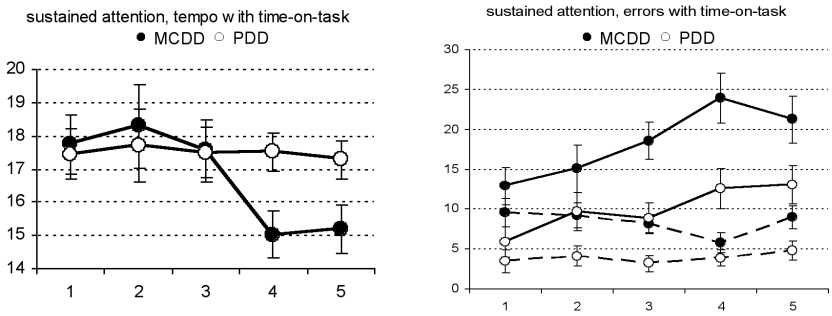

Figure 3 Sustained attention: changes with time-on-task in speed (left panel), and accuracy (right panel: solid lines = misses, dashed lines = false alarms).

Differences from the norm (**Figure 4**)

Both groups were slower [($t_{MCDD}(21) = 2.30$, $p = 0.016$, $d = 1.00$; $t_{PDD}(22) = 2.10$, $p = 0.024$, $d = 0.89$] on Baseline speed. The MCDD group was also less stable compare to the norm [($t_{MCDD}(21) = 1.77$, $p = 0.046$, $d = 0.77$, whereas the PDD group was not ($p = .44$). The groups did not differ in speed from the norm on the GoNoGo task ($p > .32$). Both groups made more false alarms [($t_{MCDD}(19) = 8.20$, $p < 0.001$, $d = 3.76$; $t_{PDD}(21) = 3.68$, $p < 0.001$, $d = 1.64$]. The MCDD group made also more misses compared to the norm [($t_{MCDD}(19) = 2.06$, $p = 0.027$, $d = 0.94$], whereas the PDD group did not differ from the norm ($p = .12$). The groups differed on the Sustained

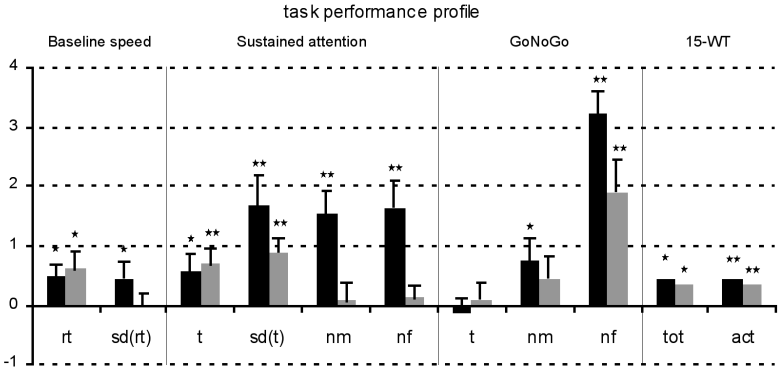

Figure 4 Task performance profile as a function of Group. Significant differences are indicated with * ($p < .05$), and ** ($p < .01$). rt, sd(rt): speed and speed stability; t, sd(t), nm, nf: tempo, tempo fluctuation, n of misses, n of false alarms; t, nm, nf: speed, n of misses, n of false alarms; tot, act: total learning and active recall score (mean decile scores transformed to percentiles to z-score).

attention task from the norm on tempo fluctuation [($t_{MCDD}(11) = 3.54$, $p = 0.002$, $d = 2.13$; $t_{PDD}(18) = 4.17$, $p < 0.001$, $d = 1.97$], and tempo [($t_{MCDD}(11) = 1.98$, $p = 0.037$, $t_{PDD}(18) = 3.08$, $p = 0.002$, $d = 1.45$]. The MCDD group made more errors [($t_{misses}(11) = 3.74$, $p < 0.002$, $d = 2.25$; $t_{false\ alarms}(11) = 3.95$, $p = 0.001$, $d = 2.38$] compared with the norm, but the PDD group did not ($p > .28$).
The mean total IQ of both groups differed significantly from 100 [($t_{MCDD}(23) = -3.25$, $p = 0.002$; ($t_{PDD}(23) = -2.0$, $p = 0.028$], although staying well within the normal range (85-115). The groups differed from the norm on the 15-WT task on total learning score [($t_{MCDD}(18) = -2.43$, $p = 0.013$, $d = 1.18$; $t_{PDD}(21) = -2.10$, $p = 0.024$, $d = 0.92$], and on the active recall score [($t_{MCDD}(18) = -2.83$, $p < 0.006$, $d = 1.37$; $t_{PDD}(21) = -2.79$, $p = 0.006$, $d = 1.22$].

Discussion

To our knowledge, only two other studies have directly compared children with PDD-NOS with children with MCDD (De Bruin et al., 2007; Herba et al., 2007). In this study the group of MCDD was defined as a subgroup within the PDD-NOS group to get more insight in the ill-defined group of PDD-NOS. The present study is the first one that focuses on deficits in executive functioning and contributes to the literature by showing whether the two groups can be differentiated on the executive function domain. The comparison of children with PDD-NOS, subtype MCDD, and children with PDD-NOS without these MCDD characteristics, reveals a specific and clear pattern of differences, always to the disadvantage of the MCDD subtype, and of similarities, depending on type of executive function. The findings also show that both groups differ from the norm, these differences varying as a function of group membership and executive function aspect.

Differences from the norm

Comparison with the norm reveals that the MCDD group was slower, less stable (sustained attention), and made more errors than the norm on all tasks, except on speed in the GoNoGo task. Differences with the norm for the PDD-NOS group without MCDD were less large and more limited as they could not be differentiated from the norm on sustained attention accuracy (including biased responding), response speed stability in simple reaction time, and inattention (misses) on the GoNoGo task. This finding underscores the view that the children with MCDD are more affected in various aspects of executive functioning than the children without MCDD.

Differences between groups

The children with MCDD were less accurate than the children with PDD-NOS on measures of inhibitory control. They made more false alarms in the GoNoGo task whereas they did not differ on the measure of inattention. The sustained attention task results show that both groups deteriorated in accuracy with time-on-task *only* on the measure of inhibition, and this deterioration was strongest in the MCDD group. This deterioration in accuracy was accompanied by an increase in speed with time-on-task *only* in children with PDD-NOS, subtype MCDD, evidently reflecting the impact of biased (thus faster) responding. The children with MCDD showed a larger fluctuation in tempo which is indicative of a lesser ability to sustain a certain performance level, which may be viewed as evidence for a flawed state regulation. The deterioration in accuracy with time-on-task is in support of this. Post-error slowing (taking more time to process signals following an error), which is assumed to be the result of appropriate behavioral adjustment to feedback, was much less in children with PPD-NOS, subtype MCDD, compared to children with PDD-NOS only. Premature responses, i.e. responses occurring within 200 ms after stimulus-onset and thus too fast to be the result of a cognitive process, were more frequent in children with MCDD. All of the above mentioned results consistently suggest deficits in the behavioral control system, in particular of inhibition/impulsivity.

Groups did not differ in global measures of intelligence (full scale, verbal and performance IQ). They also do not differ in verbal memory or learning capacity. Children with PDD-NOS, subtype MCDD, did however score lower on the passive recognition test. This outcome is interesting as it suggests that in children with MCDD the stored information is relatively more vulnerable to interference of irrelevant information, which, when we pursue this line of thought somewhat further, may be taken as evidence that they are less capable to inhibit irrelevant information.

These problems with inhibition, either at the output side of the information processing chain (response control) or at the input side (selection of relevant information), would fit several symptom characteristics of MCDD, reported by De Bruin et al. (2007), i.e. (psychotic) thought problems and disruptive behavior such as is expressed by symptoms of Oppositional Defiant Disorder, and Conduct Disorder, that separated them from children with PDD-NOS. The results also emphasize the validity for defining the subtype MCDD within the large and ill-defined PDD-NOS group.

The common denominator of these neurocognitive limitations, in particular in MCDD, can be summarized as a deficit in executive function. Attention and (verbal) memory dysfunctions have been hypothesized as vulnerability factors predicting psychosis (Erlenmeyer-Kimling et al., 2000; Yung et al., 2004). MCDD in childhood has been mentioned as a possible precursor of schizophrenia spectrum disorders

(Van Engeland & Van der Gaag, 1994) and axis II disorders (Lofgren et al., 1991). As the integrity of brain functional networks is essential for the operation of higher order cognitive processes, disruptions of these networks may compromise executive function processes. Recent neuroimaging studies focusing on functional brain connectivity in subjects with, or at risk of psychosis, provide evidence for white matter pathology, in particular in frontotemporal zones, which are known to subserve executive functioning (e.g. Whalley et al., 2005; Douaud et al., 2007; Foucher & Luck, 2007). In line with this evidence, and with the outcome of our study, are the results of studies in individuals identified as high-risk for psychosis, that revealed a pattern of neuropsychological deficits on tasks in particular requiring speeded information processing, efficient recall from memory (Niendam et al., 2006), and complex executive function (Shubert & McNeil TF, 2007).

From a clinical point of view, compromised state regulation and impaired inhibitory control in perceptual as well as response control processes would readily match up with the social problems that subjects with MCDD present with. Their cognitive style is characterized by insufficient regulation of behavior and emotion, and consequently leads to major social handicaps. Their illness derails the processes that underlie socialization and derails the emergence of personal autonomy, resulting in severe social disability (Cohen et al., 1994). In earlier studies on schizophrenia verbal memory and vigilance have been suggested to act as "neurocognitive rate-limiting factors" and thereby prevent patients from attaining optimal adaptation (Green, 1996). Finding clearly identifiable objective behavioural and/or cognitive and biological characteristics that indicate a high vulnerability for psychosis is of main importance for a better understanding of the underlying pathophysiology. Moreover, early identification of high risk can result in specific support and intervention programs for children and parents that hopefully influence the course and outcome of one of the most invalidating psychiatric illnesses.

Limitations

The number of patients in the study is limited and there is some difference in age range between the two groups, although this has been remedied by including age of testing as a covariate in all analyses. Another limitation is that no Autism Diagnostic Interview - Revised (ADI-R) (LeCouteur et al., 1989) and /or Autism Diagnostic Observation System (ADOS) (Lord et al., 1989) was used. However, all patients had an extensive psychiatric examination by experts in the field of autism. It is important to replicate the findings in another, larger sample. Furthermore, a diagnostic follow-up would be interesting to see if the patients with impaired cognitive functioning on attention, inhibition and memory are indeed the patients that develop psychotic symptoms.

References

Achenbach TM (1991). Manual for the Child Behaviour Checklist / 4-18 and 1991 profile. Burlington VT University of Vermont Department of Psychiatry.

Ad-Dab'bagh Y, Greenfield B (2001). Multiple complex developmental disorder: The "multiple and complex" evolution of the "childhood borderline syndrome" construct. J Am Acad Child Adolesc Psychiatry 40, 954-964.

Althaus M, De Sonneville LMJ, Minderaa RB, Hensen LGN, Til HB (1996a). Information processing and aspects of visual attention in children with the DSM-III-R diagnosis "Pervasive developmental disorder not otherwise specified (PDDNOS)": I. Focused and divided attention. Child Neuropsychol 2, 17-29.

Althaus M, De Sonneville LMJ, Minderaa RB, Hensen LGN, Til HB (1996b). Information processing and aspects of visual attention in children with the DSM-III-R diagnosis "Pervasive developmental disorder not otherwise specified (PDDNOS)": II. Sustained attention. Child Neuropsychol 2, 30-38.

Althaus M, Hensen LGN, Brunnekreef JA, Ormel J, De Bildt A, Minderaa RB, De Sonneville LMJ (submitted). Repeated Administration of Reaction Time Tasks: Implications for their Use in Treatment Effect Studies.

American Psychiatric Association (1987). Diagnostic and Statistical Manual of Mental Disorders, 3rd edition-revised (DSM-III-R). Washington, DC: American Psychiatric Association.

American Psychiatric Association (1994). Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Washington, DC: American Psychiatric Association.

Brunnekreef JA, De Sonneville LMJ, Althaus M, Minderaa RB, Oldehinkel AJ, Verhulst FC, Ormel J (2007). Information Processing Profiles of Internalizing and Externalizing Behavior Problems: Evidence from a Population-Based Sample of Preadolescents. J Child Psychol Psychiatry 48, 185-193.

Burgard P, Rey F, Rupp A, Abadie V, Rey J (1997). Neuropsychologic functions of early treated patients with phenylketonuria, on and off diet: results of a cross-national and cross-sectional study. Pediatr Res 41, 368-374.

Buitelaar JK, Van der Gaag RJ (1998). Diagnostic rules for children with PDD-NOS and Multiple Complex Developmental Disorder. J Child Psychol Psychiatry 39, 911-919.

Cherkassky VL, Kana RK, Keller TA, Just MA (2006). Functional connectivity in a baseline resting-state network in autism. Neuroreport 17, 1687-1690.

Cohen J (1988). Statistical power analysis for the behavioral sciences (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates.

Cohen DJ, Paul R,, Volkmar FR (1986). Issues in the classification of pervasive and other developmental disorders: toward DSM-IV. J Am Acad Child Pychiatry 25, 213-220.

Cohen DJ, Paul R, Volkmar F (1987). Issues in the classification of Pervasive Developmental Disorders and Associated Conditions. In D.J. Cohen & A. M. Donnellan & P. Rhea (eds.). Handbook of Autism and Pervasive Developmental Disorders (pp.20-39). New York: Wiley & Sons.

Cohen DJ, Towbin K, Mayes L, Volkmar F (1994). Developmental psychopathology of multiplex developmental disorder. In: Friedman, S.L., & Haywood, H.C. (eds.), Developmental Follow-up: Concepts, Genres, Domain and Methods. Orlando, FL: Academic Press, pp. 155-179.

Courchesne E, Pierce K (2005). Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection. Curr Opin Neurobiol 15, 225-230.

Courchesne E, Redcay E, Morgan JT, Kennedy DP (2005). Autism at the beginning: microstructural and growth abnormalities underlying the cognitive and behavioral phenotype of autism. Dev Psychopathol 17, 577-597.

De Bruin EI, Ferdinand RF, Meester S, De Nijs PFA, Verheij, F (2007). High rates of psychiatric co-morbidity in PDD-NOS. J Autism Dev Disord 37, 877-886.

De Bruin EI, De Nijs PFA, Verheij F, Hartman CA, Ferdinand RF (2007). Multiple complex developmental disorder delineated from PDD-NOS. J Autism Dev Disord 37, 1181-1191.

De Sonneville LMJ (1999). Amsterdam Neuropsychological Tasks: a computer-aided assessment program. In: B.P.L.M. den Brinker, P.J. Beek, A.N. Brand, S.J. Maarse, & L.J.M. Mulder (eds), Cognitive ergonomics, clinical assessment and computer-assisted learning: Computers in Psychology, Vol 6. Lisse, Swets & Zeitlinger, pp. 187-203.

De Sonneville LMJ (2005). [Amsterdam Neuropsychological Tasks: Scientific and clinical applications]. Tijdschr Neuropsychol 0, 27-41. Dutch.

De Sonneville LMJ, Geeraets MHW, Woestenburg JC (1993). Information processing in children with minor neurological dysfunction: behavioural and neurophysiological indices. Early Hum Dev 34, 69-78.

De Sonneville LMJ, Njiokiktjien C, Bos H (1994). Methylphenidate and Information Processing. Part 1: Differentiation between responders and nonresponders; Part 2: Efficacy in responders. J Clin Exp Neuropsychol 16, 877-897.

Douaud G, Smith S, Jenkinson M, Behrens T, Johansen-Berg H, Vickers J, James S, Voets N, Watkins K, Matthews PM, James A (2007). Anatomically related grey and white matter abnormalities in adolescent-onset schizophrenia. Brain 130, 2375-86.

Erlenmeyer-Kimling L, Rock D, Roberts SA, Janal M, Kestenbaum C, Cornblatt B, Adamo UH, Gottesman II (2000), Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: the New York High-Risk Project. Am J Psychiatry 157, 1416-1422.

Foucher JR, Luck D (2006). Psychosis related to neurological conditions: pro and cons of the dis-/mis-connectivity models of schizophrenia. Diaoquesl Clin Neurosci 8, 17-27.

Geurts HM, Verté S, Oosterlaan J, Roeyers H, Sergeant JA (2004). How specific are executive functioning deficits in attention deficit hyperactivity disorder and autism? J Child Psychol Psychiatry 45, 836-854.

Goldberg MC, Mostofsky SH, Cutting LE, Mahone EM, Astor BC, Denckla MB, Landa RJ (2005). Subtle executive impairment in children with autism and children with ADHD. J Autism Dev Disord 35, 279-93.

Green MF (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 153, 321-330.

Groot AS, De Sonneville LMJ, Stins JF, Boomsma DI (2004). Familial influences on sustained attention and inhibition in preschoolers. J Child Psychol Psychiatry 45, 306-314.

Günther T, Herpertz-Dahlmann B, Konrad, K (2005). [Reliability of attention and verbal memory tests with normal children and adolescents--clinical implications]. Z Kinder Jugendpsychiatr Psychother 33, 169-179. German.

Hajcak G, McDonald N, Simons R F (2003). To err is autonomic: Error-related brain potentials, ANS activity, and post-error compensatory behavior. Psychophysiol 4, 895-903.

Happé F, Booth R, Charlton R, Hughes C (2006). Executive function deficits in autism spectrum disorders and attention-deficit/hyperactivity disorder: examining profiles across domains and ages. Brain Cogn 61, 25-39.

Herba CM, De Bruin E, Althaus M, Verheij F, Ferdinand RF (2007). Face and Emotion Recognition in MCDD Versus PDD-NOS. J Autism Dev Disord Aug 25; [Epub ahead of print].

Huijbregts SCJ, De Sonneville LMJ, Licht R, Van Spronsen FJ, Verkerk PH, Sergeant JA (2002). Sustained attention and inhibition of cognitive interference in treated phenylketonuria: associations with concurrent and lifetime phenylalanine concentrations. Neuropsychol 40, 7-15.

Johnson KA, Robertson IH, Kelly SP, Silk TJ, Barry E, Dáibhis A, Watchorn A, Keavey M, Fitzgerald M, Gallagher L, Gill M, Bellgrove MA (2007). Dissociation in performance of children with ADHD and high-functioning autism on a task of sustained attention. Neuropsychol 45: 2234-2245.

Jansen,LMC, Gispen-de Wied CC, Van der Gaag RJ, Ten Hove F, Willemsen-Swinkels SWM, Harteveld E, Van Engeland H (2000), Unresponsiveness to psychosocial stress in a subgroup of autistic-like children, Multiple Complex Developmental Disorder. Psychoneuroendocrinol 25: 753-764.

Jansen,LM, Gispen-de Wied CC, Van der Gaag RJ, Van Engeland H (2003). Differentiation between autism and multiple complex developmental disorder in response to psychosocial stress. Neuropsychopharmacol 28, 582-590.

Kemner C, Van der Gaag RJ, Verbaten M, Van Engeland H (1999). ERP differences among subtypes of pervasive developmental disorders. Biol Psychiatry 46, 781-789.

Konrad K, Günther T, Hanisch C, Herpertz-Dahlmann B (2004). Differential effects of methylphenidate on attentional functions in children with attention-deficit/ hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 43, 191-198.

LeCouteur A, Rutter M, Lord C, Rios P, Robertson S, Holdgrafer M, McLennan J (1989). Autism diagnostic interview: A standardized investigator-based instrument. J Autism Dev Disord 19, 363-387.

Lincoln AJ, Bloom D, Katz M, Boksenbaum N (1998). Neuropsychological and neurophysiological indices of auditory processing impairments in children with multiple complex developmental disorder. J Am Acad Child Adolesc Psychiatry 37, 100-112.

Lofgren DP, Bemporad J, King J, Lindem K, O'Driscoll G (1991). A prospective follow-up-study of so-called borderline children. Am J Psychiatry 148, 1541-1547.

Lord C, Rutter M, Goode S, Heemsburgen J, Jordan H, Mawhood L, Schopler E (1989). Autism diagnostic observation schedule: A standardized observation of communicative and social behaviour. J Autism Dev Disord 19, 185-212.

Minshew NJ, Williams DL (2007). The new neurobiology of autism: cortex, connectivity, and neuronal organization. Arch Neurol 64, 945-950.

Murias M, Webb SJ, Greenson J, Dawson G (2007). Resting state cortical connectivity reflected in EEG coherence in individuals with autism. Biol Psychiatry 62, 270-273.

Niendam TA, Bearden CE, Johnson JK, McKinley M, Loewy R, O'Brien M, Nuechterlein,KH, Green MF,Cannon TD (2006). Neurocognitive performance and functional disability in the psychosis prodrome. Schizophr Res 84, 100-111.

Pennington BF, Ozonoff S(1996). Executive Functions and Developmental Psychopathology. J Child Psychol Psychiatry 37, 51-87.

Polderman TJC, Posthuma D, De Sonneville LMJ, Stins JF, Verhulst FC, Boomsma DI (2007). Genetic analyses of the stability of executive functioning during childhood. Biol Psychology 76, 11-20.

Saan RJ, Deelman B (1986). De 15-woordentest A en B. Een voorlopige handleiding (Intern rapport). Groningen: AZG, Afd. Neuropsychologie.

Schubert EW, McNeil TF (2007). Neurobehavioral deficits in young adult offspring with heightened risk for psychosis who developed schizophrenia-spectrum disorder. Schizophr Res 94, 107-113.

Slaats-Willemse,DS, Swaab-Barneveld H, De Sonneville L, Van der Meulen E, Buitelaar J (2003). Deficient response inhibition as a cognitive endophenotype of ADHD. J Am Acad Child Adolesc Psychiatry 42, 1242-1248.

Stevens JP (2002). Applied multivariate statistics for the social sciences. (4th ed.) New Jersey: Lawrence Erlbaum Associates.

Swaab-Barneveld H, De Sonneville L, Cohen-Kettenis P, Gielen A, Buitelaar J, Van Engeland H (2000). Visual sustained attention in a child psychiatric population. J Am Acad Child Adolesc Psychiatry 39, 651-659.

Towbin KE, Duykens EM, Pearson GS, Cohen DJ (1993). Conceptualizing "borderline syndrome of childhood" and "childhood schizophrenia" as a developmental disorder. J Am Acad Child Adolesc Psychiatry 32, 775-82.

Van der Gaag RJ, Buitelaar J, Van den Ban E, Bezemer M, Njio L, Van Engeland H (1995). A controlled multivariate chart review of multiple complex developmental disorder. J Am Acad Child Adolesc Psychiatry 34, 109-106.

Van der Gaag RJ, Caplan R, Van Engeland H, Loman F, Buitelaar JK (2005). A controlled study of formal thought disorder in children with autism and multiple complex developmental disorders. J Child Adolesc Psychopharmacol 15, 465-476.

Van Engeland H, Van der Gaag RJ (1994). MCDD in childhood - a precursor of schizophrenia spectrum disorders. Schizophr Res 11, 197-197.

Vandersteene G, Van Haassen PP, De Bruyn EEJ, Coetsier P, Pijl YL, Poortinga YH, Lutje Spelberg HC, Spoelders-Claes R, Stinissen J (1986). WISC-R, Wechsler Intelligence Scale for Children-Revised, Nederlandstalige uitgave. Lisse: Swets and Zeitlinger.

Verté S, Geurts HM, Roeyers H, Oosterlaan J, Sergeant JA (2006). Executive functioning in children with an autism spectrum disorder: can we differentiate within the spectrum? J Autism Dev Disord 36, 351-372.

Walker DR, Thompson A, Zwaigenbaum L, Goldberg J, Bryson SE, Mahoney WJ et al. (2004). Specifying PDD-NOS: A comparison of PDD-NOS, Asperger syndrome, and autism. J Am Acad Child Adolesc Psychiatry 43, 172-180.

Wechsler D (1974). Manual for the Wechsler Intelligence Scale for Children-Revised (WISC-R). New York: Psychological Corporation.

Whalley HC, Simonotto E, Marshall I, Owens DG, Goddard NH, Johnstone EC, Lawrie SM (2005). Functional disconnectivity in subjects at high genetic risk of schizophrenia. Brain 128, 2097-2108.

Yung AR, Phillips LJ, Yuen HP, McGorry PD (2004). Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. Schizophr Res 67, 131-42.

[5]

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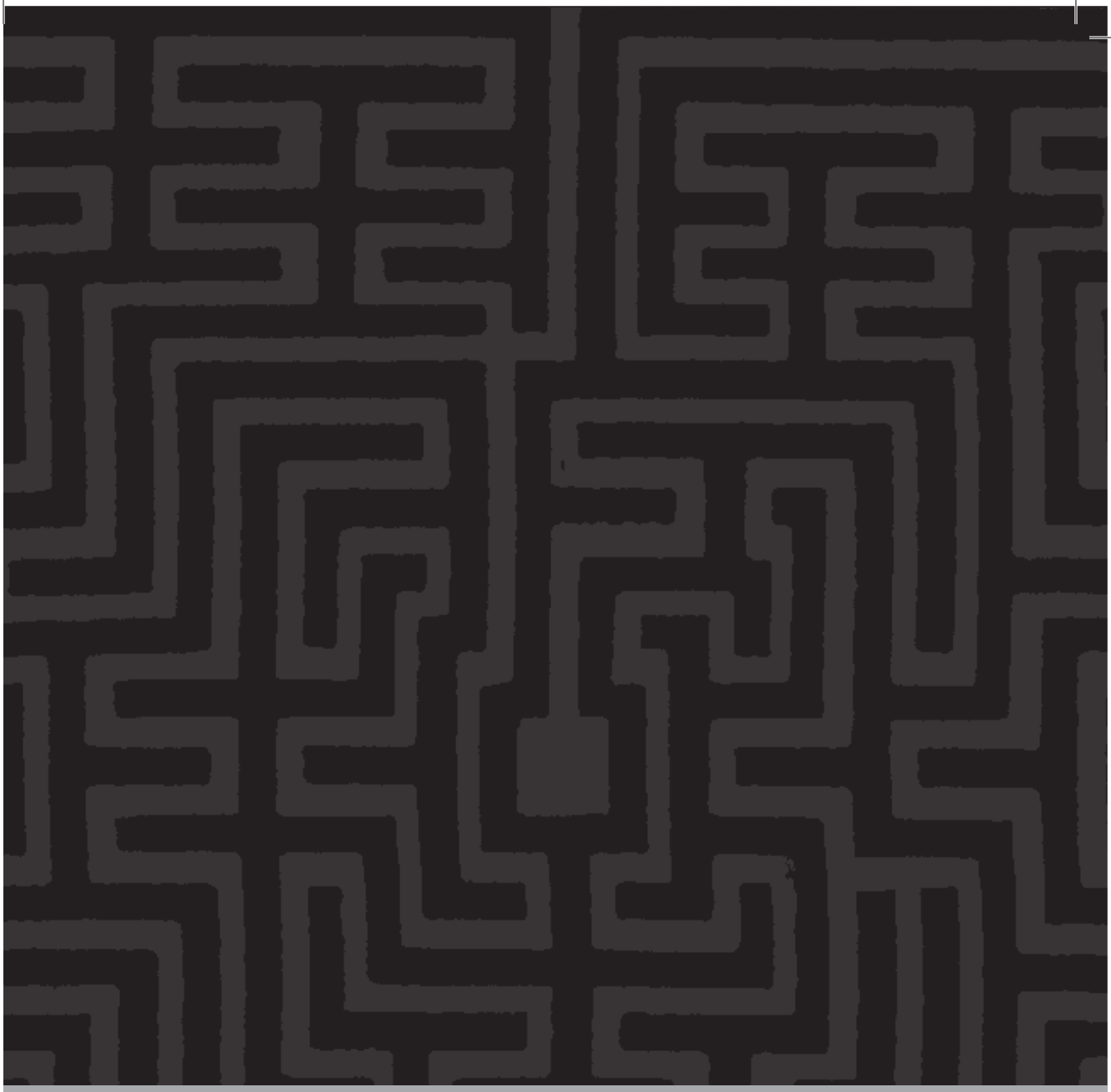


Smooth Pursuit Eye Movement (SPEM) in patients with Multiple Complex Developmental Disorder (MCDD), a subtype of the Pervasive Developmental Disorder (PDD).

Abstract

Objective:

Multiple Complex Developmental Disorder (MCDD) is a well defined and validated behavioral subtype of Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) and is thought to be associated with a higher risk of developing a schizophrenic spectrum disorder. The question was addressed whether patients with MCDD show the same psychophysiological abnormalities as seen in patients with schizophrenia.

Method

Smooth pursuit eye movement (pursuit gain and saccadic parameters) was measured in children with either MCDD (n=18) or autism (n=18), and in age- and IQ matched controls (n=36), as well as in a group of adult patients with schizophrenia (n=14) and a group of adult controls (n=17).

Results:

We found the expected effect of lower velocity gain and increased number of saccades in schizophrenic patients. Children with MCDD also showed a lower velocity gain compared to controls children. In contrast, velocity gain was similar in autistic subjects and controls. No differences for velocity gain were found in a direct comparison between MCDD and autism. Saccadic parameters were not significantly different from controls in either MCDD or autistic subjects.

Conclusion

Children with MCDD, like schizophrenic adults, show a reduced velocity gain, which could indicate that schizophrenia spectrum disorders and MCDD share (at least to some degree) a common neurobiological background.

Introduction

While autism is a relatively rare but well-characterized child psychiatric disorder (American Psychiatric Association, 1994), pervasive developmental disorder- not otherwise specified (PDD-NOS) is more common but is ill defined. Epidemiological studies reported an incidence of 30-60 cases per 10 000, with about a quarter of those meeting the full criteria for autism (Rutter, 2005). However, recent studies even find epidemiological numbers up till 1:150 for the risk of having a diagnosis within the autistic spectrum (MMWR Surveill Summ, 2007).

Patients present with problems in social interaction and communication and display rigid and stereotyped behavior but fail to satisfy the DSM-IV criteria for autistic disorder (American Psychiatric Association, 1994). The heterogeneity of the patient population and the lack of research hampers consensus on the diagnostic status of PDD-NOS. Identifying subtypes on the basis of clinical and / or biological characteristics could provide insight into the broad phenotypic variance of PDD-NOS. One of the suggested subtypes is multiple complex developmental disorder (MCDD) (Towbin et al., 1993; Van der Gaag, 1993; Van der Gaag et al., 1995). Clinically, children with MCDD are characterized by deficits in affect and anxiety regulation, poor social skills, problems in social behavior, cognitive deficits, and periods of thought disorder (Cohen et al. 1986). While the disturbances of social interaction, communication, and stereotyped and rigid behavior are less marked than those seen in children with autism, children with MCDD have greater impairments in the domains of thought disorders, primitive anxieties, and aggression. This suggests that the etiology or developmental trajectory of MCDD and autism spectrum disorders (ASD) is different (Buitelaar & Van der Gaag, 1998). However, a high percentage (22% of the adolescents and 66% of young adults) of patients with MCDD is later diagnosed with a schizophrenia spectrum disorder (Van Engeland and Van der Gaag, 1994). Unfortunately there is no research on the incidence of PDD-NOS, subtype MCDD.

There is an urgent need for biological markers to better characterize MCDD and other different subtypes of ASD. Several psychophysiological markers of schizophrenia have been validated, of which abnormalities of smooth pursuit eye movements (SPEM), such as reduced gain and increased frequency of saccades, are among the most consistent and reproducible (Jacobsen et al., 1996; Ross et al., 1999a, 2002, 2003; Kumra et al., 2001). Indeed, global SPEM dysfunction is significantly associated with the disorganization dimension (defined primarily by thought disorder) of schizophrenia (Lee et al., 2000). Also, abnormalities of eye tracking measured in the relatives of subjects with a broad schizophrenia spectrum disorder appear to be associated with traits for "sensitivity" and "suspiciousness", as scored in the Structured Interview for Schizotypy (SIS) (Lencer et al., 2003). These data indicate a relation between clinical characteristics and this biological marker.

There have been two studies of SPEM in children with autism, and in, neither study were abnormalities of pursuit gain found (Kemner et al., 2004; Takarea et al., 2004), which contrasts with findings reported in the schizophrenia literature (Jacobsen et al., 1996; Ross et al., 1999a, 2002, 2003; Kumra et al., 2001). Therefore, SPEM parameters could be used to determine whether subjects with MCDD have neurobiological characteristics resembling those of subjects with autism (i.e. normal smooth pursuit) or subjects with schizophrenia (i.e., abnormal smooth pursuit).

In the present study, we compared the smooth pursuit characteristics of non-mentally retarded children and adolescents with MCDD with those of autistic subjects and controls, matched for age and total IQ. We hypothesized that, in contrast to the autistic group, the patients with MCDD would show the same characteristic SPEM abnormalities reported to occur in individuals with schizophrenia, namely an increased number of saccadic intrusions and diminished pursuit gain. We included a group of schizophrenic adult patients and age-matched controls, to evaluate a possible effect of our research conditions. Abnormal smooth pursuit characteristics would support the idea that individuals with MCDD are at high risk of developing psychotic symptoms within the autistic spectrum.

Method

Procedure

Subjects

Twenty-three MCDD subjects were eligible, all of whom met the criteria for PDD-NOS (American Psychiatric Association, 1994) and the criteria for MCDD as defined by Cohen (1987) (a minimum of six of 14 criteria, including at least two criteria from each of the three domains; see **List 1**). Five subjects were excluded because of poor tracing results or lack of motivation during the task. Twenty-eight autistic subjects were selected, all of whom met the criteria for Autistic Disorder (American Psychiatric Association, 1994). Five subjects were excluded because of poor tracing results or lack of motivation during the task and five subjects were excluded because of matching reasons. Thirty-six subjects were selected as controls and matched for total IQ and age; all were medication naive. Healthy controls had no history of psychiatric or neurological disorder. All patients came from the (out) patient clinic of the Child Psychiatry Unit of the University Medical Center Utrecht or were recruited through the National Autism Society. The psychiatric diagnosis was established by expert clinical opinion and verified with the results of the Autism Diagnostic Interview- Revised version (ADI-R) (LeCouteur et al., 1989). Twenty-two patients (13 autistic, 9 MCDD) reached thresholds for all three domains (social interaction, social communication, repetitive & stereotyped behaviour), 12 patients (5 autistic, 7 MCDD) reached thresholds when modified criteria were applied (i.e.

List 1 Diagnostic criteria for MCDD (Cohen et al., 1987)

MCDD is a serious, early onset and persistent disturbance affecting several major domains of functioning, including the following three major areas:

1. Regulation of affective state and anxiety is impaired beyond that seen in children of comparable age, as exemplified by several of the following: (at least two of the following)
   a) intense generalized anxiety or tension
   b) fears and phobias (often unusual and peculiar)
   c) recurrent panic episodes or 'flooding' with anxiety
   d) episodes of behavioral disorganization punctuated by markedly immature, primitive or violent behaviors
   e) significant and wide emotional variability with or without environmental precipitants.
   f) frequent idiosyncratic or bizarre anxiety reactions
2. Consistently impaired social behavior/sensitivity, as exemplified by the following types of disturbances: (at least two of the following)
   a) social disinterest, detachment, avoidence or withdrawal despite evident competence
   b) severely impaired peer relationships
   c) markedly disturbed attachments; high degrees of ambivalence to adults (esp.parents/ caretakers)
   d) profound limitations in the capacity for empathy or understanding others affects accurately
3. Impaired cognitive processing (thinking disorder), as exemplified by some of the following difficulties: (at least two of the following)
   a) irrationality,sudden intrusions on normal thought process, magical thinking, neologism or repetitions of nonsense words, desultory thinking, blatantly illogical, bizarre ideas
   b) confusion between reality and inner fantasy life
   c) perplexity and easy confusability (trouble with understanding ongoing social processes or keeping one's thoughts 'straight')
   d) 'delusions', over valued ideas including fantasies of omnipotence, paranoid preoccupations, overengagement with fantasyfigures, grandiose fantasy of special powers, and referential ideation
4. The syndrome appears during the first several years of life
5. The child is not suffering from autism or schizophrenia

score within 2 points of full criteria). Two MCDD patients scored within 3 points of full criteria (no scores for repetitive and stereotyped behaviour). The mean score on the MCDD criteria of the subjects with autism was 3.47, compared with 8.78 for subjects with MCDD ($F(1,34) = 65.9$; $p<0.005$). Eighteen subjects with autism and 36 typical controls were matched to 18 subjects with MCDD for age and total IQ. The mean total IQ in the three groups was significantly different ($F(2, 67) = 3.2$; $p=0.046$) (see **Table 1**). However, analysis did not reveal a significant correlation between total IQ scores and velocity gain, a measure of eye movement, in any of

the three groups. Two subjects with MCDD, one with autism, and 14 of the controls were female. Five of 18 subjects with MCDD and one of 18 autistic subjects were on medication (five on risperidone for MCDD [mean daily dosage 1.3 mg ± 0.45 mg), and 1 on dipiperon (4 mg/day) for autism). All subjects were asked to participate in the SPEM session and a neuropsychological assessment in order to estimate full-scale IQ (WISC-R) (Vandersteene et al., 1986).

In order to evaluate our research conditions, we investigated the smooth pursuit characteristics of a group of schizophrenic adult patients. Fourteen patients (mean age 260 ± 25.4 months) were eligible, all meeting the criteria for schizophrenia or related disorder. They were diagnosed having schizophrenia (n=8), schizophreniform disorder (n=5) and schizoaffective disorder (n=1) (American Psychiatric Association, 1994). Seventeen subjects were selected as controls (mean age 240 ± 40 months) and matched for age ($F(1,29)=2.92;p=0.1$); all were medication naive. All patients came from the (out) patient clinic of the Adult Psychiatry Unit of the University Medical Center Utrecht. The psychiatric diagnosis was established by expert clinical opinion and verified with the results of the Comprehensive Assessment of Symptoms and History by two independent raters (CASH) (Andreasen et al., 1992). Severity of illness was measured with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). All schizophrenia subjects and their (age) matched controls were male. All subjects were free of recent substance abuse, seizure disorders, neurological diseases, head trauma or mental retardation. Thirteen of 14 subjects with schizophrenia used medication (five on olanzepine [mean daily dosage 15 ± 6.1 mg], four on clozapine [mean daily dosage 362.5 ± 110.9 mg], three on risperidone [mean daily dosage 4.3 ± 1.5 mg], one on penfluridol [weekly dosage 30 mg]), and six patients used additional medication (haloperidol [0.2 mg/day], citalopram [20 mg/day], lithium [800 mg/day], oxazepam [one patient 50 mg/day and one patient 20 mg/day], temazepam [10 mg/day], lorazepam [3 mg/day], biperideen [one patient 4 mg/day and one patient 2 mg/week]). No IQ assessment was done (see **table 1**).

All persons gave their informed consent prior to their inclusion of the study. The procedure was approved by the institutional review board of the University Medical Center in Utrecht, the Netherlands, and designed in accordance with the Declaration of Helsinki.

Because both age (Ross RG et al., 1999b, 2002, 2003; Kumra et al., 2001) and medication status (Litman et al., 1994; Hutton et al., 2001) affect SPEM performance, we age-matched the control subjects to the MCDD patients to minimize this effect and performed analyses including and excluding subjects on medication. For patients with schizophrenia the analysis was rerun excluding patients (four) using lithium or benzodiazepine because this is likely to have an effect on SPEM (Holzman et al., 1991; Radant et al., 1997).

Apparatus

Stimuli were displayed on a 21-inch computer screen (42 x 32 cm), which was positioned 1 meter in front of the subject (measured from the position of the eyes). The display resolution was 640 by 480 pixels (600 pixels were measured to cover a distance of 36.5 cm of the screen). Eye movements were recorded using electro-oculography (EOG), either by means of the Psylab hardware provided by Contact Precision Instruments (London, UK) (fixed built-in bandpass filter of 0.1-100 Hertz (Hz), sampled at 500 Hz using Neuroscan software), or by means of BioSemi (Amsterdam, The Netherlands) hard- and software (DC coupled, sampled at 2048 Hz). Electrodes were placed supra- and infraorbital of the left eye and at the outer canthi of both eyes. The ground electrode was placed at Afz (central frontal electrode).

Stimuli

The target was a white dot of 1 pixel on the 2-inch monitor, which was clearly visible on the black background. This dot was moving horizontally in a harmonic (sinusoidal) motion described by $X(t)=A \sin(2\pi ft)$ (A=300 pixels, f see below). The subject was seated at such a distance that the amplitude A of 300 pixels was 10 º of visual angle, and the eyes moved from left to right over a total of 20 º. Seven trials were presented, each consisting of at least five full periods of the sinusoidal motion. For each of these trials the dot started slowly in the middle of the screen and then speeded up to the desired speed for the trial in the course of 2 s. The frequencies used were respectively 0.2, 0.325, 0.4, 0.5, 0.6, 0.725, 0.875 Hz with average speeds of respectively: 8, 13, 16, 20, 24, 29 and 35 º per second. For training purposes the subject was shown two trials with the slowest velocities and asked to follow the dot carefully. After the experimenter was convinced that the task requirements were understood well, the experiment was started (**Figure 1**).

Smooth Pursuit analysis

After filtering the horizontal electro-oculography (HEOG) signal (low pass filter at 15 Hz), a calibration factor was obtained from the trial with lowest target frequency. The velocity was determined from the calibrated signal following the method of Kumra et al. (2001). For each sample point the velocity of the tracking was calculated by subtracting the position value at 10 ms before the given point from the position value at 10 ms after the given point and dividing the result by 20 ms. Saccadic onsets and offsets were then determined by a computer program, and only if the calibrated signal between onset and offset differed more than 0.5º, they were taken to mark a saccade. Saccades are defined as a period of absolute velocity above 35 º/sec between two successive acceleration peaks of opposite sign. To find the onset

Table 1 Demographic data SPEM. The number of subjects (N), use of medication and the mean (and standard deviation of) age, Total IQ (TIQ), Autism Diagnostic Interview-Revised version scores (ADI-R) and Cohen's Multiple Complex Developmental Disorder (MCDD) scale scores for the MCDD group, autism group, schizophrenia group (adults) and the control group (adults and children).

	N	Age (months)	TIQ	Medication	ADI-R Domain scores		
		Mean ± SD	Mean ± SD		Mean ± SD		
					Social interaction	Communication	Repetitive & stereotyped behavior
MCDD	18	145.72 sd ± 27.47	98 sd ± 15*	5 risperidon (mean 1.3 mg sd 0.45)	17.9 sd ± 4.7	14.64 sd ± 4.2	4.29 sd ± 2.59
Autistic	18	165.22 sd ± 28.5	105 sd ± 12	1 dipiperon (4 mg)	18.18 sd ± 4.5*	14.3 sd ± 5.56*	3.83 sd ± 2.79*
Child Controls	36	162.89 sd ± 30.0	107 sd ± 12*				
Schizophrenic	14	260 sd ± 25.4		5 olanzepine (mean 15 ± 6.1mg) 4 clozapine (mean 362.5 ±110.9mg) 3 risperidone (mean 4.3 ± 1.5mg) 1 penfluridol (30 mg /wk) additional: haloperidol, citalopram, lithium, oxazepam, temazepam, lorazepam, biperideen			
Adult controls	17	240 sd ± 40					

* One missing value.

Table 1 Continued

Score on Cohen's MCDD scale	PANSS positive symptoms	PANSS negative symptoms	PANSS psycho-pathology	Age at first symptoms (years)	Duration of illness (years)
Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD		Mean ± SD
8.78 sd ± 2.41					
3.47 sd ± 1.23*					
	15.4 sd ± 5.1	17.6 sd ± 6.3	33.3 sd ± 9.6	18.6 sd ± 4.9	2.6 sd ± 2.4

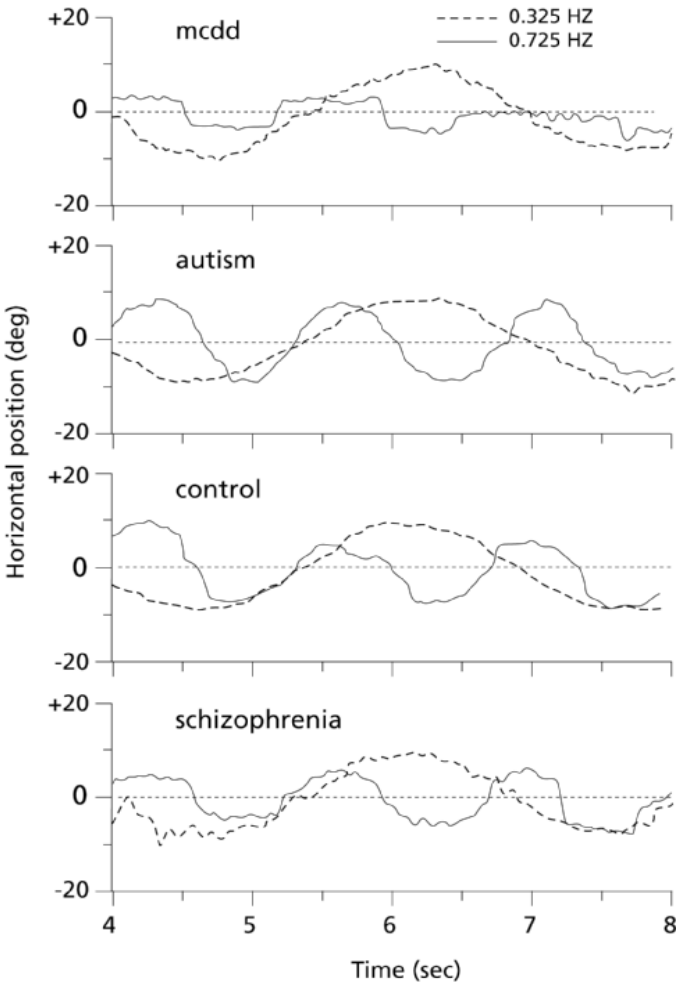


Figure 1. Eye movement traces of two frequencies (0.325 and 0.725 Hz) in patients with autism, MCDD, schizophrenia and typical controls.

and offset points of a saccade, first peaks of acceleration in the velocity pattern were determined with an absolute value over 200 ^{o} / s ^{2}. Velocity gain is defined as mean eye velocity divided by target velocity. Velocity gain was determined from points that were not marked as saccades and for which the target was at least 5^{o} away from the extremities where it changed its direction.

For each of the seven frequencies presented, the velocity gain and the number of saccades per second (NSAC) were calculated. Since values for the velocity gain and the saccade parameters were determined from a HEOG signal, no absolute position

of gaze information was available, so it was not possible to determine saccadic type (anticipatory, leading, catch-up, etc).

Statistical Analysis

All statistical analyses were conducted using the SPSS statistical package (version 11.5). Two analyses of variance were carried out (velocity gain, NSAC). To test whether we could replicate in our setup the abnormal gain and saccadic parameters reported in the literature on schizophrenia, an analysis was carried out for the two adults groups with one between-factor 'Group' with two levels (schizophrenic and controls) and one within-factor 'Velocity' with seven levels (8 to 35 º/ s).

Tot test for differences between the children groups, a between-factor 'Group' with three levels (MCDD, autism, and controls) and the within-factor 'Velocity' were used. A two-sided p-value of 0.05 was adopted. All analyses that yielded significant results were rerun excluding subjects on medication.

Results

For the patients with schizophrenia a significant effect on velocity gain (decreased) ($F(1,29)= 7.3$; $p=0.011$) and number of saccades (increased) ($F(1,29)= 7.4$; $p=0.011$) was found compared to the adult control group. Excluding the patients using lithium or benzodiazepines revealed even more significant results for as well velocity gain ($F(1,25)= 9.6$; $p=0.005$) as number of saccades ($F(1,25)= 9.3$; $p=0.005$).
In analysing the children groups, a main effect of frequency was found ($F(6,64) = 92,5$; $p < 0.001$), with increasing velocity leading to a decrease in velocity gain in all groups (**Figure 2**). No interaction was found between group and frequency. The overall ANOVA showed a significant group effect for velocity gain ($F(1,69) =3.1$; $p=0.052$). Subjects with MCDD displayed a significantly lower average velocity than the controls ($F(1,52) =6.6$; $p<0.05$). No significant differences in velocity gain were found between MCDD subjects and autistic subjects ($F(1,34) = 2.01$; $p =0 .17$), or between autistic and control subjects ($F(1,52) = 0.65$; $p = 0.42$). When subjects on medication were excluded from the analysis, the difference in velocity gain between MCDD subjects and controls remained significant ($F(1,47) = 6.0$; $p < 0.05$). Again, no differences were found between (unmedicated) MCDD subjects and autistic subjects ($F(1,28) = 1.5$; $p = 0.24$). No differences were found between the groups regarding the number of saccades.

Table 2 The mean (and standard deviation) of the Number of SACcades (NSAC) and velocity gain (VG) for the Multiple Complex Developmental Disorder (MCDD) group, autism group and the control group.

Group	NSAC (mean ± sd)	VG (mean ± sd)
MCDD	8.020 ± 0.972	0.269 ± 0.031*
Autism	9.558 ± 0.972	0.331 ± 0.031
Controls (children)	9.968 ± 0.687	0.362 ± 0.022
Schizophrenia	9.863 ± 0.581*	0.399 ± 0.024*
Controls (for schizophrenia)	7.729 ± 0.527	0.489 ± 0.022

* Indicates a significant difference from the control group at the $p < 0.05$ level.

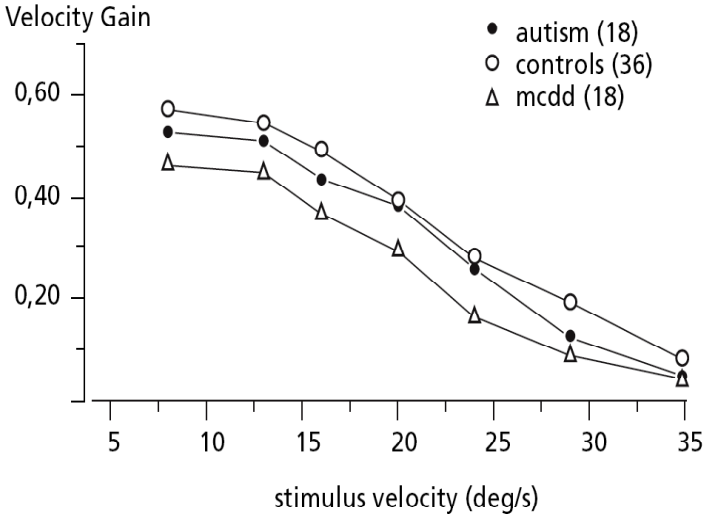


Figure 2. Smooth pursuit gain as a function of stimulus velocity for autism, MCDD and typical controls.

Discussion

We compared SPEM parameters measured in a group of children with PDD-NOS, subtype MCDD, with those measured in a group of children with autism and a group of typical controls, with the aim of determining whether SPEM parameters were similar to those of subjects with autism (i.e. normal smooth pursuit) or subjects with schizophrenia. More specifically, we hypothesized that because MCDD subjects have a high likelihood of developing symptoms of schizophrenia later in life, the SPEM characteristics of this group would resemble those of subjects with schizophrenia, namely an increased saccadic frequency and reduced gain. In

this study the EOG method was used. Although better methods are known, EOG is widely used in research. In this study the same method is used for all groups (PDD-NOS- subtype MCDD, autism and schizophrenia).

First, we tested whether we could replicate the earlier findings on abnormal gain and saccadic frequency in adults with schizophrenia. As expected, we found that saccadic frequency and velocity gain were both abnormal in schizophrenia, as shown before (e.g. Jacobsen et al., 1996; Ross et al., 1999a, 2002, 2003; Kumra et al., 2001). With respect to the analysis of the younger age groups, indeed velocity gain was found to be lower in the MCDD subjects than in the typical controls, whereas saccadic frequency in this group was not different. No differences between autistic subjects and controls were found on either measure.

The impaired SPEM gain in the MCDD group is in line with an earlier report on SPEM in a group of patients with psychotic disorder- not otherwise specified (PD-NOS), called Multi Dimensionally Impaired (MDI) by Kumra et al. (2001). These patients have many symptoms (impaired social skills, emotional lability, cognitive deficits, poor ability to distinguish fantasy from reality) similar to those seen in patients with MCDD (Towbin et al., 1993; Van der Gaag et al., 1995; Kumra et al., 2000, 2001; Ad-Dab'Bagh & Greenfield, 2001). In the study of Kumra et al. (2001), adolescents with PD-NOS / MDI were compared with a group of adolescents with childhood-onset schizophrenia (COS) and healthy subjects. The authors found a reduced gain and a higher rate of saccades in the COS group compared with controls (as expected), but only reduced gain in the MDI group patients compared with controls.

Earlier studies on biological parameters for MCDD revealed differences between MCDD and autistic subjects on psychosocial stress and event-related potential parameters and differences between MCDD and typical controls on the psychosocial stress parameter (Kemner et al., 1999; Jansen et al., 2000, 2003). Blunted cortisol responses to stress for schizophrenia and MCDD (Jansen et al., 1998, 2000) and the (partial) overlap in SPEM abnormalities in schizophrenia and PDD-NOS, subtype MCDD found in the present study could indicate that schizophrenia spectrum disorders and MCDD share (to some degree) a common neurobiological background.

The high frequency of saccades reported in schizophrenia has been suggested to be a compensatory mechanism for the low pursuit gain. However, an alternative explanation is that the increase in saccades and abnormal gain seen in schizophrenic subjects reflect different neurobiological abnormalities (Abel & Ziegler, 1988; Clementz & Sweeney, 1990; Ross, 2003). The current finding of lowered gain, but no increase in saccadic intrusions in the MCDD group in the present study, suggests that pursuit gain and saccadic intrusions are indeed independent phenomena. Global eye tracking dysfunction (a combination of pursuit gain and saccadic intrusions) and an increase in the frequency of saccades are closely associated with

genetic vulnerability to schizophrenia (Ross, 2002, 2003). Recently, this relation was also found for pursuit gain abnormalities (Louchart-de la Chapelle et al., 2005).
The SPEM parameters of the autistic subjects and controls were not statistically different, which is consistent with the earlier findings of Kemner et al. (2004) and Takarae et al. (2004). The SPEM parameters of the MCDD subjects and autistic subjects did not differ significantly either, although the mean values suggest a lower average gain in the MCDD group. The lack of a significant difference between the MCCD and autistic groups could be due to limited power, because our groups were relatively small. Therefore, the results should be replicated in a study with larger groups. Another limitation of the present study is that the EOG was used to determine SPEM instead of the more common eye-tracking technique. Although we showed the expected effects for the schizophrenia group using EOG, and could convincingly show abnormalities in pursuit gain in MCDD, a more detailed analysis of several saccadic parameters is only possible using eye-tracking.
The present study shows that MCDD subjects, but not subjects with autism, have a lower velocity gain than typical controls. This underlines the known clinical heterogeneity within the autistic spectrum. Of interest is that the reduced velocity gain associated with MCDD was partially similar to that found in schizophrenia (and related disorders). This suggests that MCDD patients are at risk of developing symptoms of schizophrenia and emphasizes the need for careful clinical evaluation of this group of patients.

References

Abel LA & Ziegler AS (1988).Smooth pursuit eye movements in schizophrenics-what constitutes quantitative assessment? Biol Psychiatry 24:747-761.

Ad-Dab'Bagh Y, Greenfield B (2001). Multiple Complex Developmental Disorder: The "Multiple and Complex" evolution of the "Childhood Borderline Syndrome" construct. J Am Acad Child Adolesc Psychiatry 40(8):954-964.

American Psychiatric Association (1994). Diagnostic and Statistical Manual of Mental Disorders (4th.ed). Washington, DC, 1994.

Andreassen NC, Arndt S (1992). The comprehensive assessment of symptoms and history (CASH); An instrument for assessing diagnosis and psychopathology. Arch Gen Psychiatry 49:615-623.

Buitelaar JK, van der Gaag RJ (1998). Diagnostic rules for children with PDD-NOS and Multiple Complex Developmental Disorder. J Child Psychol Psychiatry 39 (6): 911-919.

Clementz BA & Sweeney JA (1990). Is eye movement dysfunction a biological marker for schizophrenia? A methodological review. Psychol Bull 108(1), 77-92.

Cohen DJ, Paul R, Volkmar FR (1986). Issues in the classification of pervasive and other developmental disorders: toward DSM-IV. J Am Acad Child Adolesc Psychiatry 25 (2): 213-220.

Cohen DJ, Paul R, & Volkmar F (1987). Issues in the classification of Pervasive Developmental Disorders and Associated Conditions. In D.J. Cohen & A. M. Donnellan & P. Rhea (eds.). Handbook of Autism and Pervasive Developmental Disorders, (pp.20-39). New York: Wiley & Sons.

Holzman PS, O'Brian C, Waternaux C (1991). Effects of lithium treatment on eye movements. Biol Psychiatry 15; 29(10):1001-15

Hutton SB, Crawford TJ, Gibbins H, Cuthbert I, Barnes TRE, Kennard C, et al. (2001). Short and long term effects of antipsychotic medication on smooth pursuit eye tracking in schizophrenia. Psychopharmacology 157: 284-291.

Jacobsen LK, Hong WL, Hommer DW, Hamburger SD, Castellanos FX, Frazier JA, et al. (1996). Smooth pursuit eye movements in childhood-onset schizophrenia: comparison with attention-deficit hyperactivity disorder and normal controls. Biol Psychiatry 1; 40(11): 1144-1154.

Jansen LMC, Gispen-de Wied CC, Gademan PJ, De Jonge RCJ, Van der Linden JA, Kahn RS (1986). Blunted cortisol response to a psychosocial stressor in schizophrenia. Schizophr Res 33, 87-94.

Jansen LMC, Gispen-de Wied CC, Van der Gaag RJ, ten Hove, Willemsen-Swinkels SWM, Harteveld E, et al. (2000). Unresponsiveness to psychosocial stress in a subgroup of autistic-like children, Multiple Complex Developmental Disorder. Psychoneuroendocrinology 25: 753-764.

Jansen LM, Gispen-de Wied CC, Van der Gaag RJ, Van Engeland H (2003). Differentiation between autism and multiple complex developmental disorder in response to psychosocial stress. Neuropsychopharmacology 28(3): 582-590.

Kay SR, Fiszbein A, Opler LA (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13:261-276.

Kemner C, van der Gaag RJ, Verbaten M, van Engeland H (1999). ERP differences among subtypes of pervasive developmental disorders. Biol Psychiatry 46: 781-789.

Kemner C, van der Geest JN, Verbaten MN, van Engeland H (2004). In search of neurophysiological markers of pervasive developmental disorders: smooth pursuit eye movements? J Neural Transm 111:1617-1626.

Kumra S, Sporn A, Hommer DW, Nicolson R, Thaker G, Israel E, et al. (2001). Smooth pursuit eye-tracking impairment in childhood-onset psychotic disorders. Am J Psychiatry 158: 1291-1298.

LeCouteur A, Rutter M, Lord C, Rios P, Robertson S, Holdgrafer M, et al. (1989). Autism diagnostic interview: A standardized investigator-based instrument. J Autism Dev Disord 19: 363-387.

Lee KH, Williams LM, Loughland CM, Davidson DJ, Gordon E (2001). Syndromes of schizophrenia and smooth-pursuit eye movement dysfunction. Psychiatry Res 101, 11-21.

Lencer R, Trillenberg-Krecker K, Schwinger E, Arolt V (2003). Schizophrenia spectrum disorders and eye tracking dysfunction in singleton and multiplex schizophrenia families. Schizophr Res 60 (1): 33-45.

Litman R, Hommer DW, Radant AD, Clem T, Pickar D (1994). Quantitative effects of typical and atypical neuroleptics on smooth pursuit eye tracking in schizophrenia. Schizophr Res 12: 107-120.

Lord C, Rutter M, & Le Couteur A (1994). Autism Diagnostic Interview-Revised. J Autism Dev Disord 24, 659-686.

Louchart-de la Chapelle S, Nkam I, Houy E, Belmont A, Menard J, Roussignol A, et al. (2005). A concordance study of three electrophysiological measures in schizophrenia. Am J Psychiatry 162:466-474.

MMWR Surveill Summ.(2007). Prevalence of autism spectrum disorders--autism and developmental disabilities monitoring network, 14 sites, United States, 2002. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2002 Principal Investigators; Centers for Disease Control and Prevention 9;56(1):12-28

Ross RG, Olincy A, Harris JG, Radant A, Hawkins, Adler LE, et al. (1999a). Evidence for bilineal inheritance of physiological indicators of risk in childhood-onset schizophrenia. Am J Med Genet 16; 88(2): 188-199.

Ross RG, Olincy A, Harris JG, Radant A, Adler LE, Compagnon N, et al. (1999b). The effects of age on a smooth pursuit-tracking task in adults with schizophrenia and normal subjects. Biol Psychiatry 46, 383-391.

Ross RG, Olincy A, Mikulich SK, Radant AD, Harris JG, Waldo M, et al. (2002). Admixture analysis of smooth pursuit eye movements in probands with schizophrenia and their relatives suggests gain and leading saccades are potential phenotypes. Psychophysiology 39 (6): 809-819.

Ross RG (2003). Early expression of a psychophysiological feature of schizophrenia: saccadic intrusions into smooth-pursuit eye movements in school-age children vulnerable to schizophrenia. J Am Acad Child Adolesc Psychiatry 42(4): 468-476.

Rutter M (2005). Incidence of autism spectrum disorders: changes over time and their meaning. Acta Paediatr. 2005 Jan;94(1):2-15

Takarea Y, Minshew NJ, Luna B, Krisky CM, Sweeney JA (2004). Pursuit eye movement deficits in autism. Brain 127: 2584-2594.

Towbin KE, Duykens EM, Pearson GS, Cohen DJ (1993). Conceptualizing "borderline syndrome of childhood" and "childhood schizophrenia" as a developmental disorder. J Am Acad Child Adolesc Psychiatry 32(4): 775-82.

Van der Gaag RJ (1993). Multiplex developmental disorder. An exploration of borderlines on the autistic spectrum. Thesis, Utrecht University, the Netherlands.

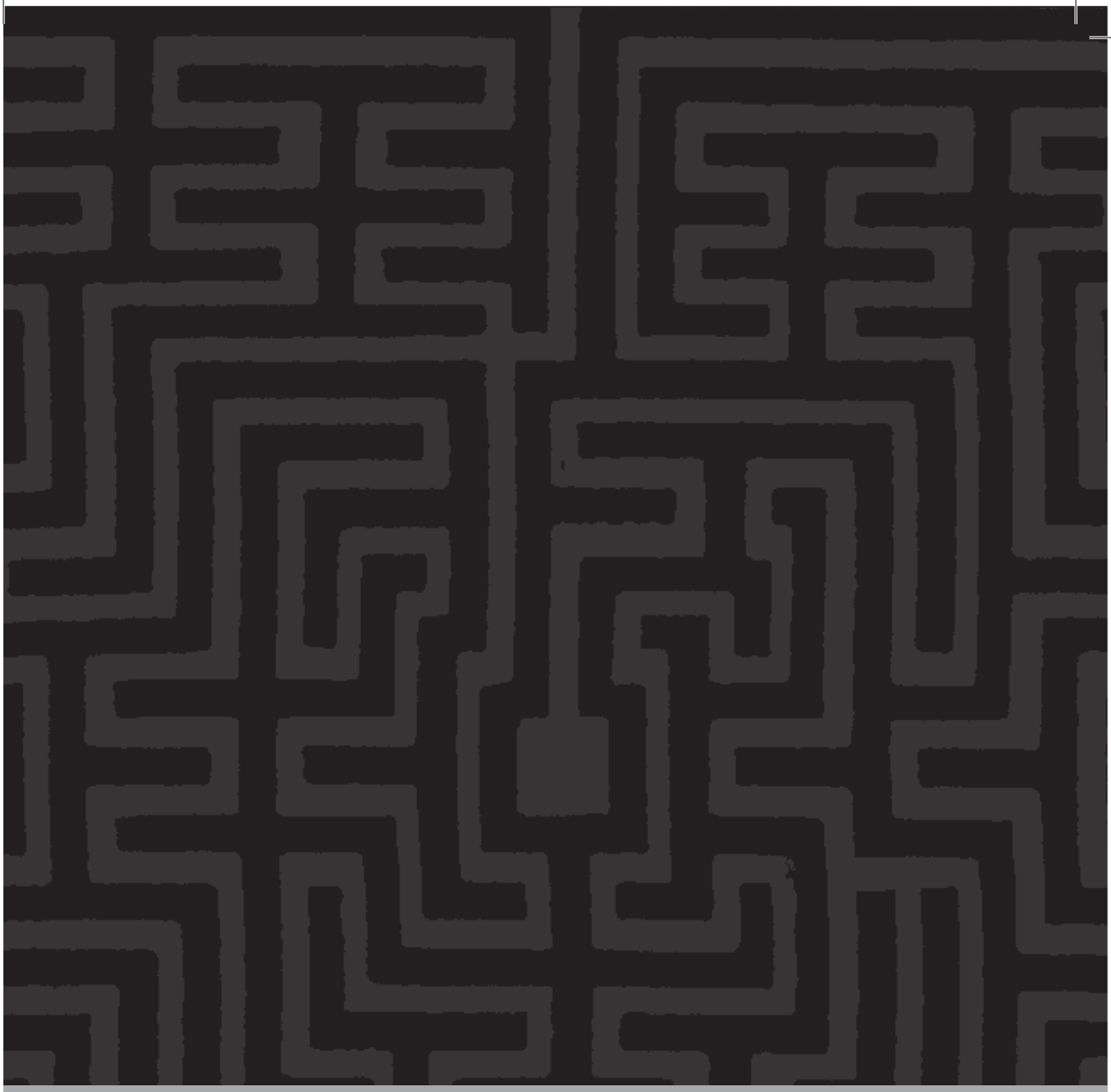
Van der Gaag RJ, Buitelaar J, Ban van den E, Bezemer M, Njio, L, Engeland van H. (1995). A controlled multivariate chart review of multiple complex developmental disorder. J Am Acad Child Adolesc Psychiatry 34(8): 109-106.

Vandersteene G, Van Haassen PP, De Bruyn EEJ, Coetsier P, Pijl YL, Poortinga YH, et al. (1986). WISC-R, Wechsler Intelligence Scale for Children-Revised, Nederlandstalige uitgave. Lisse: Swets and Zeitlinger.

Van Engeland H, Van der Gaag RJ (1994). MCDD in childhood: a precursor of schizophrenic spectrum disorders. Schizophr Res 11: 2, 197.

[6]

Lahuis BE, Oranje B, Van Engeland H, Van der Gaag RJ, Kemner C
Submitted for publication



Aspects of stimulus filtering (Prepulse Inhibition and P50 suppression) in a subgroup of Pervasive Developmental Disorders; the Multiple Complex Developmental Disorders (MCDD).

Abstract

Objective:

Multiple Complex Developmental Disorder (MCDD) is a well defined and validated behavioral subtype of PDD-NOS with a suggested risk of developing a schizophrenic spectrum disorder. The question was addressed if additional validation for this subgroup could be demonstrated with a sensory filtering paradigm which is already known to reveal gating deficits in patients with schizophrenia.

Method:

P50 suppression and Prepulse Inhibition of the Startle reflex were explored in patients with Multiple Complex Developmental Disorder (MCDD n=14), Autism (n=13) and healthy controls (n=12).

Results:

No differences were found for either of the 2 paradigms between the MCDD patients, autistic patients and healthy controls.

Conclusion:

No abnormalities in sensory filtering could be detected for autism or MCDD. Since sensory gating deficits are commonly regarded as possible endophenotypic markers for schizophrenia, the current results suggest less similarity between schizophrenia and MCDD than earlier assumed.

Introduction

Autism is one of the best defined and validated psychiatric disorders of childhood. It is characterized by problems in social interaction, social communication and restricted and repetitive behaviours and interests. Pervasive Developmental Disorder- Not Otherwise Specified (PDD-NOS) however, represents a heterogeneous group of patients failing to meet the full criteria for an autistic disorder (American Psychiatric Association, 1994). This group of patients is not rare and even outnumbers the group of autistic patients up to three times (Wing and Gould, 1979; Fombonne, 2003, 2005). Because the lack of homogeneity in this group is hampering biological research, more homogenous subgroups have been proposed. One of these subgroups is Multiple Complex Developmental Disorder (MCDD), first described by Cohen, Paul & Volkmar (1986). MCDD patients are characterized by 1. impaired regulation of affective state and anxiety, 2. impaired social behaviour/ sensitivity, and 3. impaired cognitive processing (thought disorder) (Cohen et al., 1986; Towbin et al., 1993; Van der Gaag et al., 1995; Buitelaar and Van der Gaag, 1998; Ad-Dab'Bagh and Greenfield, 2001). Although sharing impairments in social behaviour and sensitivity with autistic patients, children with MCDD are found to be more impaired than children with autism on thought disorders (psychotic thinking), primitive anxieties, and aggression (Van der Gaag et al., 1995; Buitelaar and Van der Gaag, 1998). Follow-up of MCDD children revealed a shift towards schizophrenic spectrum disorders in adulthood (66 %), suggesting that MCDD might be seen as a high risk group of patients within the autistic spectrum for developing schizophrenic spectrum disorders (Van der Gaag, 1993; Van der Gaag et al., 1995).

In order to characterise subjects with MCDD better and to underline that autistic spectrum disorders include different subtypes, there is a great need for (biological) markers. For subjects with schizophrenia several psychophysiological markers have been validated in different paradigms. Two of these paradigms are thought to measure different aspects of stimulus filtering, namely, the prepulse inhibition (PPI) of the acoustic startle response and the gating of the auditory evoked potential (P50 suppression). In PPI a startle response to a stimulus is muted or inhibited in magnitude when preceded by a weak stimulus (the prepulse). In humans, the eyeblink component of startle is most often assessed, using electromyographic (EMG) recordings of the orbicularis oculi muscle. It has been shown that startle latencies become shorter with increasing age across the childhood years (Ornitz et al., 1993). P50 gating also involves a suppressive effect of an initial stimulus on the P50 potential in the response to a second identical stimulus ('clicks'). P50 gating can be reliable measured in children between 10 and 14 years of age, showing the same

ratio of P50 suppression as adults (Myles-Worsley et al., 1996). An advantage of both paradigms is that they require neither motivation nor significant cooperation.

Abnormalities for PPI and P50 suppression have been clearly demonstrated across the schizophrenia spectrum, including probands, their unaffected relatives, and schizotypal patients (see for references Braff et al., 2001;Swerdlow et al., 2006). The schizophrenia patients exhibited reduced PPI independently of whether auditory, tactile, or electrocutaneous stimuli were used to elicit startle and PPI. It was also concluded that medications did not account for schizophrenia related PPI deficits (Braff et al., 2001). Also, PPI deficits were found to correlate significantly with symptoms of thought disorder and were associated with greater distractibility, an earlier age of onset, and greater positive and negative symptoms (Braff et al., 1999, 2001). For the P50 suppression paradigm, a deficit in the inhibition of the P50 evoked response (less amplitude reduction to the second stimulus) was found for both medicated and unmedicated patients with schizophrenia (Freedman et al., 1983). There is evidence suggestive of an association between P50 suppression and measures of attention, but multiple studies have failed to document a cross-sectional or longitudinal relationship between P50 suppression and positive, negative or other symptoms (for a review see Potter et al., 2006).
Although earlier it has been assumed that reduced inhibition in PPI and P50 suppression in subjects with schizophrenia reflects a common, unitary, underlying information-processing or 'gating' abnormality, in the last decade it has become clear that the neurobiological substrates of PPI and P50 suppression only partially overlap, and that they probably involve different genetic architectures (Swerdlow et al., 2006). This is reflected in the fact that studies on the relationship between PPI and P50 suppression usually find none, or at best only weak, correlations between these two measures (Oranje et al., 1999, 2006; Schwarzkopf et al., 1993).
It has been speculated (for schizophrenia-spectrum patients) that different patterns of inhibitory deficits may be associated with different clinical profiles (Swerdlow et al., 2006). It is unclear however, whether this applies for autism spectrum patients as well.
For autism spectrum disorders and PPI the number of studies is limited. Three studies on startle response, including PPI, have been published: Ornitz et al. (1993) (54 autistic patients); McAlonan et al. (2002) (10 Asperger patients); Perry et al. (2007) (14 autistic patients). McAlonan et al. (2002) found a reduced PPI in the 120 ms/ 86 db condition for adults with Asperger disorder compared to healthy controls, and Perry et al. (2007) reported on PPI deficits in the 60 ms/ 86 db condition in adults with autism compared to healthy controls. Ornitz et al. (1993) reported no consistent significant differences between diverse groups of autism including children and adolescents, (aged 2.8-33 years, IQ 40-145, some major medical co-

morbidity) and a healthy control group. Research on the suppression of the P50 potential in autistic patients (including children) is lacking. The only study that reports on this is from our group, showing normal P50 suppression for children with autism (Kemner et al., 2002).
It would be of interest to know if indeed the MCDD subjects resemble the known abnormalities for schizophrenia on PPI and P50 suppression. By that, from a neurobiological point of view, the earlier statement that MCDD should be seen as a high-risk group for developing a diagnosis within the schizophrenic spectrum would be supported (Van Engeland and Van der Gaag, 1994). Furthermore, it is of interest to find out whether children and adolescents with autism show abnormal stimulus filtering (PPI and P50 suppression) similar to what is normally found in schizophrenia, and whether autistic children can be psychophysiologically differentiated from children with MCDD by this type of research. The aim of the current study was to determine whether children with MCDD show the same neurobiological gating abnormalities as subjects with schizophrenia. An additional purpose was to find out whether these children could be differentiated from children with PDD on these neurobiological markers. To this extent P50 suppression and PPI were assessed in a group of non-mentally retarded children and adolescents with PDD-NOS, subtype MCDD and compared to autistic subjects and controls, matched on age and performal IQ. It was hypothesized 1) that subjects with MCDD would reveal differences in PPI and P50 suppression compared to both autistic and control subjects and 2) that MCDD patients would show the same characteristic PPI and P50 suppression abnormalities as is generally reported in literature on schizophrenia, namely impaired PPI and diminished suppression of the P50 auditory evoked response.

Methods

Subjects

Participants general information

Potential patients were recruited from the (out) patient clinic of the Child and Adolescent Psychiatry Unit of the University Medical Center Utrecht or were recruited through the National Autism Society in the Netherlands. They were matched on age and performance IQ (PIQ). In total 8 patients for the PPI session and 4 patients for the P50 session were excluded because of poor tracing results due to technical problems, uncooperativeness or because they could not be matched on age or PIQ. The diagnosis of potential patients were established by expert clinical opinion (child psychiatrists) and verified by results from the Autism Diagnostic Interview- Revised version (ADI-R) (LeCouteur et al., 1989). All subjects

with MCDD met the criteria for PDD-NOS (American Psychiatric Association, 1994), and the criteria for MCDD as defined by Cohen et al. (1987) (a minimum of six of 14 criteria, including at least two criteria from each of the three domains, see **list 1**). All subjects with autism met the criteria for Autistic Disorder (American Psychiatric Association, 1994).
All subjects were asked to participate in the PPI and / or the P50 suppression session and a neuropsychological assessment in order to estimate full-scale IQ (WISC-R) (Vandersteene et al., 1986). The procedure was approved by the institutional review board of the University Medical Center in Utrecht, the Netherlands, in accordance with the Declaration of Helsinki.

Participants PPI

In total data of 33 patients were included in the analysis (11 controls, 11 autistic, 11 MCDD). Neither significant differences in age [$F(2,30) = 0.487$; $p = 0.619$], nor PIQ [$F(2,29) = 2.58$; $p = 0.09$] were found. Thirteen subjects (7 autistic, 6 MCDD) fulfilled the traditional ADI-R threshold for all three domains (Lord et al., 1994). Eight subjects (4 autistic, 4 MCDD) reached threshold when the modified criteria were applied (i.e. score within two points of full criteria). One patient with MCDD scored within 4 points of full criteria (6 points on social communication, 1 point on repetitive & stereotyped behaviour). Mean score on the MCDD criteria for the subjects with autism was 3.3 (sd 1.3), which was significantly lower compared to the score of 8.8 (sd 2.4) for subjects with MCDD [$F(1,20) = 45.8$; $p<0.001$]. Two subjects with MCDD, 2 subjects with autism, and 1 of the controls were female. Two MCDD patients were treated with risperidone, 1 autistic patient with dipiperon.

Participants P50 suppression

In total data from 39 subjects were included in the analysis (12 controls, 13 autistic patients and 14 MCDD patients). Neither significant differences in age nor PIQ were found between the groups. Fourteen subjects (7 autistic, 7 MCDD) fulfilled the traditional ADI-R threshold for all three domains (Lord et al., 1994). Twelve subjects (6 autistic, 6 MCDD) reached thresholds when the modified criteria were applied (i.e. score within two points of full criteria). One MCDD patient scored within 4 points of full criteria (6 points on social communication, 1 point on repetitive & stereotyped behaviour). Mean score on the MCDD criteria for the subjects with autism was 3.4 (sd 1.3), which was significantly different compared to the score of 8.9 (sd 2.1) for subjects with MCDD [$F(1,25) = 64.7$; $p<0.001$]. Two subjects with MCDD, 2 subjects with autism, and 1 of the controls were female. Four MCDD patients were treated with risperidone, 1 autistic patient with dipiperon.

List 1 Diagnostic criteria for MCDD (Cohen et al., 1987)

MCDD is a serious, early onset and persistent disturbance affecting several major domains of functioning, including the following three major areas:

1. Regulation of affective state and anxiety is impaired beyond that seen in children of comparable age, as exemplified by several of the following: (at least two of the following)
   a) intense generalized anxiety or tension
   b) fears and phobias (often unusual and peculiar)
   c) recurrent panic episodes or 'flooding' with anxiety
   d) episodes of behavioral disorganization punctuated by markedly immature, primitive or violent behaviors
   e) significant and wide emotional variability with or without environmental precipitants.
   f) frequent idiosyncratic or bizarre anxiety reactions
2. Consistently impaired social behavior/sensitivity, as exemplified by the following types of disturbances: (at least two of the following)
   a) social disinterest, detachment, avoidence or withdrawal despite evident competence
   b) severely impaired peer relationships
   c) markedly disturbed attachements; high degrees of ambivalence to adults (esp.parents/ caretakers)
   d) profound limitations in the capacity for empathy or understanding others affects accurately
3. Impaired cognitive processing (thinking disorder), as exemplified by some of the following difficulties: (at least two of the following)
   a) irrationality,sudden intrusions on normal thought process, magical thinking, neologism or repetitions of nonsense words, desultory thinking, blatantly illogical, bizarre ideas
   b) confusion between reality and inner fantasy life
   c) perplexity and easy confusability (trouble with understanding ongoing social processes or keeping one's thoughts 'straight')
   d) 'delusions', over valued ideas including fantasies of omnipotence, paranoid preoccupations, overengagement with fantasyfigures, grandiose fantasy of special powers, and referential ideation
4. The syndrome appears during the first several years of life
5. The child is not suffering from autism or schizophrenia

Paradigm

PPI paradigm

The prepulse and startle stimuli were bursts of white noise (duration 25 and 30 ms, intensity 86 dB and 107 dB, respectively), with a fixed interstimulus interval of 120 ms. The stimuli were gated almost instantaneously (rise/fall time, 0.1 ms) and presented binaurally through stereo insert earphones (Eartone ABR). The software settings were calibrated by means of an artificial ear (Brűel and Kjær, type 4152)

to make sure that the stimulus intensities at the subject's ear were the intended intensities. Each subject was seated upright in a dentist chair in a dimly lit sound-isolated cabin. Before the actual start of the prepulse inhibition assessment, 4 startle stimuli of rising intensity were presented, 2 of which were preceded by a prepulse stimulus, to accustom the subjects to loud noises. The actual experiment consisted of a block of 24 randomized trials: 12 preceded by a prepulse stimulus and 12 without. The intertrial intervals were randomised between 12 and 23 s.

P50 suppression paradigm

The auditory stimuli were gated almost instantaneously (rise/fall, 0.1 ms) and presented binaurally through stereo insert earphones (Eartone ABR). The software settings were calibrated by means of an artificial ear (Brűel and Kjær, type 4152) to make sure that the stimulus intensities at the subject's ear were the intended intensities. Before the actual experimental block started 2 click pairs were presented as an audiometric test. After instruction a block of 36 click pairs with an interstimulus interval of 500 ms, and an intertrial interval of 10 s was presented. The clicks consisted of a white noise burst of 1.5 ms, with an intensity of 86 dB.

Recording PPI and P50 suppression

Recordings were made with one of the two systems[1]. Using the Psylab hardware (Contact Precision Instruments, London), signals were sampled at 500 Hz and recorded as a continuous signal. A ground electrode was placed at the middle of the forehead and electroencephalogram (EEG) signals were referenced to the left mastoid. EEG signals were filtered online with a high-pass filter of 0.05 Hz and a low-pass of 70 Hz. EMG signals were filtered online with a high-pass filter of 30 Hz and a low-pass filter of 200 Hz. The second system consisted of the Active Two system (Biosemi, Amsterdam), and in this case the EEG was sampled at 2048 Hz and stored as a continuous signal. Two electrodes in the electrode cap, the CMS (=common mode sense) and DRL (=driven right leg) provided an active ground in this system. An electrode placed on the left mastoid was used as reference for EEG measurement. Data were resampled offline at 500 Hz.

Data analysis

PPI

EMG data were analysed using the software package Brain Vision Analyser (Biosemi, Amsterdam) and filtered offline with a high-pass filter of 30 Hz and a low-pass-filter of 200 Hz. Epochs from -50 ms pre-stimulus until 200 ms post-stimulus

1 In an earlier study it was tested whether the use of the two systems resulted in comparable electrophysiological data; this was indeed the case (Kemner et al 2006).

were extracted from the continuous data, and the baseline was corrected using the data for 50 ms prior to stimulus-onset. Thereafter, the data were rectified. Last, assessment of the maximal peak amplitude and PPI quantification took place within a window of 20–90 ms, after stimulus onset, using a computerized algorithm for peak detection.
PPI was defined as the percentage of reduction of the startle amplitude over preupulse-pulse trials, compared to the pulse alone trials (PPI=100*(1-pp/p), where pp indicates amplitude over prepulse trials and p indicates amplitude over pulse alone trials.

P50 suppression

All EEG data were analysed using the software package Brain Vision Analyser (Biosemi, Amsterdam) and filtered offline with a high-pass filter of 1.6 Hz (24 dB), a low-pass filter of 70 Hz (24 dB), and a Notch filter of 50 Hz. In order to compute ERPs, epochs from 100 ms pre-stimulus until 400 ms post-stimulus were extracted from the continuous data, and the baseline was corrected using the 100 ms registration prior to stimulus-onset. Electrooculogram (EOG) artefacts were removed (Gratton et al., 1989). EEG artifacts were removed if they were larger than 100 or –100 μV, if there was an amplitude difference per sample point larger than 50 μV or if the difference between maximum and minimum amplitudes in a window of 200 ms was smaller than 3 μV. Segments were averaged to produce separate average evoked response potential (ERP) waveforms for the conditioning and test click stimuli.
The P50 waves were identified and scored as described by Nagamoto et al. (1989). P50 peaks elicited by the first (conditioning) stimulus were identified as the greatest positivity in a window between 40 and 90 ms, after stimulus presentation. The amplitude was assessed as being the difference between this peak and the preceding trough, the latency was assessed as being the time from the onset of the conditioning stimulus to the maximum amplitude of this peak. The P50 peak elicited by the second (testing) stimulus was assessed accordingly, with a further constraint that its peak latency had to lay in a window formed by the latency of the conditioning stimulus ± 10 ms. Two raters were used to identify the P50 wave; the interrater reliability was higher than 95%. The P50 ratio was calculated as the amplitude of the P50 potential elicited by the testing stimulus divided by the

Table 1 Demographic data P50. The number of subjects (N), use of medication and the mean (and standard deviation of) age, Performal IQ (PIQ), Autism Diagnostic Interview-Revised version scores (ADI-R) and Cohen's Multiple Complex Developmental Disorder (MCDD) scale scores for the MCDD group, autism group and the control group.

	N	Age	PIQ	Medication	ADI-R Domain scores			Score on Cohen's MCDD scale
		Mean (months) ± SD	Mean ± SD		Mean ± SD			Mean ± SD
					Social interaction	Communication	Repetitive & stereotyped behavior	
MCDD	14	137.29 ± 18.53	96.5 ± 8.8	4 pt on risperidon	19.07 ± 5.33	14.19 ± 5.34	4.0 ± 2.35	8.93 sd ± 2.13
Autistim	13	143.54 ± 20.65	97.2 ± 11.4	1 pt on dipiperon	17.69 ± 5.04	13.46 ± 4.93	4.31 ± 2.56	3.38 ± 1.33
Controls	12	136.92 ± 20.19	105.8 ± 12.0	-	-	-	-	-

Table 2 Demographic data Startle. The number of subjects (N), use of medication and the mean (and standard deviation of) age, Performal IQ (PIQ), Autism Diagnostic Interview-Revised version scores (ADI-R) and Cohen's Multiple Complex Developmental Disorder (MCDD) scale scores for the MCDD group, autism group and the control group.

	N	Age (months)	PIQ	Medication	ADI-R Domain scores			Score on Cohen's MCDD scale
		Mean ± SD	Mean ± SD		Mean ± SD			Mean ± SD
					Social interaction	Communication	Repetitive & stereotyped behavior	
MCDD	11	136.5 ± 15.7	97.5 ± 7.6	2 pt on risperidon	20.5 ± 5.0	16.3 ± 5.6	3.8 ± 2.0	8.8 ± 2.4
Autistic	11	141.5 ± 21.3	97.6 ± 5.6	1 pt on dipiperon	17.0 ± 4.9	12.7 ± 4.9	4.5 ± 2.5	3.3 ± 1.3
Controls	11	132.9 ± 23.4	104.7 ± 11.2	-	-	-	-	-

amplitude elicited by the conditioning stimulus (T/C).

Results

PPI

The (raw) data were analyzed using a mixed-model analysis of variance (ANOVA) with the within-subjects factor stimuli (pulse alone vs. prepulse-pulse trials) and the between-subjects factor group (MCDD vs. autistic vs. normal control), using SPSS 14.0 for Windows software package (SPSS, Inc., Chigaco, III).
A main effect of stimulus was found [F(1,30)=12,3; p=0.001] indicating a larger EMG activity in response to startle trials than to prepulse-pulse trials, i.e. PPI occurred. No significant main effect of group was found [F(2,30)=1.39; p=0.27], nor an interaction of groups with stimulus [F(2,30)=2.0;p=0.16]. PPI was analyzed with a one-way ANOVA with between factor group; however, no significant difference in PPI was found between the three groups [F(2,32) = 0.44; p = 0.649]. Rerunning the analyses excluding subjects with medication revealed no significant differences on any of the parameters.

P50 suppression

The data were analyzed using a mixed-model analysis of variance (ANOVA) with the within-subjects factor stimuli (conditioning vs. testing stimulus) and the between-subjects factor group (MCDD vs. autistic vs. normal control), using SPSS 14.0 for Windows software package (SPSS, Inc., Chigaco, III). Two subjects (one control subject and one MCDD subject) showed no P50 amplitude on the conditioning stimulus and were not included in the P50 analysis.
A main effect of stimulus was found [F(1,34) = 20.5; p <0 .001] indicating that the amplitude to the testing stimulus was significantly smaller than the amplitude to the conditioning stimulus, i.e. P50 suppression occurred. Neither a significant main effect of group was found [F(2,34) = 0.57; p = 0.57], nor a significant interaction of groups with stimulus [F(2,34) = 0. 33; p = 0.72]. P50 suppression was analyzed with a one-way ANOVA, however, no significant differences in P50 ratio between the groups was found [F(2,34)= 0.64;p= 0.53] (see **Figure 1**). Rerunning the analyses excluding subjects with medication revealed no significant differences on any of

Table 3 The mean (and standard deviation) of the PrePulse Inhibition (PPI) and P50 for the Multiple Complex Developmental Disorder (MCDD) group, autism group and the control group.

Group	PPI (mean ± SD)	P50 (mean ± SD)
MCDD	60.5 sd 30.6	0.65 sd .53
Autism	62.5 sd 21.8	0.65 sd .57
Controls	51.2 sd 35.9	0.56 sd .51

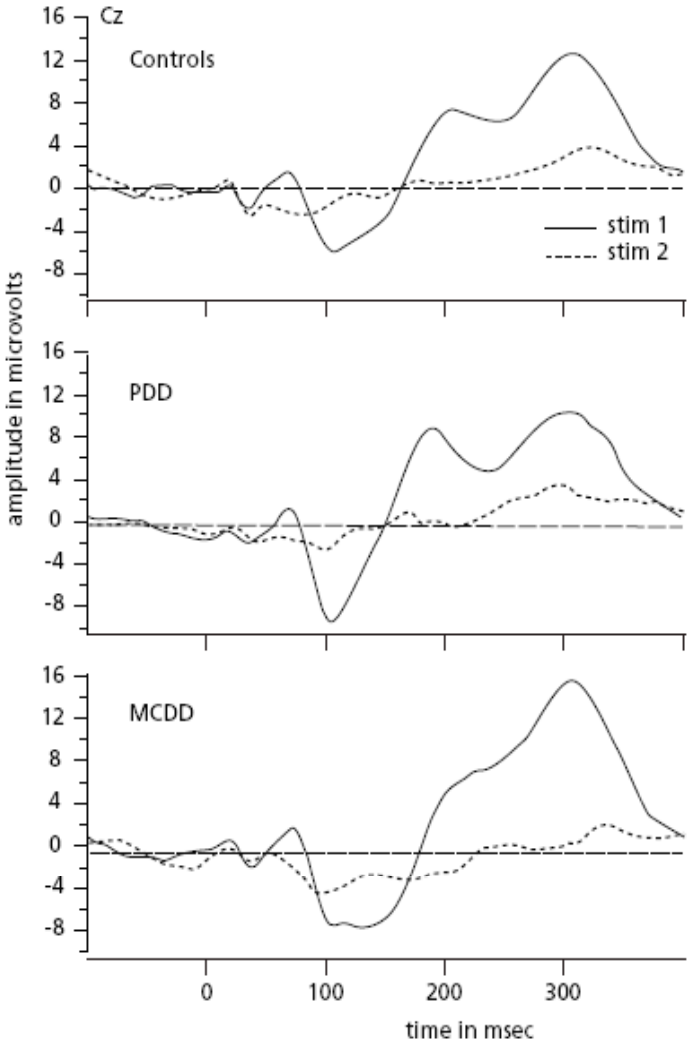


Figure 1 P50 Grand average event-related potentials to stimulus 1 (C) and stimulus 2 (T) for the MCDD group, autism group and the control group. P50 suppression is displayed.

the parameters.

Discussion

The present study was designed to investigate PPI and P50 suppression in a group of children with PDD-NOS, subtype MCDD, children with autism and healthy controls, all matched on age and PIQ. Since children with MCDD have an enhanced

risk developing psychosis, it was expected that they would show abnormalities in PPI and P50 suppression comparable to those seen in subjects with schizophrenia. However, the main finding of this study is that no differences were found between subjects with MCDD on the one hand and subjects with autism and healthy controls on the other hand, neither for PPI nor P50 suppression.

Autistic patients also showed normal P50 suppression, confirming the results of an earlier study from our laboratory (Kemner et al., 2002). With respect to PPI, no differences were found between children with autism and healthy controls. This is in agreement with the study of Ornitz et al. (1993) in which no consistent significant differences were found between diverse patient groups with autism, including children. Two other studies however, do describe PPI differences between adult subjects with PDD (autism or Asperger) and controls (McAlonan et al., 2002; Perry et al., 2007). However, in these studies different prepulse conditions were used, and group differences were seen in some (120 ms/86 db in the study of McAlonan et al. (2002), or 60 ms/86 db in the study of Perry et al. (2007)), but not in other (30 ms/74 or 86 db or 120 ms/74 db in the study of McAlonan et al. (2002) and 30 ms/86 db and 120 ms/86 db in the study of Perry et al. (2007)). In the current study only the 120 ms/86 db condition was used.

Intact sensory gating prevents overload of higher brain functions by filtering out irrelevant stimuli. Impairment in this mechanism has been thought to underly psychotic symptoms (McGie and Chapman, 1961; Braff et al., 1990; Perry et al., 1999). Indeed for PPI (but not for P50 suppression), correlations and associations with thought disorder and intensity of positive or negative symptoms are described (Braff et al., 1999, 2001). Aspects of thinking disorder (e.g. magical thinking, bizarre ideas, confusion between reality and inner fantasy life, easy confusability and 'delusions') are part of the MCDD syndrome, and therefore an abnormality in gating could have been expected in this group: impaired PPI and diminished suppression of P50 auditory evoked response would resemble deficits in sensory filtering as frequently reported for schizophrenia patients and by that be supportive for the idea that MCDD has neurobiological similarities with the schizophrenia spectrum. In general, deficits in sensory gating are assumed to be trait – as opposed to state –phenomena in schizophrenia, indicating possible endophenotypic markers (Braff et al., 2007; Calkins et al., 2007). However, no abnormal sensory gating was found in the present study in subjects with MCCD. This finding suggests that gating processes and thinking disorder are not functionally related, and that MCDD is less related to schizophrenia than was expected. Another explanation could be that the groups are too small to find a significant difference. However, this is unlikely since the mean percentages PPI and P50 suppression do not differ much over the three groups. Alternatively, impairments in gating could be a developmental abnormality that increases with age, and is relatively small in childhood (Braff et al., 2001).

This study has some limitations. First, the sample size of the groups is relatively small. However, the high p-values make it unlikely that only limited power could clarify these results. Second, in this study only one condition was tested (86 dB/120 ms). However, in schizophrenia research abnormalities are mostly found in this condition (Braff et al., 2001). Third, we only included individuals (MCDD, autism and controls) with PIQ-scores in the normal range in this study. Therefore it is unclear how well our findings would generalize to lower-functioning individuals with a diagnosis in the PDD-spectrum.

In summary, in this study no deficits in stimulus filtering (PPI or P50 suppression) for children with MCDD were found. Since sensory gating deficits are commonly regarded as possible endophenotypic markers for schizophrenia, the current results suggest less similarity between schizophrenia and MCDD than generally assumed. Future studies should include a larger variability in age between the groups to investigate whether age is a relevant factor.

References

Ad-Dab'Bagh Y, Greenfield B (2001). Multiple Complex Developmental Disorder: The "Multiple and Complex" evolution of the "Childhood Borderline Syndrome" construct. J Am Acad Child Adolesc Psychiatry 40:954-964.

American Psychiatric Association (1994). Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Press.

Braff DL, Freedman R, Schork NJ, Gottesman II (2007). Deconstructing schizophrenia: an overview of the use of endophenotypes in order to understand a complex disorder. Schizophr Bull 33(1):21-32.

Braff DL and Geyer MA (1990). Sensorimotor gating and schizophrenia: Human and animal model studies. Arch Gen Psychiatry 47: 181-188

Braff DL, Geyer MA, Swerdlow NR (2001). Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. Psychopharmacology 156:234-258.

Braff DL, Swerdlow NR, Geyer MA (1999). Symptom correlates of prepulse inhibition deficits in male schizophrenic patients. Am J Psychiatry 156:596-602.

Buitelaar JK, Van der Gaag RJ (1998). Diagnostic rules for children with PDD-NOS and Multiple Complex Developmental Disorder. J Child Psychol Psychiatry 39(6):911-919.

Calkins ME, Dobie DJ, Cadenhead KS, Olincy A, Freedman R, Green MF, Greenwood TA, Gur RE, Gur RC, Light GA, Mintz J, Nuechterlein KH, Radant AD, Schork NJ, Seidman LJ, Siever LJ, Silverman JM, Stone WS, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky BI, Braff DL (2007.) The Consortium on the Genetics of Endophenotypes in Schizophrenia: model recruitment, assessment, and endophenotyping methods for a multisite collaboration. Schizophr Bull 33: 33-48.

Cohen DJ, Paul R, Volkmar FR (1986). Issues in the classification of pervasive and other developmental disorders: toward DSM-IV. J Am Acad Child Adolesc Psychiatry 25(2):213-220.

Cohen DJ, Paul R, Volkmar F (1987). Issues in the classification of Pervasive Developmental Disorders and Associated Conditions. In: D.J. Cohen & A. M. Donnellan & P. Rhea, eds. Handbook of Autism and Pervasive Developmental Disorders. New York: Wiley & Sons; 20-39.

Fombonne E (2003). Epidemiological surveys of autism and other pervasive developmental disorders: an update. J Autism Dev Disord 33(4):365-82.

Fombonne E (2005). Epidemiology of autistic disorder and other developmental disorders. J Clin Psychiatry 66:10:3-8.

Freedman R, Adler LE, Waldo MC, Pachtman E, Franks, RD (1983). .Neurophysiological evidence for a defect in inhibitory pathways in schizophrenia: comparison of medicated and drug-free patients. Biol Psychiatry 18(5):537-51.

Gratton G, Coles MG, Donchin E (1983). A new method for off-line removal of ocular artifact. Electroencephalogr Clin Neurophysiol 55(4): 468-84.

Kemner C, Oranje B, Verbaten MN, Van Engeland H (2002). Normal P50 gating in children with autism. J Clin Psychiatry 63(3):214-7.

LeCouteur A, Rutter M, Lord C, Rios P, Robertson S, Holdgrafer M, McLennan J (1989). Autism diagnostic interview: A standardized investigator-based instrument. J Autism Dev Disord 19:363-387.

Lord C, Rutter M, Couteur A (1994). Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 24(5):659-85.

McAlonan GM, Daly E, Kumari V, Critchley HD, Van Amelsvoort T, Suckling J, Simmons A, Sigmundsson T, Greenwood K, Russell A, Schmitz N, Happe F, Howlin P, Murphy DG (2002). Brain anatomy and sensorimotor gating in Asperger's syndrome. Brain 125:1594-606.

McGie A, Chapman J (1961). Disorders of attention and perception in early schizophrenia. Br J Medical Psychol 34:103-16.

Myles-Worsley M, Coon H, Byerley W, Waldo M, Young D, Freedman R, (1996). Developmental and genetic influences on the P50 sensory gating phenotype. Biol Psychiatry 15; 39(4):289-95.

Nagamoto HT, Adler LE, Waldo MC, Freedman R (1989). Sensory gating in schizophrenics and normal controls: effects of changing stimulation interval. Biol Psychiatry 1; 25(5):549-61.

Oranje B, van Berckel BNM, Kemner C, Van Ree JM, Kahn RS, Verbaten MN (1999). P50 Suppression and prepulse inhibition of the startle reflex in humans: a correlational study. Biol Psychiatry 45:883-890.

Oranje B, Geyer MA, Bocker KB, Kenemans JL, Verbaten MN (2006). Prepulse inhibition and P50 suppression: commonalities and dissociations. Psychiatry Res Epub 28.

Ornitz .M, Lane SJ, Sugiyama T, Traversay J (1993). Startle modulation studies in autism. J Autism Dev Disord 23(4):619-37.

Perry W, Geyer,MA, Braff DL(1999). Sensorimotor gating and thought disturbance measured in close temporal proximity in schizophrenic patients. Arch Gen Psychiatry 56: 277-281

Perry W, Minassian A, Lopez B, Maron L, Lincoln A (2007). Sensorimotor Gating Deficits in Adults with Autism. Biol Psychiatry 15:61(4):482-6.

Potter D, Summerfelt J, Gold A, Buchanan RW (2006). Review of clinical correlates of P50 sensory gating abnormalities in patients with schizophrenia. Schizophr Bull 32(4):692-700.

Schwarzkopf SB, Lamberti JS, Smith DA (1993). Concurrent assessment of acoustic startle and auditory P50 evoked potential measures of sensory inhibition. Biol Psychiatry 33, 11-12:815-28.

Swerdlow NR, Geyer MA, Shoemaker,JM, Light GA, Braff DL, Stevens KE, Sharp R, Breier M, Neary A, Auerbach PP (2006). Covergence and divergence in the neurochemical regulation of prepulse inhibition of startle and N40 suppresion in rats. Neuropsychopharmacol 31:506-515.

Towbin KE, Duykens EM, Pearson GS, Cohen DJ (1993). Conceptualizing "borderline syndrome of childhood" and "childhood schizophrenia" as a developmental disorder. J Am Acad Child Adolesc Psychiatry 32(4):775-82.

Van der Gaag RJ (1993) Multiplex developmental disorder. An exploration of borderlines on the autistic spectrum. Thesis, Utrecht University, the Netherlands.

Van der Gaag RJ, Buitelaar JK, Ban van den E. Bezemer M, Njio L, Van Engeland H (1995). A controlled multivariate chart review of multiple complex developmental disorder. J Am Acad Child Adolesc Psychiatry 34(8):109-106.

Van Engeland H, Van der Gaag RJ (1994). MCDD in childhood: a precursor of schizophrenic spectrum disorders. Schizophr Res 11:2,197.

Vandersteene G, Van Haassen PP, De Bruyn EEJ, Coetsier P, Pijl YL, Poortinga YH, Lutje Spelberg HC, Spoelders-Claes R, Stinissen J (1986). WISC-R, Wechsler Intelligence Scale for Children-Revised, Nederlandstalige uitgave. Lisse: Swets and Zeitlinger.

Wing L, Gould J (1979). Severe impairments of social interaction and associated abnormalities in children: Epidemiology and classification. J Autism Dev Disord 9:11-29.

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Summary and General Discussion

Autism Spectrum Disorders (ASD), including autism, Asperger and PDD-NOS, are nowadays frequently diagnosed psychiatric illnesses at the age of childhood. Increases in epidemiological figures are found up till 1:150 (MMWR Surveill Summ, 2007). Earlier and better diagnostic methods are the best explanation for these increases till now. Many of these patients require a huge amount of treatment and care in childpsychiatry settings. Research to broaden our understanding of the neurobiology of autism spectrum disorders, and gaining insight in specific vulnerable subgroups is needed. Research on the prevalence and pattern of co-occuring psychopathology in ASD (at the age of childhood and at follow-up) is limited but reveales high rates of co-morbidity (Stahlberg et al., 2004; De Bruin et al., 2007; Mouridsen et al., 2007). This heterogeneity at time of diagnosis and at follow-up, underlines the need for better defined and validated subgroups, especially within the broad and poorly defined PDD-NOS category.

One of the suggested subtypes is the Multiple Complex Developmental Disorder (MCDD) which is the subject of this thesis (Cohen et al., 1987). The MCDD patients are of special interest because they reveal clinical characteristics of autism (social deficits) and schizophrenia (cognitive deficits). Because of the thought disorder problems and the follow-up study of MCDD patients by Van Engeland and Van der Gaag (1994), whereby a high percentage (in the adultgroup up to 66 %) developed a disorder towards the schizophrenia spectrum, the MCDD subtype is of interest according to a specific prevalence and pattern of co-morbidity (and by that vulnerability) and follow-up within ASD.

Although earlier studies supported the view that autism and schizophrenia are seen as two distinct disorders (Kolvin et al., 1971a&b; Rutter, 1972; Volkmar et al., 1991), other studies on premorbid characteristics (Asarnow et al., 1988, 1995; Done et al., 1994; Hollis, 1994, 1995; Jones et al., 1994; Olin and Mednick 1996; Olin et al.,1998; Cannon et al., 1999, 2002; Eggers et al., 2000; Nicolson et al., 2000), co-morbidity (Sporn et al., 2004), follow-up (Konstantareas and Hewitt 2001; Stahlberg et al., 2004; Bölte and Bosch 2005; Mouridsen et al., 2007) and psychiatric family history (Larsson et al., 2005) suggested that these disorders are more related than viewed in the past.

Especially the recent studies of Stahlberg et al. (2004), Sporn et al. (2004) and Mouridsen et al. (2007) are of interest. Sporn et al. (2004) found that of a cohort of childhood-onset schizophrenia 25% also fullfilled the PDD diagnosis (mostly PDD-NOS). This confirmed earlier research on childhood-onset schizophrenia (COS) groups showing PDD features (see for an overview Sporn et al., 2004). Stahlberg et al. (2004) found in a group of adults diagnosed within the ASD spectrum in nearly 15% an additional psychotic disorder (schizophrena spectrum, bipolar with psychotic problems or other psychotic disorders). Mouridsen et al. (2007) found for patients receiving a diagnosis of atypical autism as a child, in nearly 35% a diagnosis of a schizophrenia spectrum disorder later in life.

This group of MCDD patients is characterized by impairments in the social interaction and social sensitivity, impairments in the regulation of affective state and impairments in the regulation of thought disorders. Validation for the concept of MCDD was found by Towbin et al. (1993) and by Van der Gaag et al. (1995). Van der Gaag et al. (1995) showed in their chart review study that compared to children with autism, MCDD children proved to be less disturbed in social interaction, communication and stereotyped and rigid behaviour. In contrast, MCDD children were found to be more impaired on thought disorders, primitive anxieties and aggression, compared to the children with autism. Also some neurobiological differences between children with MCDD and autism were found (Kemner et al., 1999; Jansen et al., 2003).

The main focus of interest for this thesis was to evaluate

(1) if MCDD as an ASD subtype can be differentiated from other ASD subtypes on neurobiological parameters, and
(2) if these neurobiological parameters in MCDD are similar as found in schizophrenia, supporting MCDD as a represententive of a more close relationship between ASD and schizophrenia than earlier suggested, or if these parameters are more like what has been found in autism.

We investigated brain morphology (structural imaging), psychophysiological parameters (Smooth Pursuit Eye Movement, Prepulse Inhibition and P50) and neuropsychological (executive functioning) differences.

In **chapter 2** the literature on structural MRI was reviewed for autism compared to (childhood-onset) schizophrenia in children and adolescents. Three main problems which hinder the inter alia comparison of these studies were found. First, the diagnostic variability (e.g., diagnostic methods, comorbidity), second the variations within and between the subject groups (e.g. age, gender, IQ) and third, the various quantitative and qualitative MRI methods (e.g., slice thickness, orientation and position).
For autism most studies found a larger cerebrum (intracranial volume) and its separate structures (especially frontal and temporal gray matter), and a larger cerebellum and ventricles (especially lateral ventricles). In trying to understand what happens in the brain of patients with autism, not only 'where' abnormalities are found but also 'when' and 'what process in the developing brain is taking a different route' needs to be addressed. To answer these questions, longitudinal studies which suggest an enlargement of the brain during a time-limited period and "normalization" after that are of interest. However, the literature is not consistent on this point. For the smaller structures the number of studies is limited

and therefore conclusions can not be made. For childhood-onset schizophrenia (and very early onset schizophrenia [VEOS]), most studies report a (progressively) smaller cerebrum, as well as volumetric decreases in its separate structures (mainly frontal, temporal and parietal gray matter). This is in line with what is known in the literature on late-onset schizophrenia. A (progressive) enlargement of the (mainly lateral) ventricles is another replicated finding. For the cerebellum and other smaller structures the number of studies is too limited to draw any conclusions. The only consistent abnormality found in autism as well as in VEOS / COS is a larger (lateral) ventricle volume (Giedd et al., 1999; Kumra et al., 2000; Howard et al., 2000; Badura et al., 2001; Kates et al., 2004; Palmen et al., 2005). What does this mean in terms of overlapping symptoms in both psychiatric illnesses? In earlier literature correlations between ventricular enlargement and negative symptoms (Andreassen et al., 1990) and positive symptoms (Young et al., 1991) have been described. Also suggestions on correlations between ventricular enlargement and early transient autistic features have been made (Rapoport et al., 1997). However, there is a lack of studies which consequently used standardized (symptoms) scoring scales for the included patients and made correlations with the results of the sMRI findings.

In **chapter 3** we describe a structural MRI study where brain volumetric measures of a group of high-functioning children with MCDD is compared to those from (1) typically developing children and (2) high-functioning children with autism (all closely matched for gender, age, height, weight, IQ, handpreference and socio-economic status). Differences in structural imaging measures of brain volume were found in both children with MCDD and children with autism compared to typically developing controls. Both groups show increases in gray matter and cerebellar volume, but no evidence was found of intracranial enlargement in MCDD, contrary to our findings in autism. Children with autism had larger intracranial and ventricular volumes than children with MCDD and showed a trend towards an increase in total brain volume. Our main finding is that children with MCDD show no enlargement of intracranial volume, whereas head size is significantly enlarged in children with autism. Intracranial volume increases during the first years of life, under the influence of the growing brain. It continues to grow up until approximately age five years and then stabilizes (Durston et al., 2001). The finding of differences in head size between these two forms of autism spectrum disorder is provocative as it suggests that neurobiological differences may map onto clinical differences: If the lack of intracranial enlargement can be confirmed in other studies, it suggest that the onset of MCDD may be later than that of autism. These results suggest that although neurobiological changes associated with MCDD are similar to those in autism, there may be differences in the developmental trajectories associated with these two subtypes of autism spectrum disorders.

In **chapter 4** it was explored if specific cognitive impairment could be found in the PDD-NOS, subtype MCDD group. The study focuses on deficits in executive functioning and contributes to the literature by showing whether the two groups can be differentiated on the executive function domain. The comparison of children with PDD-NOS, subtype MCDD, and children with PDD-NOS without these MCDD characteristics, reveals a specific and clear pattern of differences, always to the disadvantage of the MCDD subtype, and of similarities, depending on type of executive function. The findings also show that both groups differ from the norm, these differences varying as a function of group membership and executive function aspect.The findings suggest compromised state regulation and impaired inhibitory control in perceptual (input) as well as response control (output) processes in children with MCDD.
In line with this evidence, and with the outcome of our study, are the results of studies in individuals identified as high-risk for psychosis, that revealed a pattern of neuropsychological deficits on tasks in particular requiring speeded information processing, efficient recall from memory (Niendam et al., 2006), and complex executive function (Shubert and McNeil, 2007).

From a clinical point of view, compromised state regulation and impaired inhibitory control in perceptual as well as response control processes would readily match up with the social problems that subjects with MCDD display. Their cognitive style is characterized by insufficient regulation of behavior and emotion, and consequently leads to major social handicaps. Their illness derails the processes that underlie socialization and derails the emergence of personal autonomy, resulting in severe social disability (Cohen et al., 1994). In earlier studies on schizophrenia verbal memory and vigilance have been suggested to act as "neurocognitive rate-limiting factors" and thereby prevent patients from attaining optimal adaptation (Green, 1996).

In **chapter 5** we report on a psychophysiological method, the Smooth Pursuit Eye Movement (SPEM). Children with MCDD are compared to (1) high functioning children with autism and (2) typical controls. A group of young adults with schizophrenia and a matched control group was added to evaluate a possible effect of our research conditions. It was demonstrated that MCDD patients in this SPEM study, revealed a lower velocity gain than the typical controls, whereas saccadic frequency was not different. The SPEM parameters of the autistic subjects and controls were not statistically different, which is consistent with the earlier findings of Kemner et al. (2004) and Takarae et al. (2004), and nor were the SPEM parameters of the MCDD subjects and autistic subjects significantly different, although the average gain was lower in the MCDD group. The lack of a significant

difference between the MCCD and autistic groups could be due to limited power, because our groups were relatively small. This finding of a lower velocity gain in the MCDD group, compared to controls in contrast to no differences for the autistic group, underlines the known clinical heterogeneity within the autistic spectrum. Of interest is that the reduced velocity gain associated with MCDD was similar to that found in (childhood-onset) schizophrenia (and related disorders) (Jacobsen et al., 1996; Ross et al., 1999a, 2002, 2003; Kumra et al., 2001). Previous two studies of SPEM in children with autism were carried out, and in neither study abnormalities of pursuit gain were found (Kemner et al., 2004; Takarea et al., 2004). In contrast, for (childhood-onset) schizophrenia abnormalities of smooth pursuit eye movements (SPEM), such as reduced gain and increased frequency of saccades, are among the most consistent and reproducible (Jacobsen et al., 1996; Ross et al., 1999a, 2002, 2003; Kumra et al., 2001). Global SPEM dysfunction is significantly associated with the disorganization dimension (defined primarily by thought disorder) of schizophrenia (Lee et al., 2001). Additionally, abnormalities of eye tracking (velocity gain and frequency of saccades) measured in the relatives of subjects with a broad schizophrenia spectrum disorder appear to be associated with traits for "sensitivity" and "suspiciousness", as scored in the Structured Interview for Schizotypy (SIS) (Lencer et al., 2003). These data indicate a relation between clinical characteristics and this biological marker. We reasoned that abnormal smooth pursuit characteristics would support the idea that individuals with MCDD are at high risk of developing psychotic symptoms within the autistic spectrum. We considered that this outcome supported the hypothesis that MCDD patients do reveal some biological similarities with schizophrenia and by that are at risk of developing symptoms of schizophrenia.

In **chapter 6** we looked at aspects of stimulus filtering (Prepulse Inhibition and P50 suppression). Aspects of thinking disorder (e.g. magical thinking, bizarre ideas, confusion between reality and inner fantasy life, easy confusability and 'delusions') are part of the MCDD syndrome, and therefore an abnormality in gating could have been expected in this group: impaired PPI and diminished suppression of P50 auditory evoked response would resemble deficits in sensory filtering as frequently reported for schizophrenia patients and by that be supportive for the idea that MCDD has neurobiological similarities with the schizophrenia spectrum. In general, deficits in sensory gating are assumed to be trait – as opposed to state – phenomena in schizophrenia, indicating possible endophenotypic markers (Braff et al., 2007; Calkins et al., 2007).
The main finding of this study is that no differences were found between subjects with MCDD on the one hand and subjects with autism and healthy controls on the other hand, neither for PPI nor P50 suppression. Autistic patients also showed

normal P50 suppression, confirming the results of an earlier study from our laboratory (Kemner et al., 2002). With respect to PPI, no differences were found between children with autism and healthy controls. This is in agreement with the study of Ornitz et al. (1993) in which no consistent significant differences were found between diverse patient groups with autism, including children. Two other studies however, do describe PPI differences between adult subjects with PDD (autism or Asperger) (McAlonan et al., 2002; Perry et al., 2007) and controls. However, in these studies different prepulse conditions were used, and group differences were seen in some (120 ms/86 db in the study of McAlonan et al. [2002], or 60 ms/86 db in the study of Perry et al. [2007]), but not in other (30 ms/74 or 86 db or 120 ms/74 db in the study of McAlonan et al. [2002] and 30 ms/86 db and 120 ms/86 db in the study of Perry et al. [2007]). In the current study only the 120 ms/86 db condition was used.

Intact sensory gating prevents overload of higher brain functions by filtering out irrelevant stimuli. Impairment in this mechanism has been thought to underly psychotic symptoms (McGie, 1961; Braff and Geyer, 1990; Perry et al., 1999). Indeed for PPI (but not for P50 suppression), correlations and associations with thought disorder and intensity of positive or negative symptoms are described (Braff et al., 1999, 2001).

In summary, in this study no deficits in stimulus filtering (PPI or P50 suppression) for children with MCDD were found. Since sensory gating deficits are commonly regarded as possible endophenotypic markers for schizophrenia, the current results suggest less similarity between schizophrenia and MCDD than earlier assumed.

General conclusion

It is widely known and accepted that the autism spectrum disorders do reflect a heterogeneous group of patients. Not only by differences in intellectual functioning and verbal abilities but also by the variety of the clinical behavioural presentation. This thesis is focused on a specific group of patients within the PDD-NOS group, namely the Multiple Complex Developmental Disorders (MCDD). This group of patients is of interest because of the ongoing discussion on autism and schizophrenia as possibly being more related than viewed in the past. Although earlier constructs of schizophrenia and autism assumed the principle of 'developmental homotypy', time has come to give more emphasis to the principle of 'developmental heterotypy', which asserts that symptoms, or manifestations, of psychopathological disorders can vary with age (Hollis 2007). A follow-up study on childhood-onset schizophrenia (Asarnow et al., 1994b) in which 28% of the subjects were at follow-up classified as having a good outcome underlines the possibility of etiological heterogeneity. For ASD the MCDD as group of patients is particularly interesting because of the results of the small follow-up study by Van Engeland

and Van de Gaag in 1994, revealing a high percentage (66%) of patients developing towards the schizophrenia spectrum. The main aim of the here presented studies was to emphasize the validity of subtyping MCDD within the ASD group, by using neurobiological parameters which are known to reveal abnormalities in patients within the schizophrenia spectrum in contrast to the findings for patients with autism. Finding these characteristics could be helpful in predicting the risk for psychotic symptoms and development towards the schizophrenia spectrum for patients within the autistic spectrum.

Combining all studies we can conclude that some support is found for subtyping within the ASD on biological grounds. Differences in brainvolume (smaller intracranial and ventricular volumes compared to subjects with autism); a lower velocity gain in the SPEM task (compared to controls, contrary to what was found in autism) and significant more impairment on attention and executive functioning (compared to other autism spectrum disorders [PDD-NOS]) are found. The neuropsychological and smooth pursuit tasks are partly the same as what is known from the literature on schizophrenia (and related) disorders, namely (1) problems in executive functions, especially attention, (2) a lower velocity gain in SPEM.

These differences do emphasize the validity for subtyping MCDD within the autism spectrum disorders (our first aim of the study). And indeed some of the characteristics were identical to what is known from patients with schizophrenia or schizophrenia spectrum disorders (our second aim of the study).

Although some of the above described characteristics are similar to what is known in patients with schizophrenia, the amount of literature on relating symptoms on one hand and imaging, psychophysiology and neuropsychology characteristics on the other hand, is limited. Studies on neurobiological parameters and clinical characteristics in the MCDD group of patients are on their way in our clinic ('DUPS' project, by Sprong et al., 2008 and Ziermans et al., in preparation for submission). This implicates that at this time MRI, psychophysiology and neuropsychology remain research tools in the evaluation and differentiation of autism spectrum disorders. While it is valuable in furthering our understanding of the neurobiological substrates of this disorder, MRI scanning and psychophysiology are not appropriate for diagnostic purposes. However, neuropsychological evaluation can be (limited but) valuable in better understanding the handicap of the patient and subsequently initiating the needed support.

Strenghts and limitations of the studies

Strenghts

These studies are the first on imaging, psychophysiology and exploration of the neuropsychological profile on patients with MCDD compared to other autism spectrum disorders, schizophrenia (SPEM study) and typical controls. All patients are carefully assessed. All have been clinically diagnosed based on the DSM-IV and many of them even had a clinical observational period in our clinic. Additionally, the ADI-R as a standardized diagnostic instrument (Lord, Rutter, and LeCouteur, 1994) and the symptom checklist for MCDD as formulated by Cohen et al., (1987) were used. Patients with neurological disorders or mental retardation were excluded.

Limitations

Although these are the first studies on these topics for MCDD patients, with no unusual number of included patients compared to earlier studies on these topics, the sample sizes are limited. Only high-functioning individuals in all groups, with average or above average IQ-scores were included. Therefore we are unable to say how well our findings generalize to lower-functioning individuals with diagnoses in the PDD-spectrum. Most children with autism in our studies were medication-naïve (only one patient with autism in the psychophysiological studies used medication). As this is unusual in daily practice, it raises the question of how representative this sample is of children with high-functioning autism. In contrast, many of the subjects with MCDD were using medication at the time of data collection. However, all analyses (except neuropsychology data) that yielded significant results were repeated without these subjects, and the findings were comparable.
In most studies the patients were carefully matched to patients with autism or controls. In the neuropsychological study however, there is some difference in age range between the two groups (MCCD versus other autism spectrum diagnosis). However, age was taken as a covariate in all these analyses.

Concluding remarks and implications for the future

First, the research reported in this thesis provides some evidence for subjects with MCDD being a biologically different subtype compared to patients with an autistic disorder or an autistic spectrum disorder without MCDD characteristics. There is also evidence for MCDD patients being biological different from typical controls. The here presented studies supported from this neurobiological point of view the earlier studies on the validation of the concept MCDD, and thereby the differentiation within the autism spectrum group. Second, some of the neurobiological parameters are indeed similar to the known (abnormal) neurobiological parameters in schizophrenia (related) disorders.

However, no conclusive remarks can be made on the biology of MCDD patients. From a clinical point of view the most remarkable and recognizable findings in daily clinical practice, are the neuropsychological problems (problems in attention, inhibition, and variability in performance) and the SPEM results whereby in schizophrenia research a link between lower velocity gain and the Disorganization dimension and traits for sensitivity and suspiciousness was found. This Disorganization dimension represents an inappropriate affect, poverty of content of speech, and disturbances of the form of thought. And these traits and aspects of Disorganization are the typical clinical features of the MCDD patients, as formulated in the diagnostic criterium 'Thinking Disorder'.

The here presented studies are in line with the ongoing discussion on the possible relationship between autism and schizophrenia, which might be more close than viewed in the past. The nowadays used classification systems (DSM or ICD-10) have no direct relation to the underlying etiology of the disorders. It is however, very plausible that psychiatric disorders (just as many somatic disorders) show different clinical presentations at different ages as manifestations of the same underlying disorder (Hollis, 2001). The principle of developmental heterotypy (meaning that manifestations of psychopathological disorders can vary with age) needs to be given more emphasis to solve ongoing questions on co-morbid developing psychiatric disorders and symptoms over time and their possible relationship to the etiology. In the Netherlands e.g. more knowlegde on psychiatric disorders starting at the age of childhood (developmental disorders) for adult psychiatrists could be helpful (education). In addition to using a classification system, the use of a symptom dimension system could be helpful.

No specific clinical recommendations can be given regarding the studies of this thesis. Regarding the neuropsychological observations and conclusions (impairment on attention and executive functioning as inhibition and variability in performance) it seems suggestive that (pharmacological) treatment of these aspects could be helpful in daily life. Given the lack of prospective studies on the clinical and neurobiological development of MCDD patients and the chronic nature of ASD and MCDD as far as known, additional research and replication of the here presented research, is needed. Research in large groups on the follow-up with parallel clinical, neuropsychological and neurobiological evaluation is essential for a better understanding of this subtype of ASD. This can be helpful in our search on predictive factors and / or endophenotypes in patients within the autistic spectrum having a higher risk of developing psychotic symptoms. This research is necessary for developing new and better intervention strategies for this intriguing, vulnerable and care consuming group of MCDD patients.

References

Andreasen NC, Ehrhardt JC, Swayze V et al. (1990). Magnetic resonance imaging of the brain in schizophrenia: The pathophysiologic significance of structural abnormalities. Arch Gen Psychiatry 47:35-44.

Asarnow JR, Ben-Meir S (1988). Children with schizophrenia spectrum and depressive disorders: a comparative study of premorbid adjustment, onset pattern and severity of impairment. J Child Psychol Psychiatry 29: 477-488.

Asarnow RF, Asamen J, Granholm E, Sherman T, Watkins JM, Williams ME (1994a). Cognitive / neuropsychological studies of children with a schizophrenic disorder. Schizophr Bull 20: 647-669.

Asarnow JR, Thompson MC, Goldstein MJ (1994b). Childhood-onset schizophrenia:a follow-up study. Schizophr Bull 20: 599-617.

Asarnow RF, Brown W & Stranburg R (1995). Children with a schizophrenic disorder: neurobehavioural studies. Eur Arch Psychiatry Clin Neurosci 245: 70-79.

Badura F, Trott GE, Mehler-Wex C, Scheuerpflug P, Hofmann E, Warmuth-Metz M, Nadjmi M, Solymosi L, Warnke A (2001). A study of cranial computer tomograms in very early and early onset schizophrenia. J Neural Transm.108(11):1335-44.

Bölte S, Bosch B (2005). The long-term outcome in two females with autism spectrum disorder. Psychopathology 38:151-154.

Braff DL, Freedman R, Schork NJ, Gottesman II (2007). Deconstructing schizophrenia: an overview of the use of endophenotypes in order to understand a complex disorder. Schizophr Bull 33(1):21-32.

Braff DL, Geyer MA, Swerdlow NR (2001). Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. Psychopharmacology 156:234-258.

Braff DL, Swerdlow NR, Geyer MA(1999). Symptom correlates of prepulse inhibition deficits in male schizophrenic patients. Am J Psychiatry 156:596-602.

Braff DL and Geyer MA, (1990). Sensorimotor gating and schizophrenia: Human and animal model studies. Arch Gen Psychiatry 47: 181-188

Calkins ME, Dobie DJ, Cadenhead KS, Olincy A, Freedman R, Green MF, Greenwood TA, Gur RE, Gur RC, Light GA, Mintz J, Nuechterlein KH, Radant AD, Schork NJ, Seidman LJ, Siever LJ, Silverman JM, Stone WS, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky BI, Braff DL (2007). The Consortium on the Genetics of Endophenotypes in Schizophrenia: model recruitment, assessment, and endophenotyping methods for a multisite collaboration. Schizophr Bull 33: 33-48.

Cannon M, Avshalom C, Moffitt TE, Harrington H, Taylor A, Murray RM, Poulton R (2002). Evidence for early childhood, pan-developmental impairment specific to schizophreniform disorder. Arch Gen Psychiatry 59:449-456.

Cannon M, Jones P, Huttunen MO, Tanskanen A, Huttunen T, Rabe-Hesketh S, Murray RM (1999). School performance in Finnish children and later development of schizophrenia: a population-based longitudinal study. Arch Gen Psychiatry 56: 457-463.

Cohen, D.J., Towbin, K., Mayes, L., & Volkmar, F. (1994). Developmental psychopathology of multiplex developmental disorder. In: Friedman, S.L., & Haywood, H.C. (eds.), Developmental Follow-up: Concepts, Genres, Domain and Methods. Orlando, FL: Academic Press, pp. 155-179.

Cohen DJ, Paul R, Volkmar F (1987). Issues in the classification of Pervasive Developmental Disorders and Associated Conditions. In D.J. Cohen & A. M. Donnellan & P. Rhea (eds.). Handbook of Autism and Pervasive Developmental Disorders (pp.20-39). New York: Wiley & Sons.

De Bruin EI, Ferdinand RF, Meester S, De Nijs PFA,Verheij F (2007). High rates of psychiatric co-morbidity in PDD-NOS. J Autism Dev Disord 37, 877-886.

Done DJ, Crow TJ, Johnstone EC, Sacker A (1994). Childhood antecedents of schizophrenia and affective illness: social adjustment at ages 7 and 11. Br Med J 309: 699-703.

Durston S, Hulshoff Pol HE, Casey BJ, Giedd JN, Buitelaar JK, van Engeland H (2001). Anatomical MRI of the developing human brain: what have we learned? J Am Acad Child Adolesc Psychiatry 40(9): 1012-20

Hollis C (1995). Child and adolescent (juvenile onset) schizophrenia: a case control study of premorbid development impairments. Br J Psychiatry 166:489-495.

Hollis C (2001). Diagnosis and differential diagnosis. In: Remschmidt (Eds), Schizophrenia in Children and Adolescents. Cambridge University Press pp 82-118.

Eggers C, Bunk D, Krause D (2000). Schizophrenia with onset before the age of eleven: Clinical Characteristics of the onset and course. J Autism Dev Disord 30(1), 29-38.

Giedd JN, Jeffries NO, Blumenthal J, Castellanos FX, Vaituzis AC, Fernandez T, Hamburger SD, Liu H, Nelson J, Bedwell J, Tran L, Lenane M, Nicolson R, Rapoport JL (1999). Childhood-onset schizophrenia: progressive brain changes during adolescence. Biol Psychiatry 1;46(7):892-8.

Green MF (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 153: 321-330.

Hollis CP (1994). Developmental language impairment in child and adolescent-onset schizophrenia. Schizophr Res 11: 183-184.

Howard MA, Cowell PE, Boucher J, Broks P, Mayes A, Farrant A, Roberts N (2000). Convergent neuroanatomical and behavioural evidence of an amygdala hypothesis of autism. Neuroreport 11; 11(13):2931-5

Jacobsen LK, Hong WL, Hommer DW, Hamburger SD, Castellanos FX, Frazier JA, et al. (1996). Smooth pursuit eye movements in childhood-onset schizophrenia: comparison with attention-deficit hyperactivity disorder and normal controls. Biol Psychiatry 1; 40(11): 1144-1154.

Jansen LM, Gispen-de Wied CC, Van der Gaag RJ, Van Engeland H (2003). Differentiation between autism and multiple complex developmental disorder in response to psychosocial stress. Neuropsychopharmacology 28(3): 582-590.

Jones P, Rodgers B, Murray R, Marmot M (1994). Child development risk factors for adult schizophrenia in the British 1946 birth cohort. Lancet 344: 1398-1402.

Kates WR, Burnette CP, Eliez S, Strunge LA, Kaplan D, Landa R, Reiss AL, Pearlson GD (2004). Neuroanatomic variation in monozygotic twin pairs discordant for the narrow phenotype for autism. Am J Psychiatry.161(3):539-46.

Kemner C, van der Geest JN, Verbaten MN, van Engeland H (2004). In search of neurophysiological markers of pervasive developmental disorders: smooth pursuit eye movements? J Neural Transm 111:1617-1626.

Kemner C, Oranje B, Verbaten MN, Van Engeland H (2002). Normal P50 gating in children with autism. J Clin Psychiatry 63(3):214-7.

Kemner C, van der Gaag RJ, Verbaten M, van Engeland H (1999). ERP differences among subtypes of pervasive developmental disorders. Biol Psychiatry 46: 781-789.

Kolvin I (1971a). Studies in the childhood psychoses. I. Diagnostic criteria and classification. Br J Psychiatry 118(545):381-4.

Kolvin I, Ounstad C, Humphrey M, McNay A (1971b). Studies in the childhood psychoses, II: the phenomenology of childhood psychoses. Br J Psychiatry 118(545):385-395.

Konstantareas MM, Hewitt T (2001). Autistic disorder and schizophrenia: Diagnostic overlaps. J Autism Dev Disord 31 (1): 19-28.

Kumra S, Giedd JN, Vaituzis AC, Jacobsen LK, McKenna K, Bedwell J, Hamburger S, Nelson JE, Lenane M, Rapoport JL (2000). Childhood-onset psychotic disorders: magnetic resonance imaging of volumetric differences in brain structure. Am J Psychiatry 157(9):1467-74.

Kumra S, Sporn A, Hommer DW, Nicolson R, Thaker G, Israel E, et al. (2001). Smooth pursuit eye-tracking impairment in childhood-onset psychotic disorders. Am J Psychiatry 158: 1291-1298.

Larsson HJ, Eaton WW, Madsen KM, Vestergaard M, Olesen AV, Agerbo E, Schendel D, Thorsen P, Mortensen PB (2005). Risk factors for autism: Perinatal factors, parental psychiatric history, and socioeconomic status. Am J Epidemiol 161:916-925.

Lee KH, Williams LM, Loughland CM, Davidson DJ, Gordon E (2001). Syndromes of schizophrenia and smooth-pursuit eye movement dysfunction. Psychiatry Res 101, 11-21.

Lencer R, Trillenberg-Krecker K, Schwinger E, Arolt V (2003). Schizophrenia spectrum disorders and eye tracking dysfunction in singleton and multiplex schizophrenia families. Schizophr Res 60 (1): 33-45.

Lord C, Rutter M, Couteur A (1994). Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 24(5):659-85.

McAlonan GM, Daly E, Kumari V, Critchley HD, Van Amelsvoort T, Suckling J, Simmons A, Sigmundsson T, Greenwood K, Russell A, Schmitz N, Happe F, Howlin P, Murphy DG (2002). Brain anatomy and sensorimotor gating in Asperger's syndrome. Brain125:1594-606.

McGie A, Chapman J (1961). Disorders of attention and perception in early schizophrenia. Br J Med Psychol 34:103-16.

Mouridsen SE, Rich B, Isager T (2007). Psychiatric disorders in adults diagnosed as children with atypical autism. A case control study. J Neural Transm Sept 5 Epub.

MMWR Surveill Summ (2007). Prevalence of autism spectrum disorders--autism and developmental disabilities monitoring network, 14 sites, United States, 2002. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2002 Principal Investigators; Centers for Disease Control and Prevention 9; 56(1):12-28

Nicolson R, Lenane M, Singaracharlu S, Malaspina D, Giedd JN, Hamburger SD, Gochman P, Bedwell J, Thaker GK, Fernandez T, Wudarsky M, Hommer DW, Rapoport JL (2000). Premorbid speech and language impairments in childhood-onset schizophrenia: association with risk factors. Am J Psychiatry 157:794-800.

Niendam TA, Bearden CE, Johnson JK, McKinley M, Loewy R, O'Brien M, Nuechterlein KH, Green MF, Cannon TD (2006). Neurocognitive performance and functional disability in the psychosis prodrome. Schizoph Res 84, 100-111.

Olin Sc, Mednick SA (1996). Risk factors of psychosis: identifying vulnerable populations premorbidly. Schizophr Bull 22(2):223-40.

Olin SS, Mednick SA, Cannon T, Jacobsen B, Parnas J, Schulsinger F, Schulsinger H (1998). School teacher ratings predictive of psychiatric outcome 25 years later. Br J Psychiatry 173: 536-539.

Ornitz EM, Lane SJ, Sugiyama T, Traversay J (1993). Startle modulation studies in autism. J Autism Dev Disord 23(4):619-37.

Palmen SJ, Hulshoff Pol HE, Kemner C, Schnack HG, Durston S, Lahuis BE, Kahn RS, Van Engeland H (2005). Increased gray-matter volume in medication-naive high-functioning children with autism spectrum disorder. Psychol Med 35(4):561-70.

Parry-Jones WII (2001). Childhood psychosis and schizophrenia: a historical review. In: Remschmidt (Eds), Schizophrenia in Children and Adolescents. Cambridge University Press pp 1-24

Perry W, Geyer MA, Braff DL (1999). Sensorimotor gating and thought disturbance measured in close temporal proximity in schizophrenic patients. Arch Gen Psychiatry 56: 277-281

Perry W, Minassian A, Lopez B, Maron L, Lincoln A (2007). Sensorimotor Gating Deficits in Adults with Autism. Biol Psychiatry 15:61(4):482-6.

Rapoport JL, Giedd J, Kumra S (1997). Childhood-onset schizophrenia. Arch Gen Psychiatry 54:897-903.

Ross RG, Olincy A, Harris JG, Radant A, Hawkins, Adler LE, et al. (1999a). Evidence for bilineal inheritance of physiological indicators of risk in childhood-onset schizophrenia. Am J Med Genet 16; 88(2): 188-199.

Ross RG, Olincy A, Mikulich SK, Radant AD, Harris JG, Waldo M, et al. (2002). Admixture analysis of smooth pursuit eye movements in probands with schizophrenia and their relatives suggests gain and leading saccades are potential phenotypes. Psychophysiology 39 (6): 809-819.

Ross RG (2003). Early expression of a psychophysiological feature of schizophrenia: saccadic intrusions into smooth-pursuit eye movements in school-age children vulnerable to schizophrenia. J Am Acad Child Adolesc Psychiatry 42(4): 468-476.

Rutter M (1972). Childhood schizophrenia reconsidered. J Autism Child Schizophr 2 : 315-337.

Schubert EW, McNeil TF (2007). Neurobehavioral deficits in young adult offspring with heightened risk for psychosis who developed schizophrenia-spectrum disorder. Schizophr Res 94, 107-113.

Sporn AL, Addington AM, Gogtay N, Ordoňez AE, Gornick M, Clasen L, Greensyein D, Tossell JW, Gochman P, Lenane M, Sharp WS, Straub RE, Rapoport JL (2004). Pervasive developmental disorder and childhood-onset schizophrenia: comorbid disorder or a phenotypic variant of a very early onset illness? Biol Psychiatry 55(10): 989-994.

Sprong M, Becker HE, Schothorst PF, Swaab H, Ziermans TB, Dingemans PM, Linszen D, van Engeland H (2008). Pathways to psychosis: A comparison of the pervasive developmental disorder subtype Multiple Complex Developmental Disorder and the "At Risk Mental State". Schizophr Res 99(1-3):38-47. Epub 2007 Dec 4

Stahlberg O, Soderstrom H, Ratam M, Gillberg C (2004). Bipolar disorder, schizophrenia, and other psychotic disorders in adults with childhood onset AD/HD and / or autism spectrum disorders. J Neural Transm 111: 891-902.

Takarea Y, Minshew NJ, Luna B, Krisky CM, Sweeney JA (2004). Pursuit eye movement deficits in autism. Brain 127: 2584-2594.

Towbin KE, Duykens EM, Pearson GS, Cohen DJ (1993). Conceptualizing "borderline syndrome of childhood" and "childhood schizophrenia" as a developmental disorder. J Am Acad Child Adolesc Psychiatry 32(4): 775-82.

Van der Gaag RJ, Buitelaar J, Ban van den E, Bezemer M, Njio, L, Engeland van H (1995). A controlled multivariate chart review of multiple complex developmental disorder. J Am Acad Child Adolesc Psychiatry 34(8): 109-106.

Van Engeland H, Van der Gaag RJ (1994). MCDD in childhood: a precursor of schizophrenic spectrum disorders. Schizophr Res 11: 2, 197.

Volkmar FR, Cohen DJ (1991). Comorbid association of autism and schizophrenia. Am J Psychiatry 148: 1705-1707.

Young AH, Blackwood DHR, Roxborough H, Mcqueen JK, Martin MJ, Kean D (1991). A magnetic resonance imaging study of schizophrenia: brainstructure and clinical symptoms. Br J Psychiatry 158:158-164.

Yung AR, Phillips LJ, Yuen HP, McGorry PD (2004). Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. Schizophr Res 67(2-3):131-42.

Ziermans T, in preparation for submission

Nederlandse samenvatting
(Summary in Dutch)

Inleiding

Een Autisme Spectrum Stoornis (ASS) is tegenwoordig een frequent gestelde psychiatrische stoornis op de kinderleeftijd. Eén op de 150 kinderen heeft een ASS, zo blijkt uit epidemiologische studies. Eerdere en betere diagnostiek is tot op heden de beste verklaring voor deze toename. Veel van deze patiënten doen een beroep op behandeling en zorg binnen een kinderpsychiatrische setting. Onderzoek is nodig om meer inzicht te krijgen in de neurobiologie van ASS en in specifieke kwetsbare subgroepen. Onderzoek naar het voorkomen en patroon van co-morbide psychopathologie bij ASS (op de kinderleeftijd en bij follow-up) is gelimiteerd, maar laat een frequent voorkomen hiervan zien. De heterogeniteit ten tijde van de diagnose en later bij follow-up, onderstreept het belang van goed gedefinieerde en gevalideerde subgroepen, met name binnen de brede en matig gedefinieerde Pervasieve Ontwikkelings Stoornissen- Niet anders Omschreven (vertaald: PDD-NOS) groep.

Onderzoeksonderwerp

Het onderwerp van dit proefschrift is de Multiple Complex Developmental Disorder (MCDD). MCDD-patiënten zijn in het bijzonder interessant omdat zij klinische karakteristieken laten zien van zowel autisme (sociale tekortkomingen) als van schizofrenie (cognitieve tekortkomingen). Deze patiënten hebben naast hun sociale problemen en problemen in het reguleren van hun affecten, ook denkstoornissen en ontwikkelen in veel gevallen (bij volwassenen tot ruim 65%) een stoornis binnen het schizofrene spectrum, zo blijkt uit een follow-up studie van Van Engeland and Van der Gaag (1994).

Achtergrond

De eerste studies van Kolvin en Rutter (1971, 1972) ondersteunen het beschouwen van autisme en schizofrenie als twee afzonderlijke ziekte-entiteiten. Latere studies over premorbide autistische symptomen bij schizofrenie, co-morbide ASS bij schizofrenie, schizofrenie en gerelateerde psychotische stoornissen in de follow-up van ASS en het vaker voorkomen van schizofrenie in families van ASS-patiënten, suggereren echter dat autisme en schizofrenie mogelijk meer verwant zijn dan in het verleden werd gedacht.
Met name de studies verricht door Stahlberg (2004), Sporn (2004) en Mouridsen (2007) zijn interessant in het licht van deze discussie. Sporn (2004) vond in een groep van kinderen met schizofrenie dat 25% ook voldeed aan de diagnose PDD-NOS. Dit was een bevestiging van wat in eerder onderzoek bij kinderschizofrenie ook al werd gevonden en gesuggereerd. Stahlberg (2004) vond in een groep volwassenen met

ASS bij bijna 15% tevens een psychotische stoornis (schizofrenie, bipolaire stoornis met psychotische kenmerken, of psychotische stoornis anderszins). Mouridsen (2007) vond in een groep van patiënten die als kind de diagnose ASS hadden gekregen, bij follow-up in bijna 35% van de gevallen een diagnose binnen het schizofrene spectrum.

De groep van MCDD-patiënten wordt gekarakteriseerd door problemen in de sociale interactie en gevoeligheid voor sociale signalen (bijvoorbeeld moeite met relaties met leeftijdsgenootjes en ambivalente relaties naar volwassenen), problemen in de regulatie van de affecten (bijvoorbeeld heftige angsten en agressie), en problemen in het denken (bijvoorbeeld moeite met het onderscheid tussen fantasie en werkelijkheid; opgaan in fantasieën). In studies van Towbin (1993) en Van der Gaag (1995) vinden we validatie voor het concept MCDD. Van der Gaag liet in zijn studie zien dat kinderen met MCDD in vergelijking met de autistische kinderen minder verstoord waren in hun sociale interactie en communicatie, en in hun stereotype en rigide gedrag. Daarentegen waren MCDD- kinderen meer verstoord op het gebied van de denkstoornissen, angsten en agressie. Twee studies vonden tevens biologische verschillen tussen de autistische kinderen en kinderen met MCDD (Kemner 1999 en Jansen 2003).

Onderzoeksvragen

In dit proefschrift zijn de volgende vragen onderzocht:
(1) Kan MCDD als subtype binnen de ASS worden onderscheiden op een aantal neurobiologische parameters, en
(2) Zijn deze gevonden parameters gelijk aan wat bekend is bij patiënten met schizofrenie? (En is er daarmee inderdaad sprake van een nauwere relatie tussen autisme en schizofrenie, welke tot uiting komt in dit subtype MCDD?) Of lijken deze parameters op wat gevonden is bij autisme?

Wij onderzochten hersenstructuren (structurele imaging), psychofysiologische parameters (Smooth Pursuit Eye Movement, Prepulse Inhibitie en P50), en neuropsychologische (in het bijzonder executief functioneren) aspecten.

Literatuuronderzoek

In **hoofdstuk 2** is de literatuur over structurele magnetic resonance imaging (sMRI) voor autisme en (kinder) schizofrenie bij kinderen en adolescenten gereviewed. Drie belangrijke problemen die een goede vergelijking van al deze studies in de weg staan. Als eerste de diagnostische variabiliteit (o.a. de gebruikte methoden en aanwezige co-morbiditeit), als tweede de variatie in en tussen de subjectgroepen

(o.a. leeftijd, geslacht, intelligentie niveau), en als laatste de verschillen in de kwantitatieve en kwalitatieve MRI-methoden (o.a. verschillen in plakdikte, oriëntatie en positie). Voor autisme werd in de meeste studies een toename gevonden van het hersenvolume (intracranieel volume) en haar afzonderlijke structuren (in het bijzonder frontale en temporale grijze stof), cerebellum (kleine hersenen) en ventrikels (m.n. de laterale ventrikels). Om te begrijpen wat er gebeurt in de hersenen van kinderen met autisme, is het van belang niet alleen antwoord te vinden op de vraag naar 'waar' in de hersenen de afwijkingen zijn, maar ook naar het 'wanneer' (in de ontwikkeling) en 'welk proces' in het zich ontwikkelende brein anders verloopt dan bij een normale ontwikkeling. Om meer zicht te krijgen op deze vragen zijn vooral de longitudinale studies interessant. Deze laten een vergroting van het brein zien gedurende een bepaalde periode. Met betrekking tot de kleinere structuren kan worden gezegd dat deze studies tot op heden te gelimiteerd zijn om conclusies te kunnen trekken. Voor kinderschizofrenie (en tevens de zeer vroege ontstane schizofrenie) werd in de meeste studies een afname van het hersenvolume en haar afzonderlijke structuren gevonden (vooral frontaal, temporaal en parietale grijze stof). Deze bevindingen zijn conform de bevindingen bij schizofrenie die is ontstaan op (jong) volwassen leeftijd. Een (progressieve) vergroting van de (vooral laterale) ventrikels is een andere bij herhaling gevonden bevinding. Voor de kleine hersenen en andere kleinere structuren zijn de studies te beperkt van opzet (waardoor vaak methodologische problemen) om duidelijke conclusies te trekken. De enige bevinding die zowel bij autisme als schizofrenie voorkomt, is een vergroting van het (laterale) ventrikelvolume. De vraag is wat hiervan de betekenis is in relatie tot de overlappende symptomen bij autisme en schizofrenie. In eerdere studies werden correlaties gevonden tussen ventrikelvergroting en zowel negatieve als positieve symptomen. Ook werden voorzichtige suggesties gedaan omtrent de correlatie ventrikelvergroting en vroege voorbijgaande autistische symptomen. Samenvattend zijn het aantal studies en de daarbij gebruikte methoden te beperkt om een uitspraak te doen over een correlatie tussen sMRI en symptomatologie.

MRI-studie

Hoofdstuk 3 beschrijft een MRI-studie waarin een groep hoog-functionerende MCDD-patiënten wordt vergeleken met (1) een groep gezonde kinderen (als controlegroep) en (2) een groep hoogfunctionerende autisten (allen gematched op leeftijd, geslacht, lengte, gewicht, intelligentie, handvoorkeur en sociaal-economische status). Verschillen in breinvolume vonden we bij zowel de MCDD-groep als bij de groep autisten. Beide groepen lieten een toename van grijze stof en cerebellum (kleine hersenen) zien. In tegenstelling tot bij de autisten lieten de MCDD-patiënten geen intracraniele vergroting zien. Kinderen met autisme hadden een groter intracranieel en ventrikelvolume dan de MCDD-kinderen. Tevens was

er een trend zichtbaar van een vergroot totaal breinvolume. Onze belangrijkste bevinding is dat kinderen met MCDD geen vergroting van het intracranieel volume laten zien en het hoofdvolume van de autisten significant groter is. Het intracranieel volume neemt toe in de eerste levensjaren, onder invloed van het groeiende brein. De groei continueert tot ongeveer het vijfde levensjaar en stabiliseert dan. De gevonden volumeverschillen tussen deze twee ASS suggereert dat neurobiologische verschillen zichtbaar kunnen worden in klinische verschillen. Als het afwezig zijn van intracraniele groei wordt bevestigd in verdere studies, dan suggereert dat een later ontstaan van MCDD in vergelijking met autisme. De resultaten van deze sMRI- studie laten zien dat er enkele overeenkomsten zijn met autisme, maar dat er mogelijk verschillen zijn in het ontwikkelingstraject dat geassocieerd is met deze twee subtypen van ASS.

Neuropsychologie

Hoofdstuk 4 beschrijft een studie waarin wordt onderzocht of er specifieke cognitieve beperkingen zijn voor kinderen met PDD-NOS, subtype MCDD. De studie richt zich op problemen bij het executief functioneren en draagt zo bij aan de literatuur om op basis van het executieve functiedomein, twee verschillende groepen te kunnen onderscheiden. De vergelijking van kinderen met PDD-NOS met en zonder MCDD-karakteristieken laat een specifiek en duidelijk patroon van verschillen zien, altijd ten nadele van de MCDD- patiënt en enkele overeenkomsten afhankelijk van het type executieve functie. De resultaten laten ook zien dat beide groepen (PDD-NOS met en zonder MCDD- karakteristieken) afwijken van de norm. De bevindingen suggereren een aangedaan regulatiemechanisme en een verminderde inhibitiecontrole op zowel perceptuele (input) als respons (output) controleprocessen. In lijn met deze bevinding zijn de resultaten van studies waarin is gekeken naar individuen met een verhoogd risico voor psychose. Daar zien we een patroon van neuropsychologische problemen op taken van snelheid van informatieverwerking, efficiënt ophalen van geheugen en complexe executieve functies. Vanuit klinisch oogpunt passen een aangedaan regulatiemechanisme en inhibitiesysteem in perceptie en respons controleprocessen bij de sociale problemen waarmee de MCDD-patiënten zich presenteren. Hun cognitieve stijl wordt gekenmerkt door onvoldoende regulatie van hun gedrag en emoties, en die leidt tot forse sociale problemen. Hun ziekte ondermijnt de processen die nodig zijn voor socialisatie en de ontwikkeling van persoonlijke autonomie wat resulteert in ernstige sociale beperkingen.

Smooth Pursuit Eye Movement (SPEM) studie

In **hoofdstuk 5** beschrijven we een Smooth Pursuit Eye Movement (SPEM) studie, een psychofysiologische onderzoeksmethode. Kinderen met MCDD worden vergeleken met (1) hoog functionerende kinderen met autisme, en (2) met gezonde kinderen. Een groep jong volwassenen met schizofrenie en een gematchde controlegroep is toegevoegd om de mogelijke effecten van onze onderzoeksmethode te evalueren en uit te sluiten. Deze studie toonde aan dat MCDD-patiënten in deze SPEM-studie een lagere velocity gain lieten zien in vergelijking met normale controle kinderen. De frequentie van de saccades was niet verschillend. Er werden geen SPEM-verschillen gevonden tussen de autisten en de controles, conform eerder in de literatuur beschreven. Ook waren er geen significante verschillen tussen de MCDD-kinderen en autisten, hoewel de MCDD-groep wel een lagere 'average gain' lieten zien. Mogelijk dat het afwezig zijn van een significant verschil het gevolg is van relatief kleine groepen. Het gevonden verschil tussen MCDD-patiënten en autisten in relatie tot de kinderen uit de controlegroep onderstreept de heterogeniteit binnen het autistisch spectrum. Twee eerdere studies bij kinderen met autisme gaven geen verschillen voor pursuit gain. In contrast is het gegeven dat afwijkingen in SPEM (lagere velocity gain en meer saccades) een consistente en herhaalde bevinding is bij (kinder)schizofrenie. Globale smooth pursuit dysfunctie is in de literatuur geassocieerd met de dimensie 'desorganisatie' (voornamelijk gekenmerkt door denkstoornissen) bij schizofrenie. Ook bij familieleden van patiënten met schizofrene spectrumstoornissen worden associaties gevonden met 'sensitiviteit' en 'achterdocht' zoals gescoord in een specifiek interview (Structured Interview for Schizotypy). Deze data lijken een relatie te leggen tussen klinische karakteristieken en biologische markers. Onze hypothese is dat de in deze studie gevonden afwijkende smooth pursuit karakteristieken bij MCDD-patiënten een verhoogd risico op psychose, voor deze specifieke groep binnen ASS aantonen. Deze bevinding ondersteunt dat MCDD-patiënten enkele biologische overeenkomsten hebben met schizofrenie en daarmee mogelijk een verhoogd risico op het ontwikkelen van schizofrene symptomen.

Stimulusfiltering

In **hoofdstuk 6** hebben we gekeken naar de aspecten van stimulusfiltering (prepulse inhibitie en P50 suppressie). Aspecten van de denkstoornis (magisch denken, bizarre ideeën, matige realiteittoetsing, snelle verwardheid en waanachtige ideeën) zijn deel van het MCDD-syndroom, en daarom zouden afwijkingen in de gating bij deze groep verwacht kunnen worden: verminderde PPI en verminderde suppressie van de P50 (auditief opgeroepen respons) overeenkomstig de sensorische filter afwijkingen zoals beschreven bij schizofrenie patiënten.

Dit zou de gedachte bevestigen dat MCDD biologische overeenkomsten heeft met schizofrene spectrumstoornissen. Algemeen wordt aangenomen dat beperkingen in de sensorische gating 'trait' – in tegenstelling tot 'state' – fenomenen zijn, en daarmee als mogelijk endophenotypische markers geïdentificeerd kunnen worden. De belangrijkste bevinding in deze studie is dat zowel voor PPI als P50 suppressie, geen verschillen werden gevonden tussen de drie groepen (MCDD, autisme en gezonde kinderen). Dit is met betrekking tot PPI en P50 suppressie bij kinderen met autisme in vergelijking met gezonde kinderen, conform eerder onderzoek (Ornitz 1993 en Kemner 2002). Bij twee studies (McAlonan 2002 en Perry 2007) in volwassenen met autisme en Asperger werden wel PPI afwijkingen gevonden, zij het onder bepaalde onderzoekscondities (120 ms/86 db in de studie van McAlonan en 60 ms/86 db in the study of Perry). In onze studie is de 120 ms/86 dB conditie gebruikt. Intacte sensorische gating voorkomt overbelasting van hogere hersenfuncties door het uitfilteren van irrelevante stimuli. Een verminderd functioneren van dit mechanisme ligt waarschijnlijk ten grondslag aan psychotische symptomen. Inderdaad zijn er voor PPI (maar niet voor P50 suppressie) correlaties en associaties beschreven met denkstoornissen en de intensiteit van positieve en negatieve symptomen. Samenvattend, in deze studie werden geen afwijkingen gevonden voor zowel PPI als P50 suppressie bij patiënten met MCDD. Aangezien sensorische gating gezien wordt als een mogelijke endophenotypische marker van schizofrenie, suggereren de alhier gevonden resultaten dat er minder overeenkomst is tussen MCDD en schizofrenie dan eerder aangenomen.

Conclusies en discussie

Hoofdstuk 7 vat de bevindingen van de studies samen en bediscussieert deze.
Ten eerste geeft het onderzoek gepresenteerd in dit proefschrift enige evidentie dat patiënten met PDD-NOS, subtype MCDD biologisch een ander subtype zijn dan patiënten met autisme of een andere autistische spectrum stoornis zonder deze MCDD karakteristieken. Ook is er evidentie dat de MCDD-patiënten zich biologisch onderscheiden van gezonde kinderen uit de controlegroepen. De validatie van het concept MCDD wordt dan ook door deze studies vanuit neurobiologisch perspectief ondersteund. Ten tweede zijn de gevonden afwijkingen van een aantal van de neurobiologische parameters gelijk aan wat bekend is bij schizofrenie (en aan schizofrenie gerelateerde stoornissen). Op dit moment zijn imaging, psychofysiologie en neuropsychologie verschillende onderzoeks methoden om meer inzicht te krijgen in de ASS groep. Hoewel dit bijdraagt aan onze kennis over de neurobiologie van ASS, zijn deze technieken op dit moment nog niet geschikt voor het verrichten van psychiatrische diagnostiek. Van de beschreven onderzoeksmethoden kan de neuropsychologische evaluatie echter (gelimiteerd maar) aanvullend zinvol zijn om de beperkingen van de patiënt beter te begrijpen

en de juiste hulpmiddelen in te zetten. Helaas is ook de literatuur over de relatie tussen neurobiologie en klinische symptomen zeer beperkt.
De gevonden resultaten sluiten aan bij de voortgaande discussie over de mogelijk meer dan in het verleden veronderstelde relatie tussen schizofrenie en autisme. Onze huidige diagnostiek is (noodzakelijkerwijs) gebaseerd op een classificatiesysteem (optelsom van symptomen) waarvan de relatie tot etiologie waarschijnlijk wordt geacht maar onbekend is. Het is echter zeer waarschijnlijk (conform somatische ziektebeelden) dat ziektes zich op verschillende leeftijd, op verschillende wijze uiten. De weergave hiervan in het begrip 'developmental heterotypie' moet m.i. dan ook binnen de psychiatrie meer in ogenschouw worden genomen om daadwerkelijk bij te dragen aan onze kennis over oorzaak en beloop van psychiatrische stoornissen. In Nederland zou bijvoorbeeld meer kennis binnen de volwassenenpsychiatrie over psychiatrische ziektebeelden die ontstaan tijdens de kinderleeftijd (ontwikkelingsstoornissen) hiertoe kunnen bijdragen (een taak voor onderwijs en opleiding). Ook kan het toevoegen van denken in (symptoom) dimensies, naast de bestaande classificerende wijze van denken, hiertoe bijdragen.
Uit dit proefschrift komen geen specifieke klinische adviezen voort. Gezien echter de neuropsychologische conclusies (aandacht en inhibitieproblemen) die aansluiten bij de directe klinische observatie, lijkt (farmacologische) ondersteuning op deze gebieden mogelijk zinvol.
Wat betreft de toekomst het volgende. Gegeven het gebrek aan prospectieve studies over de klinische en neurobiologische ontwikkeling (en de combinatie van deze) bij MCDD-patiënten en het bekende chronisch beloop van autistische spectrumstoornissen, is replicatie van het hier gepresenteerde onderzoek nodig. Om dit subtype binnen de autistische spectrum- stoornissen beter te begrijpen is tevens (follow-up)onderzoek in grote groepen nodig, met daarbij aandacht voor de ontwikkeling van zowel het klinisch beeld als de neurobiologische ontwikkeling van MCDD. Dit kan ondersteunend zijn bij het zoeken naar predictieve factoren bij ASS patiënten die een verhoogd risico hebben op het ontwikkelen van psychotische klachten, en die daarmee tot een uiterst kwetsbare en zorgbehoevende groep behoren.

Dankwoord

Het begon in 1998 met een eerste oriëntatie of 'onderzoek iets zou zijn', en nu ligt er – ja inderdaad, vele jaren later - een heus proefschrift. Kinder- en jeugdpsychiatrie is een multidisciplinair vak, dat had ik al ervaren in de praktijk, maar het doen van onderzoek daarin bleek werkelijk een multidisciplinaire onderneming. Zo bezien zouden er eigenlijk meerdere namen op het titelblad moeten prijken. Anders gezegd: mijn dank is groot aan de velen die de tot stand koming van dit boekje mede mogelijk hebben gemaakt. Ik kan daarvoor niet iedereen bij naam bedanken, maar sommigen wel, en voor uiteenlopende redenen.

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niet publiceren van 'geen afwijkingen', dat is hard..) maakten onze afspraken vaak tot buitengewoon komisch en plezierige ontmoetingen.

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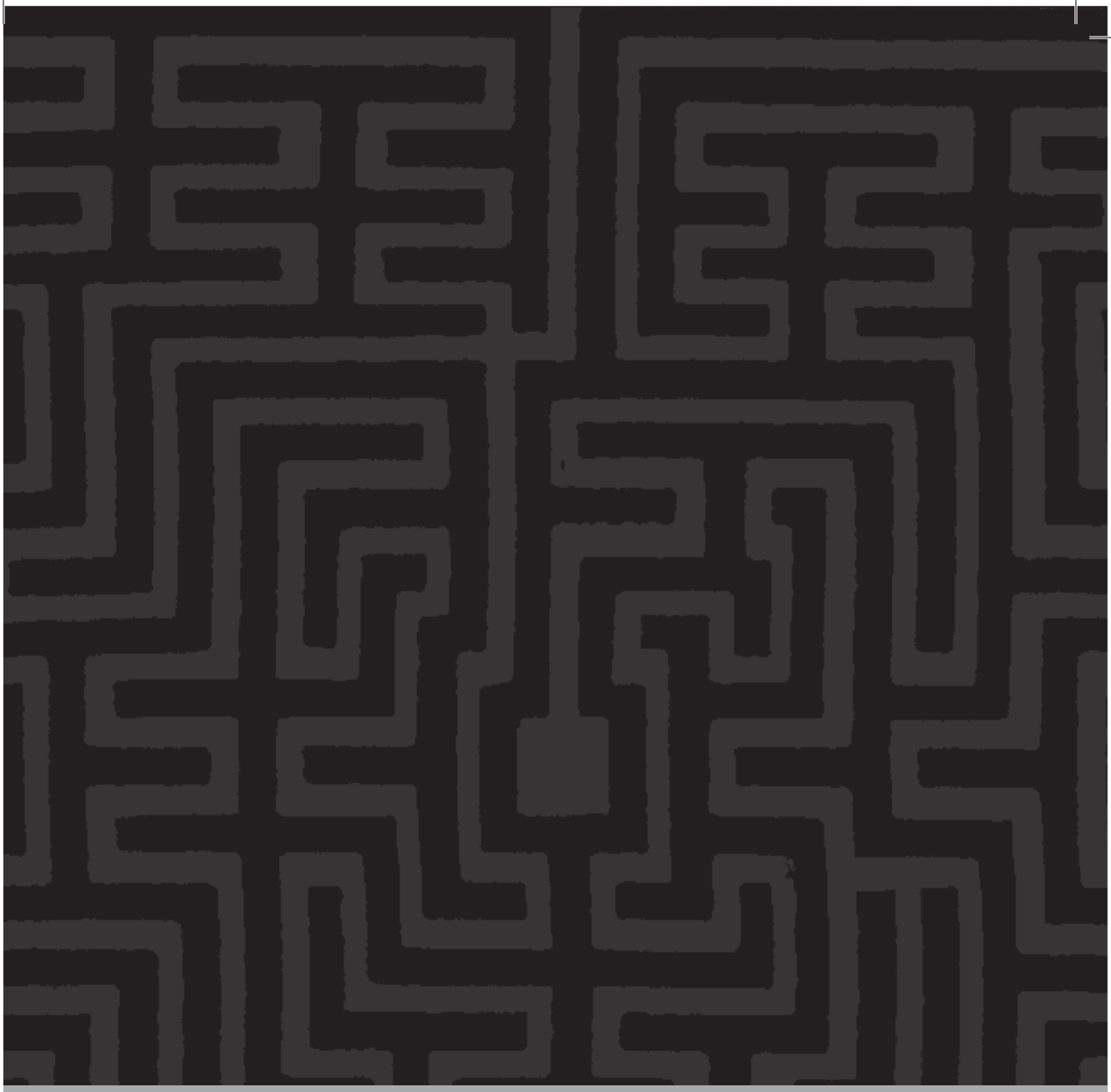

Curriculum Vitae

Bertine Enrica Lahuis werd geboren op 30 augustus 1967 te Oosterbeek. In 1985 behaalde zij haar eindexamen VWO aan het Van Lingen College te Arnhem. In 1985 studeerde zij Nederlandse Taal-en Letterkunde aan de Universiteit Utrecht, en behaalde haar Propedeuse. In 1986 startte zij de studie Geneeskunde aan de Universiteit Utrecht. Haar co-schap chirurgie volgde zij in Plymouth, Engeland. In 1993 behaalde zij haar arts-examen. Na een half jaar als AGNIO interne en cardiologie te hebben gewerkt in het Groene Hart ziekenhuis te Gouda, startte zij in 1994 de opleiding tot psychiater in het Universitair Medisch Centrum Utrecht (UMCU) (opleider prof.dr.R.S.Kahn). Haar sociale psychiatrie deelstage volgde zij part-time in Zeist (opleider drs. M. de Pater), waarnaast zij zich orienteerde op het doen van onderzoek dat uiteindelijk leidde tot dit proefschrift. Aansluitend behaalde zij haar aantekening tot Kinder- en jeugdpsychiater in het UMCU (opleider prof. dr.H.van Engeland). Vanaf 2000 is zij werkzaam als staflid van de afdeling Kinder- en jeugdpsychiatrie van het UMCU. Zij was verbonden aan de Kinderkliniek, later het poliklinisch autisme spreekuur en sinds 2005 is zij medisch hoofd van de zorglijn Autisme en Psychose. Sinds 1 april 2008 is zij tevens vervangend opleider van de Kinder- en jeugdpsychiatrie opleiding in het UMCU. Zij is getrouwd met Jord Neuteboom en samen hebben zij twee kinderen: Jeppe (2000) en Maaike (2003).

Publications

Lahuis BE, Paping MA, van Delden JJM (1993). Hoe wordt gehandeld bij psychogeriatrische patienten die niet meer eten? Ned Tijdschr Geneeskd 137:404-407

Lahuis BE, van Elburg AA (2000). Pervasieve Ontwikkelingsstoornis bij tubereuze sclerose. Tijdschr Psychiatr 42 3, 189-194

Vorstman J, **Lahuis BE**, Buitelaar JK (2001). SSRIs associated with behavioural activation and suicidal ideation, letter to the editor. J Am Acad Child Adolesc Psychiatry 40 (12): 1364-5

Lahuis BE, Buitelaar JK (2002). 'Autisme en psychofarmaca' (pp. 272-289). In: 'Behandelingsstrategieën bij kinderen en jongeren met autisme'. Didden R & Huskens B. (Red.) Cure and Care Development, Houten: Bohn Stafleu van Loghum.

Lahuis BE (2002). Autisme bij kinderen. Cobo Bulletin 35 (2); 3-9.

Lahuis BE (2002). 'Pharmacotherapy and Autism' (2002). Abstract in 'Suppl Dev Med Child Neurol'.

Lahuis BE, Kemner C, van Engeland H (2003). Magnetic Resonance Imaging studies on Autism and Childhood-onset Schizophrenia in children and adolescents; a review. Acta Neuropsychiatrica 15(3) : 140 - 147

Lahuis BE, van Engeland H (2003). 'Psychische problemen en psychiatrische stoornissen' (pp 701-724). In 'Kindergeneeskunde voor kinderverpleegkundigen'. Van de Brande e.a. (Red.) Uitgave Elsevier gezondheidszorg, Maarssen.

Lahuis BE (2003). 'Affect (dys) regulatie in de klinische praktijk; kinderen met McDD.' Tijdschr Ver Kinder- en jeugdpsychother 30(4); 40-47

Palmen SJ, Hulshoff Pol HE, Kemner C, Schnack HG, Durston S, **Lahuis BE**, Kahn RS, Van Engeland H (2005). Increased gray-matter volume in medication-naive high-functioning children with autism spectrum disorder. Psychol Med 35(4):561-70.

Troost PW, **Lahuis BE**, Steenhuis MP, Ketelaars CE, Buitelaar JK, van Engeland H, Scahill L, Minderaa RB, Hoekstra PJ (2005). Long-Term Effects of Risperidone in Children With Autism Spectrum Disorders: A Placebo Discontinuation Study. J Am Acad Child Adolesc Psychiatry 44(11):1137-1144

Cees Ketelaars, Pieter Troost, **Bertine Lahuis** (2005). Medicamenteuze behandeling bij Autisme Spectrum Stoornissen. In: Formularum psychofarmaca bij kinderen. Landelijk Kenniscentrum Kinder- en Jeugdpsychiatrie.

Troost PW, Althaus M, **Lahuis BE**, Buitelaar JK, Minderaa RB, Hoekstra PJ. (2006). Neuropsychological effects of risperidone in children with pervasive developmental disorders: a blinded discontinuation study. J Child Adolesc Psychopharmacol 16(5):561-73

Jansen LM, Gispen-de Wied CC, Wiegant VM, Westenberg HG, **Lahuis BE**, Van Engeland H (2006). Autonomic and neuroendocrine responses to a psychosocial stressor in adults with autistic spectrum disorder. J Autism Dev Disord 36(7):891-9

Troost PW, **Lahuis BE**, Hermans MH, Buitelaar JK, Van Engeland H, Scahill L, Minderaa RB, Hoekstra PJ (2007). Prolactin Release in Children Treated With Risperidone: Impact and Role of CYP2D6 Metabolism. J Clin Psychopharmacol 27(1):52-57

Lahuis BE, Durston S, Nederveen H, Zeegers M, Palmen SJ, Van Engeland H (2007). MRI-based morphometry in children with multiple complex developmental disorder, a phenotypically defined subtype of pervasive developmental disorder not otherwise specified. Psychol Med 10:1-7

Lahuis BE, Ketelaars C, Troost PW, Buitelaar JK (2008). Autisme en psychofarmaca (pp. 272-289). In: Didden, R., & Huskens, B. (Red.) (2008). Begeleiding van kinderen en jongeren met autisme. Van onderzoek naar praktijk (pp. 272-289). Houten: Bohn Stafleu van Loghum.

Lahuis BE, Van Engeland H, Cahn W, Caspers E, van der Geest JN, Van der Gaag RJ, Kemner C (2008). Smooth pursuit eye movement (SPEM) in patients with multiple complex developmental disorder (MCDD), a subtype of the pervasive developmental disorder. Accepted for publication in World J Biol Psychiatry.

Hoekstra PJ, Troost PW, **Lahuis BE**, Mulder H, Franke B, Buitelaar JK, Scahill L, Minderaa RB (2008). Risperidone-induced weight gain in children is associated with a common 5HT2C polymorphism. Submitted for publication.

Lahuis BE, Oranje B, Van Engeland H, Van der Gaag RJ, Kemner C. Aspects of stimulus filtering (Prepulse Inhibition and P50 suppression) in a subgroup of Pervasive Developmental Disorders; the Multiple Complex Developmental Disorders (MCDD). Submitted for publication.

Lahuis BE, de Sonneville CMJ, Pieterse J, van Engeland H, Swaab H. Executive functioning in MCDD and PDD-NOS; a study of inhibitory control, state regulation and behavioral adaptivity. Submitted for publication.