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Bio-social aspects of Attention Deficit Hyperactivity Disorder (ADHD): Neurophysiology, maturity, motor function and how symptoms relate to family interaction

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To

Else-Britt, Jakob and Daniel

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Papers included in the thesis

- I** Gustafsson P, Thernlund G, Ryding E, Rosén I, & Cederblad M (2000) Association between cerebral blood-flow measured by single photon emission computed tomography (SPECT), electroencephalogram (EEG), behaviour symptoms, cognition and neurological soft signs in children with attention-deficit hyperactivity disorder (ADHD). *Acta Paediatrica*, 89(7), 830-5.

- II** Gustafsson P, Hansson K, Eidevall L, Thernlund G, & Svedin CG (2007) Treatment of Attention Deficit/Hyperactivity Disorder With Amphetamine: Short-Term Effects on Family Interaction. *Journal of Attention Disorders*, Oct 29 (Epub ahead of print).

- III** Gustafsson P, Thernlund G, Besjakov J, Karlsson MK, Ericsson I, & Svedin CG (2008) ADHD symptoms and maturity – a study in primary school children. *Acta Paediatrica* 97(2): 233-8.

- IV** Gustafsson P, Thernlund G, Ericsson I, Lindén C, Karlsson MK, & Svedin CG (2008) Reliability and validity of the assessment of soft-signs in children with and without Attention Deficit Hyperactivity Disorder. (Submitted for publication).

List of abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
APA	American Psychiatric Association
CBCL	Child Behaviour Check-List
CD	Conduct Disorder
CNS	Central Nervous System
COPE	Community based Parent Education
CPT	Continuous Performance Test
DAMP	Deficits in Attention, Motor control and Perception
DCD	Developmental Coordination Disorder
DFI	Dyadic Family Interaction
DSM-III	Diagnostic and Statistical Manual of Mental Disorders. Third edition.
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders. Third edition. Revised.
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders. Fourth edition.
EEG	Electro-encephalogram
FARS	Family Relations Scale
fMRI	functional Magnetic Resonance Imaging
GAF	Global Assessment of Functioning
HKD	Hyperkinetic Disorder
ICD-10	International Classification of Diseases. Tenth edition.
IQ	Intelligence Quotient
LD	Learning Disabilities
MBD	Minimal Brain Dysfunction
MND	Minor Neurological Deficit
MPA	Minor Physical anomalies
MRI	Magnetic Resonance Imaging
MUGI	Swedish: "Motorisk Utveckling som Grund för Inläring", English: Motor skills as a base for learning
ODD	Oppositional Defiant Disorder
PET	Positron Emission Tomography
rCBF	regional Cerebral Blood-Flow
SCL-90	Symptoms Check-List 90
SD	Standard Deviation
SPECT	Single Photon Emission Computed Tomography
TRF	Teacher Report Form
WHO	World Health Organization
WISC	Wechsler Intelligence Scale for Children
WISC-III	Wechsler Intelligence Scale for Children. Third edition.

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD, for definition see table 1) is a condition that has received much attention in society during the last two decades. It has been estimated that 5-6% of children 6-12 years of age fulfil criteria for ADHD (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). Children with ADHD often have other psychiatric problems, learning problems in school, and adjustment problems as they grow up and later in life (Spencer, Biederman, & Mick, 2007). ADHD can thus be regarded as a condition with high risk for developing other psychiatric problems and difficulties concerning social adjustment. Early detection and intervention are therefore important.

Table 1. ADHD according to DSM-III-R and DSM-IV and Hyperkinetic Disorder according to ICD-10.

DSM-III-R (1987) American Psychiatric Association:

Diagnostic Criteria for 314.01 Attention-Deficit Hyperactivity Disorder

Note: Consider a criterion met only if the behavior is considerably more frequent than that of most people of the same age.

- A. A disturbance of at least 6 months during which at least eight of the following are present:
- (1) often fidgets with hands or feet or squirms in seat (in adolescents, may be limited to subjective feeling of restlessness)
 - (2) has difficulty remaining seated when required to do so
 - (3) is easily distracted by extraneous stimuli
 - (4) has difficulty awaiting turn in games or group situations
 - (5) often blurts out answers to questions before they have been completed
 - (6) has difficulty following through on instructions from others (not due to oppositional behavior or failure of comprehension), e.g., fails to finish chores
 - (7) has difficulty sustaining attention in tasks or play activities
 - (8) often shifts from one uncompleted activity to another
 - (9) has difficulty playing quietly
 - (10) often talks excessively
 - (11) often interrupts or intrudes on others, e.g., butts into other children's games
 - (12) often does not seem to listen to what is being said to him or her
 - (13) often loses things necessary for tasks or activities at school or at home (e.g., toys, pencils, books, assignments)
 - (14) often engages in physically dangerous activities without considering possible consequences (not for the purpose of thrill-seeking), e.g., runs into street without looking

Note: The above items are listed in descending order of discriminating power based on data from a national field trial of the DSM-III-R criteria for Disruptive Behavior Disorders.

- B. Onset before the age of seven
- C. Does not meet the criteria for a Pervasive Developmental Disorder.

Criteria for severity of Attention-deficit Hyperactivity Disorder:

Mild: Few, if any, symptoms in excess of those required to make the diagnosis **and** only minimal or no impairment in school and social functioning.

Moderate: Symptoms or functional impairment intermediate between “mild” and “severe”.

Severe: Many symptoms in excess of those required to make the diagnosis **and** significant and pervasive impairment in functioning at home and school and with peers.

DSM-IV (1994) American Psychiatric Association:

A. Either (1) or (2):

- (1) six (or more) of the following symptoms of **inattention** have persisted for at least six months to a degree that is maladaptive and inconsistent with developmental level:

Inattention

- (a) often fails to give close attention to details or makes careless mistakes in schoolwork, work or other activities
- (b) often has difficulty sustaining attention in tasks or play activities
- (c) often does not seem to listen when spoken to directly
- (d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
- (e) often has difficulty organizing tasks and activities
- (f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
- (g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books or tools)
- (h) is often easily distracted by extraneous stimuli
- (i) is often forgetful in daily activities

- (2) six (or more) of the following symptoms of **hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity

- (a) often fidgets with hands or feet or squirms in seat
- (b) often leaves seat in classroom or in other situations in which remaining seated is expected

- (c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
- (d) often has difficulty playing or engaging in leisure activities quietly
- (e) is often “on the go” or often acts as if “driven by a motor”
- (f) often talks excessively

Impulsivity

- (g) often blurts out answers before the questions have been completed
- (h) often has difficulty awaiting turn
- (i) often interrupts or intrudes on others (e.g., butts into conversations or games)

- B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.
- C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home)
- D. There must be clear evidence of clinically significant impairment in social, academic or occupational functioning.
- E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Code based on type:

314.01 Attention-Deficit/Hyperactivity Disorder, Combined Type: if both Criteria A1 and A2 are met for the past 6 months.

314.00 Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type: if Criterion A1 is met but Criterion A2 is not met for the past 6 months.

314.01 Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive-Impulsive Type: if Criterion A2 is met but Criterion A1 is not met for the past 6 months.

Coding note: For individuals (especially adolescents and adults) who currently have symptoms that no longer meet full criteria, “In Partial Remission” should be specified.

Hyperkinetic disorders according to ICD-10:

The same items as in DSM-IV are used but to get a diagnosis of Hyperkinetic disorder the child should fulfil at least six of the items under inattention, at least three of the items a to-e under hyperactivity and at least one of the items f to-i under hyperactivity-impulsivity. The symptoms are also required to be pervasive i.e. the criteria should be met in several situations e.g., both at home and at school or both at home and at a clinic.

THE HISTORY OF THE CONCEPT

Brain damage

There are some early references to behavioural disturbances in children of the kind seen in hyperactive disorders, such as the writings by Hoffman (1845) (in a story book for children), Maudsley (1867), Clouston (1899) and Ireland (1877). In a famous publication from 1902, G.F. Still described what he called **“defects of moral control”** in children. He believed that hyperactive and disruptive behaviour in children could be caused by a biological defect, which was either inherited or resulted from some pre- or postnatal injury. **Post encephalitic behaviour disorder** with symptoms of attention difficulties, hyperactivity and disruptive behaviour was described in conjunction with the encephalitis pandemic 1917-1918 (Ebaugh, 1923; Hohman, 1922). The concept of **minimal brain damage** was introduced in the 1920's (Ehrenfest, 1926; G. B. Smith, 1926). Hyperactive children were regarded as having symptoms reminding of adults with frontal lobe -damage, but the children's hypothetical lesions were thought to be minimal and multiple, not easily detectable with the diagnostic tools of the time. In 1934 Kahn and Cohen formulated the concept of **“organic drivenness”** as they described some children with a very hyperactive and impulsive behaviour who, they thought, had an abnormality in the brain stem originating from **“prenatal encephalopathy or birth injury”** or being congenital. In 1947 Strauss and Lehtinen described components of a syndrome (they referred to these children as **“brain-injured children”**) resulting from brain trauma at birth, infection, head injury or epilepsy. Knobloch, Rider, Harper, & Pasamanick, (1956) described what they called **“the continuum of reproductive casualty”**. They argued that complications leading to perinatal death often were caused by brain injury. They argued that unfavourable factors in pregnancy and delivery could cause damage to the brain of different severity ranging from small injuries leading to mild behaviour problems (this was often called minimal brain damage), more severe injuries leading to cerebral palsy and very severe injuries leading to the death of the child. They compared children referred to special educational services with normal controls and found a three-fold increase in the frequency of perinatal complications in the referred group, especially among children with hyperactivity. Laufer and Denhoff (Denhoff, Laufer, & Solomons, 1957; Laufer & Denhoff, 1957) did research in the period 1950-1960 with stroboscopic stimulation measuring EEG and myoclonic arm jerks on children with what they called **“hyperkinetic impulse disorder”** who, they hypothesized, had a defect in the sensory filtering function of thalamus leading to overexcitement with central stimulants improving the thalamic filtering.

Minimal Brain Dysfunction

In the beginning of the 1960's the term minimal brain damage was widely used for hyperactive and impulsive children with learning disabilities, disruptive behaviour and attention deficits. Several authors at this time criticized the idea that children with some behavioural problems were regarded as having brain damage without physical evidence (Birch, 1965; Herbert, 1964; Rapin, 1964). A study group in Oxford recommended the use of the term minimal brain dysfunction (MBD) instead of minimal brain damage (MacKeith, 1963). In the USA an official definition of MBD was presented in 1966 (Clements, 1966). In this definition children with MBD were described as having various combinations of impairment in perception, conceptualisation, language, memory, and control of attention, impulse or motor function. The impairments were thought to be associated with deviations of function of the central nervous system. The designation MBD was eventually recognized as being overinclusive and was replaced by more specific terms like dyslexia, learning disabilities, language disorders and hyperkinetic behaviour syndrome. Researchers were stimulated to abandon the concept of brain dysfunction by research showing a strong link with heredity for these problems.

Hyperactivity

In 1960 Chess and others described the hyperactive child syndrome where hyperactivity was regarded as the central symptom, a behavioural symptom possible to describe and measure.

Attention Deficit

In the 1970's and 1980's, the term MBD was used less and less frequently in the United States and in the United Kingdom. In the Nordic countries the term MBD was still used until the beginning of the 1990's when the concept gradually was replaced by the concept of Deficits in Attention, Motor control and Perception (DAMP) introduced by I.C. Gillberg & C. Gillberg (1988). Douglas (1972) and her team at the McGill University suggested that overactivity was not the core symptom in the syndrome of **hyperkinesis** (as the combination of inattention, hyperactivity and poor impulse control was called), but rather deficits in the ability to sustain attention and control impulsive responding were more important. In the DSM-III diagnostic manual (Diagnostic and Statistical Manual of Mental Disorders, 3rd edition) (APA, 1980) the concepts of attention deficit disorder with hyperactivity and the attention deficit disorder without hyperactivity were introduced. This marked a change in focus from hyperactivity towards attention deficit as the main problem.

In the DSM-III-R version from 1987 (Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised) (APA, 1987) the concept of attention deficit hyperactivity disorder (ADHD) was introduced, see table 1. The abbreviation is written AD/HD in the DSM-IV version from 1994 (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) (APA, 1994) with a

change in definition, see table 1. Since many studies have been performed with the older definition, I will use the abbreviation ADHD unless explicitly referring to the DSM-IV definition. In the United Kingdom the diagnosis Hyperkinetic Disorder (HKD) is used, which also has been used in ICD-10 according to WHO, see table 1. In Sweden and other Nordic countries, the diagnosis Deficits in Attention Motor control and Perception (DAMP) has been used in parallel with ADHD (C. Gillberg, 2003). This diagnosis emphasises the importance of difficulties in motor control and perception in combination with attention deficits as a sign of more marked dysfunction in the brain than just the occurrence of attention deficits with no signs of motor dysfunction or perceptual deficit.

RESULTS FROM THE CURRENT RESEARCH

Gender

In earlier studies ADHD was considered as predominantly a male condition affecting six times more boys than girls. Later studies have shown a considerably lower boy-girl ratio, perhaps 1:2 or even lower (Biederman et al., 2005). Girls with ADHD have thus been missed to a great extent, perhaps because girls seem to have more subtle symptoms, which are more difficult for adults to recognise (Abikoff et al., 2002; Biederman et al., 2005; Newcorn et al., 2001). In spite of the more subtle symptoms, girls with ADHD have academic problems in school, peer related problems, poor self esteem and emotional problems of the same magnitude as for the boys (Bauermeister et al., 2007; Biederman et al., 2005; Kopp, 2005).

Aetiology

The Controversy over the ADHD concept

Much criticism has been directed against the idea that behavioural symptoms among children such as attention deficits, hyperactivity and impulsivity often are caused by a brain dysfunction or a variant of brain function differing from that of normal children. In the 1970's psychoanalysts, among them Bettelheim (1973) and behaviourists including Willis and Lovaas (1977) put forward the idea of poor parenting as a causative factor in hyperactivity and impulsivity among children. Tizard & Hodges (1978) showed that there was an association between institutional upbringing and hyperactive behaviour. Social factors like social deprivation in slum areas, deteriorating schools etc were suggested as causal non-biological factors (Gadow, 1981; Gittelman, 1981; Whalen, 1980). Conrad (1976) suggested that the increase in clinical diagnoses had to do with the introduction of drug treatments, and Messinger (1975) suggested that pure profit-making motives were of importance. In Sweden Kärve (2000) claimed that there is an overdiagnosing of ADHD because of a prevailing biological paradigm influenced by drug companies, where behavioural problems among children are thought to be caused by biological factors that should be treated with medicine, thereby causing professionals to underestimate the importance of social factors such as problems in the school system.

Since central stimulants have been the most important drugs used in treatment of children with ADHD and since there also is a substantial problem with the abuse of central stimulant drugs, some people have been very critical towards medication of children with these drugs (Baughman Jr, 2006).

Psychosocial factors

Although most researchers in the field consider biological factors to be the main risk-factors for developing ADHD as described by Spencer et al (2007), some studies have shown an association between ADHD and some psychosocial factors like **low socio-economic status** among parents and **family dysfunction** (Barkley, 1996; Barkley, Fischer, Edelbrock, & Smallish, 1991; Barkley, Guevremont, Anastopoulos, & Fletcher, 1992; Johnston, 1996; Johnston & Mash, 2001; Sandberg, 2002; Wells et al., 2000). Low socio-economic status of the family might be a true aetiological factor but might also be a consequence of one or both parents having ADHD leading to academic difficulties and poor academic achievements, which lead in turn to low income (Wells et al., 2000). Theories have been formulated about the role of **early attachment** showing an increased rate of ADHD-symptoms, but not of ADHD-diagnosis, among children with reactive attachment disorder (Pinto, Turton, Hughes, White, & Gillberg, 2006). **Institutional upbringing** under severe circumstances seems to induce ADHD-like symptoms, as shown by a study of Romanian children adopted in the United Kingdom at early age and followed up to the age of eleven (Stevens et al., 2007).

Biological factors

Early research on biological risk factors pointed to the importance of factors leading to **brain damage** pre- or perinatally, among them **asphyxia**, **prematurity** or **intrauterine infections**, that in turn could account for the development of symptoms of the kind seen in children with ADHD (Sandberg, 2002). **Infections in childhood** and **traumatic brain injuries** were also suggested as important (Sandberg, 2002). Research since the 1960's has shown that **genetic factors** seem to be the most important risk factors for ADHD (Spencer et al., 2007). The heritability of ADHD has been estimated to be about 60-90% (Spencer et al., 2007). **Pre- and perinatal factors** explain somewhere between 10 and 30% of the variance (Spencer et al., 2007). Children **small for gestational age** and children **borne prematurely** have been shown to have an increased risk of developing ADHD-symptoms. Low birth weight leads to a three-fold increase in the risk of developing ADHD-symptoms (Langley, Holmans, van den Bree, & Thapar, 2007). **Toxins** such as lead and artificial food colourings have also been suggested to increase ADHD-symptoms (Spencer et al., 2007). Some researchers have claimed that **obstructive sleep apnoea** is an important aetiological factor for many cases of ADHD and that surgery (tonsillectomy and ablation of adenoid vegetations) may cure the symptoms (Huang et al., 2007). Other researchers argue that obstructive sleep apnea is not common among children with ADHD or that

obstructive sleep apnea causes only mild ADHD-like symptoms where the child usually does not fulfil criteria for ADHD (O'Brien et al., 2003; Sangal, Owens, & Sangal, 2005). Still, genetic factors seem to be the most important as concerns aetiology, followed by pre- and perinatal factors (Burt, Krueger, McGue, & Iacono, 2001; Eaves et al., 2000; Kirley et al., 2004; Spencer et al., 2007). **Dopaminergic and noradrenergic** systems in the brain and probably **acetylcholine** (acting by stimulating nicotine receptors) are neurotransmitters that have been suggested to be of importance in ADHD (Manos, Tom-Revzon, Bukstein, & Crismon, 2007).

Comorbidity

Individuals with the diagnosis ADHD have been found to have a very high frequency of comorbid conditions (Spencer et al., 2007). They have an increased rate of conduct disorder, autism spectrum disorders, language problems, specific learning disabilities, anxiety, depression and mania (Spencer et al., 2007). Of children with ADHD, 30-50% have been estimated to have oppositional defiant disorder (ODD) and conduct disorder (CD). The cognitive functions have been found to be somewhat lower compared to children without ADHD. Specific learning disabilities (LD) have been found in 40-50% of children with ADHD. The frequency of autism spectrum disorders and autistic traits is increased. Higher frequencies of anxiety, depression, mania, bipolar disorder, drug abuse, criminality and personality disorder are described (Spencer et al., 2007). Many children with ADHD have motor coordination problems, and such problems have been associated with more comorbidity and a worse prognosis (C. Gillberg, 2003; C. Gillberg & Kadesjo, 2003). The hyperactivity in ADHD has been shown to decrease in severity with age and only about 30% of children fulfilling criteria for hyperactivity will fulfil all the criteria of hyperactivity when they are 22 years of age (C. Gillberg, 2003). Adults with bad social adjustment (criminality, substance abuse) often have a background of ADHD as children and many still have ADHD as adults. Many adult psychiatric patients with depression, anxiety and personality disorders also have a background of ADHD (Biederman et al., 2005; Sandberg, 2002).

Treatment

Evidence based treatments for children with ADHD are today:

1. Information to parents and teachers concerning what is known about ADHD (Odom, 1996).
2. Parent training according to evidence based programs, like Cunningham's COPE program or Webster-Stratton's program (Brestan & Eyberg, 1998; Chronis, Chacko, Fabiano, Wymbs, & Pelham, 2004; Cunningham, Bremner, & Boyle, 1995; Pelham, Wheeler, & Chronis, 1998).
3. In 1937 Bradley described how racemic amphetamine sulphate had a beneficial effect on symptoms of hyperactivity and disruptive behaviour among children, which became the starting point for treating hyperactive children with central stimulants. Medication with central stimulants (amphetamine or methylphenidate) or atomoxetine are evidence based treatments of ADHD symptoms with good effect sizes as shown in a great number of studies (Barkley, 2004; Manos et al., 2007).

4. Pedagogic programs that use techniques from behavioural therapy (Barkley et al., 2000; DuPaul, 1997; Pelham et al., 1998).
5. Behaviour interventions in the home using techniques from behavioural therapy (Barkley, 2004; Daly, Creed, Xanthopoulos, & Brown, 2007).

BACKGROUND TO THE THESIS

I have been working clinically with children with so called neuropsychiatric diagnoses (ADHD, Aspergers syndrome, Tourettes syndrome and autism) for more than 15 years. I have been engaged in diagnostic assessments and treatment of children with ADHD. These children often have other comorbid diagnoses and varying psycho-social problems with a great risk of developing poor social adjustment and psychiatric problems as they grow up. Ever since the first descriptions of children with hyperactivity and attention difficulties, there has been a lively debate concerning why certain children have ADHD-symptoms. Behind the concept of ADHD lies the assumption that ADHD is a neuropsychiatric condition, i.e. that compared to individuals without ADHD there are differences in neuroanatomy and neurophysiology. The critics of the concept of ADHD have claimed that the underlying reason for these problems might, at least partly, be of a psychosocial nature, such as relational conflicts, poor parenting, poverty or malfunctioning schools. Many clinicians have the impression that psycho-social adversity will make ADHD-symptoms become worse. The critics of the ADHD-concept believe that at least some of the children who get a diagnosis of ADHD might have quite normal brains with quite normal functioning and that the problems lie in the child's environment rather than in the child herself. In spite of much research that has been done in the last ten to -twenty years, the picture is still not very clear. The biological factors said to lie behind the syndrome of ADHD are still poorly defined, and very different biological factors have been claimed to be of importance. Only about 5% of the genes in ADHD have been described in spite of heritability estimates of 60-90%. Severe psycho-social deprivation seems to be of some importance in explaining ADHD for some individuals. Different anatomical and neurophysiological correlates to ADHD have been described, but how do these patterns fit together? Sometimes the behaviour of children with ADHD reminds observers of the behaviour of normal children younger than the ADHD children, as younger children have lesser ability to sustain attention, display impulse control, and sit still for a long time period. This has led to the question: could ADHD represent a kind of late maturation rather than a genuine aberrant development? Motor dysfunction has been regarded as a neurological marker of dysfunction, but sometimes the motor function of a child with minor coordination difficulties reminds observers of the motor function of normal children who are younger than the ADHD children with these difficulties. How important is it to assess motor function when studying children with ADHD? It seems as though the number of questions increases as ADHD research progresses and as knowledge of ADHD deepens. Finally, one must ask if ADHD is a homogeneous or a heterogeneous concept.

With this background, I have put the following questions:

- Which neurobiological correlates of having ADHD can be identified?
- Are ADHD symptoms among children a consequence of a non-optimal parenting style rather than of a neurophysiological deviance?
- Are children with ADHD normal children with a slow pace of maturation?
- If motor function is of relevance when studying ADHD, can it be measured in a reliable and valid way?

AIMS

It is of great interest to determine how biological and social factors influence a child with ADHD and how the ADHD-symptoms of the child can influence its social environment. This thesis will focus on how biological factors may be related to the ADHD symptoms of the child, how family function relates to the ADHD symptoms and how the family reacts when the ADHD-symptoms of the child have diminished, if the ADHD-symptoms of the child can be regarded as signs of a general biological immaturity and if motor coordination problems can be assessed in a reliable and valid way.

The more specific aims were:

1. Paper 1: To study the neurophysiological background of ADHD by using Single Photon Emission Computed Tomography (SPECT), Magnetic Resonance Imaging (MRI), routine Electro Encephalogram (EEG) and quantitative frequency analysis of the EEG (Brain Electrical Activity Mapping) in order to compare results from these examinations with assessments of ADHD-symptoms made by parents and teachers, results from neurological examination and cognitive testing of the child.
2. Paper 2: To study how the family interaction and the mental well-being of the parents may be related to the ADHD-symptoms of a child and how the family interaction and the parents well-being will change when the ADHD-symptoms decrease after three months of treatment with amphetamine.
3. Paper 3 and an unpublished study: To study the association between the ADHD-symptoms of a child and signs of developmental immaturity of the child.
4. Paper 4: To study aspects of reliability and validity of neurological examinations concerning so called "soft-signs", in the assessment of motor function of children with ADHD.

SUBJECTS AND METHODS

Subjects

Table 2 shows the different child populations and the studies and papers in which specific populations were used. The studies in papers 1 and 2 were performed on clinical groups consisting of children six to 11 years of age from three cities – Malmö, Lund and Umeå. The children were recruited to participate in a study concerning the effect of long term treatment of children with ADHD with amphetamine (C. Gillberg et al 1997). The children were referred to the study if they had symptoms suggesting a diagnosis of ADHD according to the DSM-III-R (the Diagnostic and Statistical Manual of mental disorders, third Edition, Revised) with marked clinical impairment. Additional requirements were no parental alcohol or drug abuse, the IQ of the child should not be less than 50, the child should not meet criteria for autistic disorder and the child should not have a severe somatic disorder. The children examined in paper 1 were 26 boys and four girls from Malmö and Lund (mean age 9.0, SD 1.6). In the study in paper 2 this group was supplemented with children from Umeå so that this study was performed with 43 children (34 boys and nine girls) six to 11 years of age.

Papers 3, 4 and the unpublished study were based on children from the normal population of 5½ year old children from four Child Health districts of Malmö (n=784), seven to nine year old children in grade one and two from a school in Malmö (n=148) and a comparison group in grade three from the same school nine to 10 years of age (n=103). The screening of the preschool study is described in figure 1 and the screening of the school study is described in figure 2.

In the reliability study (paper 4), a group of seven children (four boys and three girls) eight to 11 years of age born in Malmö from a prospective study of children with moderate intra- uterine growth retardation, were examined with a neurological examination for soft-signs. Reliability analysis was performed on this group, on index and control children from the school study and on the seven last examined children from the pre-school study (35 children, 26 boys and nine girls).

In the test-retest study (paper 4), a group of 20 children 6-9 years of age (eight girls and 12 boys) were examined with the neurological examination for soft-signs on two occasions with a four week interval between the first and the second examination.

Table 2. Populations examined in the different studies

Population	Study group	In papers
Children from multi-centre study: n=43	Children from Malmö-Lund: n=30	1
Children from multi-centre study: n=43	Children from multi-centre study: n=43	2
School children grade 1-3: n=251	Index children examined: n=8	3, 4, unpublished study
School children grade 1-3: n=251	Control children examined: n=15	3, 4, unpublished study
Pre-school children 5½ years of age: n=784	Index children examined: n=62	4
Pre-school children 5½ years of age: n=784	Control children examined: n=27	4
Children from prospective study: n=7	Children from prospective study: n=7	4
Test-retest study, school children: n=20	Test-retest study, school children: n=20	4

Figure 1. The pre-school screening.

- Screening of motor function according to a special scheme (see methods) was performed by the nurse at the child health care centre. The scheme had 14 items and gave a maximal score of 18. The nurse also made an assessment of attention difficulties and hyperactivity during the examination.
- A parent questionnaire with 11 questions of which one was about attention deficit and hyperactivity, was used (see methods).
- A questionnaire for the pre-school teacher with 12 questions, of which one was about attention deficit and hyperactivity, was used (see methods).

- >5 points on the examination of motor function or attention deficit or hyperactivity according to the answers by the parents or the pre-school teacher were the criteria for classifying the child as an index case.
- For every index child, the next child not being an index child was chosen as a control child. Every second control child was called for examination.
- Drop-out: 60% of controls and 44% of index children did not come for examination (of which 7% was because of administrative reasons). No differences were found in frequency concerning attention deficit or hyperactivity between the examined children and the drop-out groups according to the screening questions. Concerning motor function, a significant difference between examined children and drop-out children was found ($p < 0.001$) with examined children having higher scores (median 5, 75 percentile 8) on the examination than drop-out children (median 3, 75 percentile 5).

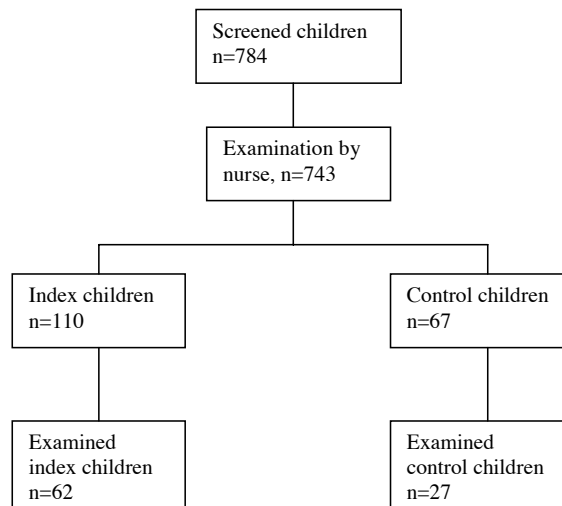


Figure 2. The school screening.

- Conners' abbreviated questionnaire (10 questions) was given to parents and teachers to all pupils in grade one and two in a primary school. Each item was scored 0-3.
- Children with more than 14 points according to parents or more than 10 points according to teachers were classified as index children.
- Control children were chosen as the next child in the list not being an index child.
- Drop-out analysis was made. In the control group there was one drop-out child and in the examined group there was a drop-out frequency of 50%. No group-differences were found concerning the Conners ratings by parents. For the Conners ratings by the teachers a significant difference was found ($p < 0.001$) with examined children having higher scores (median 15, 75 percentile 18.5) than drop-out children (median 1, 75 percentile 4.5).

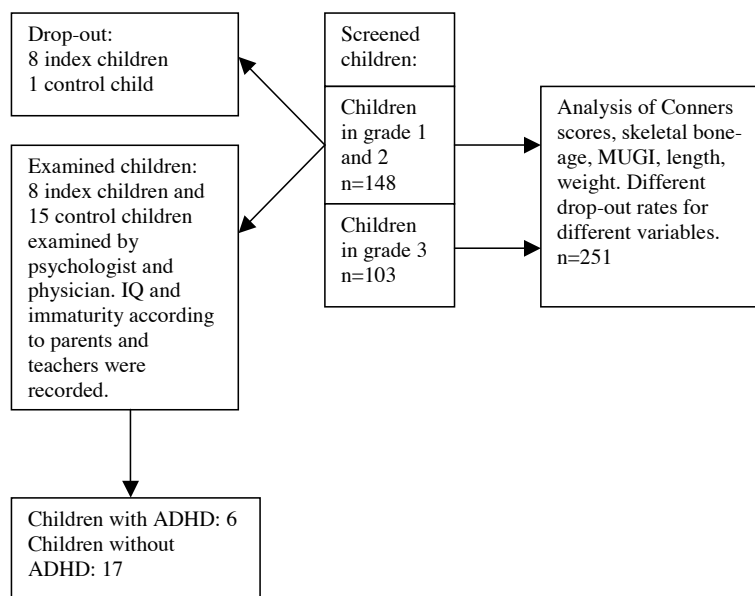


Table 3. Instruments used, in which paper and what the instrument measures.

Measure	Instrument and in which paper it is used
Motor function and maturity	pre-school screening of motor skills (paper 4), parent's description of motor development (paper 4), neurological "soft signs" examination (papers 1,3,4), MUGI (papers 3,4), parent's and teacher's ratings of maturity (paper 3), skeletal bone-age (paper 3), chronological age (paper 3), height and weight (paper 3), CBCL (unpublished study), TRF (unpublished study),
Child behaviour	Conner's abbreviated questionnaire (papers 1,2,3), Conner's teacher questionnaire (paper 2), screening questionnaire for parents (paper 4), screening questionnaire for pre-school teachers (paper 4), Rutter's questionnaire for parents (paper 1), The pre-school behaviour check-list (paper 4)
Somatic, cognitive and emotional development	Semi-structured parental interview (papers 3,4), MPA (paper 1)
Parental health and family functioning	SCL-90 (paper 2), FARS (paper 2)
Neuroanatomy and neurophysiology	MRI (paper 1), SPECT (paper 1), EEG (paper 1)
Cognitive function	WISC (paper 1 and unpublished study)
ADHD diagnosis	DSM-III-R (papers 1,2,4, and unpublished study)
Family observations	Beavers family competence scale (paper 2), DFI (paper 2)

Measures

Table 3 shows which instruments were used in which paper. More detailed descriptions of the different measures are found in the papers, except for the pre-school screening for motor skills, the parents' and teachers' ratings of immaturity and screening questionnaires for parents and preschool teachers, which are described here.

Examination of motor function and maturity

Pre-School screening of motor skills (paper 4): A slightly modified scheme developed by Christopher Gillberg was used (C. Gillberg, Rasmussen, Carlstrom, Svenson, & Waldenstrom, 1982). The pre-school children (5½ years of age) were called in by nurses in the Child Health Care Service and were examined by the nurses with screening of motor skills. The examination was scored by assigning points from zero to one or two depending on item (14 items, maximal score 18 points). The items were: standing on the right and left leg 10 seconds (scores 0-1 for each leg), handclapping (alternating with one hand over the other) (scores 0-1), walking on a line (scores 0-1), jumping on the right and left leg (scores 0-1 for each leg), cutting a circle from a paper (scores 0-1), copying a square (scores 0-1), tracing with a pencil in a labyrinth (scores 0-1), drawing a human (scores 0-1), hand dominance (scores 0-2 with left handedness as 1 and ambidexterity as 2), hand and body movements when drawing (scores 0-2), grip of the pencil when drawing (scores 0-2), movements and position of the supporting hand when drawing (scores 0-2). The nurse made a notation if the child showed signs of attention difficulties or hyperactivity during the examination. Children with a notation of attention difficulties or hyperactivity or scoring more than five points on the motor examination were considered as index children with suspicion of ADHD.

Parents' description of motor development (paper 4): Questions concerning motor function were answered by the parents.

Neurological examination (papers 1, 3 and 4): Children with ADHD and control children were examined with a method used by I. C. Gillberg (1985) based on earlier work by Touwen and Prechtl (Touwen, 1979, 1987), see appendix I.

Examination by physical education teacher with MUGI (papers 3 and 4): The children in the school-study were examined by a physical education teacher according to a scheme called MUGI. (Ericsson, 2003), see appendix II.

Parents' and teachers' ratings of immaturity (unpublished study): Parents of all children examined by physician and psychologist were asked to fill in the CBCL (Child Behaviour Check-list) (Achenbach, 1991). The answer to the question "acts too young for his/her age" was used as a measure of immaturity. Teachers and pre-school teachers of all children that were examined by physician and psychologist were asked to fill in the TRF (Teacher Report

Form) (Achenbach, 1991). The answer to the question “acts too young for his/her age” was used as a measure of immaturity. Ratings of immaturity by parents and teachers were gathered from the Achenbach questionnaire for parents and for teachers each containing such a question. The answers from parents and teachers were rated 0-2 according to the Achenbach questionnaire.

Skeletal bone-age (paper 3): The skeletal age was determined by an x-ray examination, which made it possible to determine skeletal age according to Greulich-Pyle (Acheson et al., 1963). The difference between skeletal age and chronological age was calculated.

Chronological age, sex height and weight (paper 3): The age of each subject when examined, was registered and used in comparisons with skeletal age and to adjust height, weight and results from neurological examination for age, allowing comparisons between children of different age.

Questionnaires of child behaviour

Conners abbreviated questionnaire (papers 1, 2 and 3): The Conners abbreviated questionnaire (ten questions) was used in the School-study and in the study of SPECT and family interaction (Conners, 1990).

Conners teacher questionnaire (paper 2): This questionnaire was used in the family interaction study to get the teachers' ratings of ADHD-symptoms. This questionnaire is one of Conners' different questionnaires for ADHD problems which have been used extensively to get teacher ratings in different studies (Conners, 1990). No Swedish normative data were available for the Conners teacher questionnaire.

Screening questionnaire for parents (paper 4): The questions in the parent questionnaire were: 1. Has your child another native language than Swedish? 2. Has your child difficulties pronouncing words and sentences clearly? 3. Is your child late in his/her speech development? 4. Does your child have difficulties staying calm and being patient? Does he/she have difficulties sitting still when required or does he/she have attention difficulties? 5. Is your child clumsy in his/her movements (walking, running, climbing)? 6. Do you think your child often makes a mess during meals? 7. Do you think it is difficult to be together with your child (does not listen when talked to, has temper tantrums, does not obey adults)? 8. Does your child have difficulties playing with other children? 9. Does your child have eating or sleeping difficulties? 10. Does your child have any allergic symptoms? 11. Does your child have any special diet? The question number four was used in the screening, so that the answer yes made the child an index child with a suspicion of ADHD.

Screening questionnaire for pre-school teachers (paper 4): The questions in the pre-school teacher questionnaire were: 1. Does the child have difficulties staying calm and being patient? Can the child sit still and pay attention required? 2. Is the child late in speech development? 3. Does the child have difficulties pronouncing words or sentences? 4. Does the child have difficulties listening to a story read by someone or from a tape recording? 5. Does the child

have difficulties understanding information given to the whole group? 6. Does the child have difficulties saying something in complete and correct sentences? 7. Does the child have difficulties understanding opposite words (like long-short)? 8. Does the child make immature drawings? 9. Does the child have difficulties working by him/her self in a group? 10. Does the child often make a mess during meals? 11. Does the child have difficulties playing with children of the same age? 12. Does the child seem to be anxious during group activities? The question number one was used in the screening so that the answer yes made the child an index child with a suspicion of ADHD.

Rutter's questionnaire for parents (paper 1): This questionnaire was used in the SPECT study to measure behavioural symptoms (Rutter, 1970).

The pre-school behaviour checklist (paper 4): This questionnaire has been developed for screening emotional and behavioural problems in pre-school children and has been validated by McGuire and Richman (McGuire & Richman, 1986). The information from the pre-school teachers was used when a diagnosis of ADHD according to DSM-III-R was made.

Somatic, cognitive and emotional development

Semi-structured parental interview (paper 3 and 4): For the clinical interview a semi structured questionnaire was constructed with questions concerning the child's development, in order to standardize the interview procedure.

MPA (paper 1): The number of Minor Physical Anomalies which are thought to be associated with neurodevelopmental disturbances (Waldrop, 1971) was recorded as the child was examined with a routine pediatric examination.

Questionnaires concerning parental health and family functioning

SCL-90 (paper 2): Parental symptomatology was measured by using the SCL-90 questionnaire for both mothers and fathers at 0 months and at three months.

FARS (paper 2): The *Family Relations Scale* (FARS), which is a self-report questionnaire on family functioning, was used in paper 2 (Höök, 1992).

Examinations of neuroanatomy and neurophysiology

MRI (magnetic resonance imaging) (paper 1): Clinical routine MRI was performed on all subjects. The examinations were carried out at the Department of Radiology at the University Hospital of Malmö.

SPECT (Single Photon Emission Computed Tomography) (paper 1): This technique was used to determine regional cerebral blood-flow (rCBF).

EEG (electroencephalogram) (paper 1): Twenty-six subjects were recorded with EEG before treatment and 23 of these were also recorded during treatment with amphetamine.

Measures of cognitive function

WISC (Wechsler Intelligence Scale) (paper 1 and unpublished study): The school children were examined with the WISC-test. In paper 1 the original version was used (Wechsler, 1949) and in the unpublished study the WISC-III version (Wechsler, 1992).

ADHD-diagnosis

DSM-III-R (papers 1, 2, 4 and unpublished study): Criteria according to the DSM-III-R (APA, 1987) were used to diagnose ADHD in children that were examined. The number of DSM criteria was used as a quantitative measure of the severity of the ADHD-problems in some of the comparisons that were made.

Family observations

The families were videotaped when performing family tasks and the videotapes were rated by independent raters unaware of the child's problems. The family observations were rated according to the following instruments:

Beavers Family Competence Scale (paper 2): Three family tasks (completing a puzzle, solving a conflict situation, and planning of a shared activity) were rated according to the Beavers Family Competence Scale. This scale has been widely used and has been translated to Swedish (Beavers, 1990; Hansson, 1989).

DFI (Dyadic Family Interaction) (paper 2): A homework situation with the mother was rated with the DFI. This instrument is a Swedish translation, with minor modifications, of the Family Interaction Global Coding System devised by Mavis E. Hetherington et al (Hetherington, 1992; D. Reiss et al., 1995; D. Reiss, Plomin, R., Hetherington, E.M., Howe, G., Rovine, M., Tryon, A., 1994; Hansson, K., Eberhardt, A., & Balldin, T 1989).

RESULTS

Paper 1: Which neurobiological correlates of having ADHD can be identified?

The study in paper 1 was performed in order to answer questions concerning the neurophysiologic background of ADHD. SPECT-, MRI- and EEG-techniques were utilized and cognitive function and minor physical anomalies were determined. Parents answered the Conners and Rutter questionnaires concerning child behaviour and the children went through a neurological examination.

The MRI was done as a clinical routine examination and gave only anatomical data. The material was small and no comparison group was used, which limits the possibilities of detecting small deviations from normality. The MRI examination did not show any obvious deviances in the brain structure of the subjects examined.

By conventional interpretation, the EEG showed slight abnormalities in 10 of the 26 examined children, in all cases with a moderate increase of low frequency activity. Quantitative analysis showed no difference in relative delta and alpha power between those with abnormal EEG and those with normal EEG. There was no correlation between relative delta or alpha power and any of the clinical variables (Conners parent scale, Rutter's parent scale, WISC).

The analysis of SPECT-results showed that seven of the 28 children had suspected or clearly abnormal cerebral blood-flow distribution on visual examination. The group with suspected or abnormal SPECT had significantly higher scores on the Rutter parent scale compared to those with normal findings. The three factors from the factor analysis on blood-flow values from the different regions of interest were analyzed against EEG-results, cognitive functions, neurodevelopmental examination and behavioural symptoms. A negative correlation was found between relative alpha power on the quantitative EEG-analysis and SPECT factor 2 (with high biparietal and occipital loadings). A positive correlation was found between relative delta power on the quantitative EEG and SPECT factors 2 and 3 (high blood flow in frontal and parietal regions bilaterally). These correlations were hypothetically thought to reflect different degrees of alertness for different children. Values of factor 1 (low blood-flow in the temporal lobe and the cerebellum compared to the basal ganglia) were correlated to the WISC results and with degree of motor impairment. Values of factor 3 were correlated with behavioural deviance measured by the Rutter scores. The blood-flow in frontal regions was compared with behaviour, motor impairment, minor physical anomalies and cognitive function. Correlations were found between low blood-flow in the right frontal lobe on one hand and the child's behaviour and high scores on minor physical anomalies on the other. For minor physical anomalies a correlation was also found with low blood-flow in the left frontal lobe.

In summary the results suggests that there may be at least two functional disturbances in ADHD, one involving the frontal lobes, especially on the right side, related to behavioural deviance, and another disturbance of the integration of the temporal lobes, the cerebellum and subcortical structures related to motor planning and aspects of cognition. An association was also found between low blood-flow in the right frontal lobe and high parent ratings of disruptive behaviour.

Discussion

Barkley- (1997b) and Brown (2006) have claimed that a dysfunction in the so called executive functions of the brain is the central problem in ADHD. The executive functions are mainly dependent on circuits in the frontal lobes of the brain. Sonuga-Barke (2005) has described at least three separate neural systems that can be implicated in ADHD. One system is associated with delay aversion (difficulties waiting for a reward) (Cardinal, Winstanley, Robbins, & Everitt, 2004; Oades et al., 2005; Sagvolden, Johansen, Aase, & Russell, 2005; Schultz, 2002). This system is represented by structures in the lower parts of the frontal lobes in connection with the meso-limbic and meso-cortical systems and the nucleus accumbens. Another system is concerned with executive functions and working memory and is associated with other parts of the frontal lobes, the gyrus cinguli and connections with the striatum (Barkley, 1997b; Brown, 2006). The third system has to do with time sequences and is associated with the cerebellum, the thalamus, the striatum and the motor cortex (Ben-Pazi, Gross-Tsur, Bergman, & Shalev, 2003; Rubia, A. Taylor, E. Taylor, & Sergeant, 1999; A. Smith, E. Taylor, Rogers, Newman, & Rubia, 2002; Sonuga-Barke, Saxton, & Hall, 1998; Toplak, Rucklidge, Hetherington, John, & Tannock, 2003). Different individuals with ADHD may have a dysfunction in one or several of the three systems and ADHD might thus be a heterogeneous condition (Sonuga-Barke, 2005).

Specific EEG-patterns in ADHD have been studied by many researchers (Hobbs, Clarke, Barry, McCarthy, & Selikowitz, 2007). Increased low-frequency 2-6 Hz was described by Jasper 1938 (1938) and later by Lindsley (1940). Increased amounts of theta waves have been reported in several studies as described by Barry, Clarke, & Johnstone, (2003) and some studies have reported increase in relative delta waves (Clarke, Barry, Bond, McCarthy, & Selikowitz, 2002). Several studies have been made concerning evoked potentials. A common finding reported is reduced P300 during the so called auditory Odd ball task (Barry, de Pascalis, Hodder, Clarke, & Johnstone, 2003; Barry, Johnstone, & Clarke, 2003). A recent study by Alexander et al (2008), where they analysed event-related wave activity in EEG during an auditory Odd ball task and during visual Continuous Performance Test (CPT) showed less low-frequency activity with frequencies around 1 Hz among subjects with AD/HD compared to normal controls.

Although some progress has been made during the last decade in the research concerning important biological factors in ADHD, knowledge about these factors is still incomplete and further research is needed. The findings that have been reported need to be replicated in other studies.

The results in paper 1 from the EEG-study, showed a slightly abnormal EEG by conventional interpretation with a moderate increase of low frequency activity in 10 of the 26 subjects. Quantitative analysis of relative delta and alpha power did not show any significant difference between the children considered abnormal versus children considered normal. No correlations were found between cognitive function and behavioural variables on one side and relative delta and alpha power on the other.

Concerning MRI performed and assessed by routine clinical methods, all children were considered normal.

The results in paper 1 give support for an association between low blood-flow in the right frontal region at rest-, and ADHD-symptoms as has been described by several other researchers (Garavan, Ross, & Stein, 1999; Kim, Lee, Shin, Cho, & Lee, 2002; Lee et al., 2005). Giedd, Blumenthal, Molloy, & Castellanos, (2001) describe involvement of a right frontal-basal ganglia circuit with a modulatory influence from the cerebellum. A correlation was found between low blood-flow in the left and right frontal lobe and high scores on minor physical anomalies. Minor physical anomalies are thought to correlate with neurodevelopmental abnormalities (Waldrop, 1971) and this association gives support to the hypothesis that ADHD at least in some cases can be regarded as a neurodevelopmental deviance. The factor analysis revealed two different patterns of cerebral blood-flow in children with ADHD; one associated with motor impairment and cognitive function and the other with behavioural symptoms. The network associated with motor impairment involved the cerebellum, basal ganglia, thalamus and the temporal lobes. Teicher et al., (2000) using fMRI, describe involvement of the basal ganglia and the cerebellum with high activity in basal ganglia, especially putamen and low activity in the cerebellum in ADHD in common with our results, which also are supported by an fMRI study by Mostofsky et al., (2006) who describe a network with abnormal activation in ADHD consisting of cerebellum, thalamus, basal ganglia and motor cortex. An fMRI study by Zhu et al., (2008) showed abnormalities in thalamic activity in the resting condition among individuals with ADHD. The network associated with behavioural symptoms described in paper 1, involved fronto-parietal areas. In their fMRI study Pessoa, Kastner, & Ungerleider, (2002) describe a fronto-parietal brain system associated with ADHD. Of the three different systems proposed by Sonuga-Barke (2005) to be involved in ADHD, the system associated with time sequence and motor coordination appears to be similar to the factor associated with motor function in the present study, and the system described as associated with executive functioning is similar to the factor associated with behavioural function in the present study. The present study thus shows separate systems involved in ADHD just as other researchers report, which supports the assumption that ADHD might be a neurobiologically heterogeneous condition. Of special interest is the finding that motor difficulties are present among the studied children with ADHD, but they represent a factor separate from the behavioural symptoms, thus supporting the existence of a relevant subgroup of children with ADHD with marked motor dysfunction in accordance with the work by C. Gillberg and co workers (C.

Gillberg, 2003; C. Gillberg, Carlstrom, & Rasmussen, 1983; I. C. Gillberg & Gillberg, 1988).

Limitations: The individuals in this study do not constitute a representative sample of children with ADHD from the general population. The sample was based on clinical cases of families with a child with severe ADHD who were willing to participate in the study. Since it is considered unethical to perform SPECT-examinations on healthy children, we did not have any normal controls. Since a direct quantitative comparison to the rCBF distribution of healthy children was not possible, the rCBF results were instead evaluated by correlation to quantitative evaluations of ADHD-related symptoms.

Conclusion

This work indicate that children with ADHD have characteristic patterns of brain functioning with low activity in the right frontal lobe at rest and with two different functional networks, one fronto-parietal network correlated with behavioural symptoms and one thalamo-striatal-temporo-cerebellar network correlated with motor functioning. We have thus found different and separable neurobiological correlates of ADHD-symptoms, which is in accordance with reports by other researchers in the field.

Paper 2: Are ADHD symptoms among children a consequence of a non-optimal parenting style rather than of a neurophysiological deviance?

The study in paper 2 was performed as a part of a pharmacological study concerning long-term treatment of attention deficit hyperactivity disorder with amphetamine (C. Gillberg et al., 1997). The children and their families were examined before treatment with amphetamine was begun and after three months of treatment. The children's symptoms were assessed by parents and teachers and family functioning was assessed by questionnaires for parents to fill in and video-taped family situations rated by independent observers. Before medical treatment was begun the parents rated their children as having many ADHD symptoms according to Conners abbreviated rating scale. The families had a high degree of family dysfunction according to the family relations scale and according to video taped observer ratings. The DFI sub scales of warmth/support, monitoring of the child and social behaviour showed a higher degree of dysfunction for the families taking part in the study compared to normal control families. The only Dyadic Family Interaction (DFI) measures showing better functioning for the ADHD-families compared to normal controls were influence/control and wrath/rejection. The scores of mothers and fathers on the SCL-90 rating concerning their mental health did not differ significantly from scores of normal controls, except for fathers' scores on the subscale depression where fathers of the children in the study scored higher than normal controls. After three months of treatment with amphetamine, Conners scores according to both parents and teachers improved significantly. Total FARS scores and the sub scores of attribution and enmeshment (mothers only) improved after three months of medication. Individuals with high FARS-scores (more than 1 standard deviation above the mean for controls) improved

more than one standard deviation significantly more often than did other individuals. The same was found concerning the sub scores of attribution, isolation, chaos and enmeshment. According to the descriptions from mothers, the improvement in chaos and enmeshment did correlate with degree of symptom reduction. Total family functioning according to Beavers' Family Competence improved after three months of treatment with amphetamine, as did the measures of responsibility and empathy. Mothers showing monitoring more than one standard deviation below the normal mean before treatment-increased their monitoring more than one standard deviation significantly more often than did other mothers. Mothers showing much influence/control decreased their scores by one standard deviation significantly more often than did other mothers. Total scores on SCL-90 for mothers improved significantly as well as the subscales of anxiety and depression. The subscale of depression improved for fathers. Mothers with high values of anxiety and depression (more than one standard deviation) decreased their values one standard deviation more often than did other mothers.

In summary the study gives support to the notion that some aspects of family dysfunction may be related to the child's ADHD behaviour. When the child's symptoms improve, the family function and the mental well-being of the parents also improve.

Discussion

Families with a child with ADHD show higher levels of stress and family dysfunction (Barkley, 1996; Barkley et al., 1991; Barkley et al., 1992; Johnston, 1996; Johnston & Mash, 2001; Sandberg, 2002; Wells et al., 2000). Parents of children with ADHD have been found to be more controlling, more directive and negative towards the child. An increase in rates of divorce in families with a child with ADHD is reported. Increased stress and psychological problems are reported among siblings of a child with ADHD.

There has been a lively debate concerning the causal direction of these associations and concerning the possibility of confounding factors. Wells et al (2000) have described how many researchers claim that the family dysfunction may be a consequence rather than cause of the child's symptoms. Family dysfunction might also be a consequence of one or both parents having ADHD leading to difficulties in the parents' close social relations because of poor affect regulation and impulsive behaviour (Wells et al., 2000).

The present study looks at what happens concerning family functioning and well-being of the parents when the child's symptoms are treated with medicine, a process that has not yet been studied to a great extent. The method applied for assessment of family function by using video-taped family-situations rated by independent raters- has not been used in this kind of study before. This method should reduce the possible assessment bias that parents and the treating doctor have, who know that the child has ADHD and has received medical treatment.

When children with ADHD were treated with central stimulant medication the symptoms of ADHD improved significantly, just as the scores of family

dysfunction according to parents and according to independent raters of video taped family situations. The only intervention in the study was medical treatment i.e. a biological treatment of the ADHD-symptoms. Thus a biological intervention for treatment of ADHD-symptoms- can significantly change the family function. This seems to imply that behavioural factors in a significant way influence the relations in the families with a child with ADHD.

Limitations: This study must be interpreted with great caution. The material is limited, and the concepts are complicated, with presumably some unrevealed interactions being present among the different factors. Further studies with a greater number of families and a longer period of follow-up are needed to confirm these results. It would also be of interest to follow up a group with randomized placebo control versus treatment with central stimulants, without permission to break the double-blind condition before the end of the study.

Conclusion

Family functioning was found to be different in families with a child with ADHD with more controlling and negative behaviour from the parents. After three months of treatment with central stimulant medication the family functioning improved and the parents reported improved mental well-being. A biologic treatment thus seems to improve family dysfunction, probably at least partly caused by a biologically determined dysfunction of the child. If bad parenting was the main cause of ADHD symptoms, one would not expect that treatment with amphetamine would improve the child's symptoms at the same time as the parents show less hostility and more responsibility and empathy towards their child. Thus, when the child's symptoms decrease, the parents' behaviour towards the child normalizes. In the follow-up study after three months of treatment reported by C. Gillberg et al., (1997), very many of the families put on placebo changed to active treatment, indicating that the symptom reduction of the children was not a mere placebo-effect and also implying that the change in family-function was not the cause but rather a consequence of the child's symptom improvement.

Paper 3 and unpublished study: Are children with ADHD normal children with a slow pace of maturation?

In paper 3 two questions were posed:

1. Is there a marked decline of ADHD-symptoms with age that may possibly be determined by comparing school children from grade one, two and three in elementary school, a decline that could support the theory of maturational-lag?
2. Is there an association between ADHD symptoms and biological measures of maturity like skeletal bone-age, height, weight and motor function?

Height, weight and skeletal bone-age had a significant correlation with age of the child, but not with ADHD-symptoms rated by parents and teachers according to Conners abbreviated rating scale. Degree of motor dysfunction had a weak correlation with age. No correlation was found between the age of

the child and parents' and teachers' ratings of ADHD-symptoms. Variables measuring biological maturity had a strong relation with the age of the child, while the behavioural variables, motor function (MUGI) and Conners scores did not show an obvious relation with age. ADHD-symptoms according to the Conners ratings did not show any relation to the variables measuring general biological maturity.

Supplementary Study (unpublished)

A further study, which has not been published, was performed on 23 of the school children from grades one and two (eight children with suspected ADHD and 15 controls from a total population of 148 children) who were examined with a cognitive test (the WISC-III). Six of the eight children with suspected ADHD according to Conners ratings were diagnosed as having ADHD according to DSM-III-R. Parents and teachers were asked to fill in the CBCL and TRF questionnaires. Both CBCL and TRF have the question "acts too young for his/her age". This question was used as a measure of immaturity according to parents and teachers. This question can be answered with not true = score 0, somewhat or sometimes true = score 1, or very true or often true = score 2. The sum of parents' and teachers' ratings was calculated. When parent and teacher combined ratings of immaturity were studied, all of the index children were found to have some ratings of immaturity but only one of the control children. No significant differences were found between the groups concerning age, height, weight or skeletal bone-age. Significant differences between the groups are shown in table 4. Six children (three boys and three girls) fulfilled the criteria for a DSM-III-R diagnosis of ADHD, which corresponds to 4% of the total population studied. Among the six children who got a diagnosis of ADHD, all were rated as immature by either parents, teachers or both.

Table 4. Means and standard deviations for the different groups in the study

Item	Grade 1&2, n=148			Non-index, n=132			Index, n=16			Controls, n=15		
	n	M	SD	n	M	SD	n	M	SD	n	M	SD
Height z-score												
All	120	0.3	0.9	106	0.3	0.9	14	0.2	1.1	12	0.4	1.2
Girls	48	0.4	0.8	45	0.4	0.7	3	1.0	1.2	3	0.9	0.4
Boys	72	0.3	1.1	61	0.3	1.1	11	0.0	1.0	9	0.3	1.3
Weight z-score												
All	120	0.7	1.5	106	0.7	1.5	14	0.8	1.2	12	0.6	1.3
Girls	48	0.6	1.4	45	0.6	1.4	3	1.6	0.6	3	1.9	0.4
Boys	72	0.8	0.8	61	0.8	1.6	11	0.6	1.3	9	0.1	1.1
Diff. bone-age												
All	120	-3.2	11.5	106	-3.3	11.6	14	-2.1	10.9	12	-3.2	12.5
Girls	48	-1.6	10.2	45	-1.7	10.4	3	-0.3	8.5	3	9.7	8.1
Boys	72	-4.3	12.2	61	-4.6	12.3	11	-2.6	11.7	9	-7.4	10.7
Conners parents												
All	144	3.3	4.1	128	2.6	2.8	16	8.9	7.7 ¹	15	3.8	3.5 ²
Girls	58	2.8	3.4	54	2.3	2.8	4	9.0	5.9 ¹	3	2.3	2.5 ²
Boys	86	3.7	4.5	74	2.9	2.8	12	8.9	8.4 ¹	12	4.2	3.7 ²
Conners teachers												
All	146	2.9	5.3	130	1.5	2.5	16	14.5	7.6 ¹	15	1.5	2.6 ²
Girls	60	2.4	5.0	56	1.4	2.6	4	16.0	10.1 ¹	3	2.0	3.5 ²
Boys	86	3.3	5.5	74	1.5	2.4	12	14.0	7.0 ¹	12	1.4	2.5 ²
MUGI												
All	146	5.0	5.5	130	4.2	4.7	16	10.9	7.4 ¹	14	3.1	2.5 ²
Girls	61	4.0	4.6	57	3.6	4.2	4	8.5	7.3 ¹	3	0.7	1.2 ²
Boys	85	5.7	6.0	73	4.7	5.0	12	11.7	7.6 ¹	11	3.8	2.4 ²
Age in months												
All	124	93.2	7.2	109	93.6	7.4	15	90.0	5.1	15	93.3	7.5
Girls	49	92.0	7.0	45	92.2	7.3	4	90.3	3.3	3	88.3	1.5
Boys	75	93.9	7.3	64	94.6	7.3	11	89.9	5.7	9	94.6	7.9

¹Sign difference between non-index and index group p<0.01 (Mann-Whitney)

²Sign difference between control group and index group p<0.01 (Mann-Whitney)

A comparison between the children with an ADHD diagnosis and the control group yielded a significant difference ($p < 0.01$) concerning the MUGI examination (children with ADHD: mean 16.0, SD 7.7, control children: mean 3.1, SD 2.5) but no significant difference concerning age, difference between chronological and bone-age, standardized length or standardized weight. Table 5 shows differences between children in different maturity levels concerning other variables. Children with ADHD and low cognitive function in combination had the highest parent and teacher ratings of immaturity. In the index and control groups, none of the children without ADHD and with $IQ > 70$ had any parent or teacher ratings of immaturity (14 children). The immaturity ratings of children with and without ADHD were analyzed with the Mann-Whitney U-test and the median value of immaturity for children with ADHD ($n=6$) was found to be significantly higher than for children without ADHD ($n=17$), $p < 0.001$.

Significant correlations between immaturity ratings and other variables are shown in table 6. The biological, somatic and non behavioural signs of immaturity did not show any significant correlations with the immaturity ratings. The ratings of immaturity were dichotomized. Children where the sum of the parents' and the teacher's description of immaturity was less than or equal to one ($n=15$) were compared to children where the sum was greater than one ($n=7$). The sumscore of dichotomized IQ-Ratings ($IQ < 70$ as one and $IQ \geq 70$ as zero), dichotomized MUGI-ratings (MUGI-ratings < 11 as zero and MUGI-ratings ≥ 11 as one) and ADHD-diagnosis (no ADHD diagnosis as zero and diagnosis of ADHD as one) was calculated and an index was defined with sumscore < 1 as zero and sumscore ≥ 1 as one. Table 7 shows the relation between this index and the dichotomized immaturity rating. The positive predictive value of the dichotomized immaturity ratings predicting the index value was calculated to be 0.86 and the negative predictive value was calculated to be 0.93.

Table 5. Median and inter-quartile range for age, parent and teacher Conners ratings and motor function (according to MUGI), proportion with an ADHD-diagnosis and mean and standard deviation for IQ for the different maturity levels. One child with ADHD is not reported since cognitive testing could not be performed.

Maturity level (boys/girls)	Age Md (range)	Conners parent ratings Md (range)	Conners teacher ratings Md (range)	Index/ Control	ADHD- dia- gnosis Y/N	IQ Mean (SD)	MUGI Md (range)
0 (11/3) n=14	91.0 (86.25-101.25)	2.5 (0.8-6.0)	0 (0.0-3.8)	0/14	0/14	102.4 (14.1)	3.0 (0.5-4.5)
1 (2/0) n=2	85.5 (82.0-89.0)	18.0 (12.0-24.0)	26.0 (23.0-29.0)	2/0	1/1	122.5 (6.4)	12.0 (0.0-24.0)
2 (1/2) n=3	94.0 (90.0-102.0)	9.0 (6.0-11.0)	19.0 (0.0-28.0)	2/1	2/1	86.7 (18.7)	6.0 (3.0-7.0)
3 (0/1) n=1	97.0	15.0	12.0	1/0	0/1	98.0	22.0
4 (1/1) n=2	88.5 (86.0-91.0)	18.0 (15.0-21.0)	2.0 (0.0-4.0)	2/0	2/0	56.0 (14.1)	18.5 (18.0-19.0)

Table 6. Spearman correlations between variables for children examined by physician and psychologist

	IQ	MUGI	Immaturity	Conners parent ratings	Conners teacher ratings	ADHD-Diagnosis (yes/no)
IQ	1.000 n=23					
MUGI	-0.503* n=22	1.000 n=22				
Immaturity	-0.351 n=22	0.598** n=21	1.000 n=22			
Conners parent ratings	-0.370 n=23	0.685*** n=22	0.746*** n=22	1.000 n=23		
Conners teacher ratings	0.025 n=23	0.425* n=22	0.438* n=22	0.464* n=23	1.000 n=23	
ADHD-diagnosis (yes/no)	-0.538** n=23	0.654** n=22	0.736*** n=22	0.666** n=23	0.506* n=23	1.000 n=23

Significance levels: * = p<0.05, ** = p<0.01, *** = p<0.001

Table 7. Four field table with number of individuals with zero and one on the dichotomized immaturity ratings compared to number of individuals with zero and one on the index representing a combination of ADHD-diagnosis, cognitive function and motor function as described in the text.

	Index	
	0	1
Immaturity		
0	14	1
1	1	6

Fisher's exact test gives p=0.001

In summary variables related to general biological maturity did not correlate with ADHD-symptoms. Motor dysfunction did correlate with ADHD. Parent's and teacher's descriptions of the child as immature mainly seem to reflect difficulties in motor function, cognition and ADHD symptoms.

Discussion

ADHD symptoms have important developmental aspects and change considerably over time (Greenberg & Waldman, 1993; Hart, Lahey, Loeber, Applegate, & Frick, 1995). Children with ADHD perform like younger children in tests of executive functions (Barkley, 1997a). About 50% of children with ADHD have been described as having Developmental Coordination Disorder (DCD), which also has a developmental aspect (C. Gillberg & Kadesjo, 2003; Hartsough & Lambert, 1985). Thus, the idea of a maturational-lag as an underlying cause of ADHD-symptoms has been proposed by some researchers (Kinsbourne, 1973; Pasamanick, 1973) while others have opposed this idea and have claimed that children with ADHD have deficits in brain functioning (Drechsler, Brandeis, Foldenyi, Imhof, & Steinhausen, 2005; Jonkman, Kenemans, Kemner, Verbaten, & van Engeland, 2004; J. L. Smith, Johnstone, & Barry, 2004). El-Sayed (2002) and Steffensson (1999) propose that ADHD in some cases may be due to a relatively slower rate of mental maturation with the possibility of a catch-up occurring later. They argue that children with ADHD have patterns of EEG reminiscent of patterns in younger children with more low frequency components, thus supporting the theory that at least some children with ADHD have a slow CNS-maturation that will eventually catch up. Many researchers in the field have proposed that children with ADHD have a different brain function compared to normal controls. Some researchers have recently described qualitative differences between children with ADHD and younger normally developed children in patterns of processing of perceptual information and motor planning when studying event related potentials as well as in reaction-time patterns in tasks requiring inhibitory control and modulation of attention (Hobbs et al., 2007; Leth-Steensen, Elbaz, & Douglas, 2000; Mostofsky et al., 2006). The concept of maturational-lag or a slower pace of development is intriguing. The difference between grown-ups and children is supposed to be that the pace of development is much faster in children and that some aspects of development end at some point e.g. increase in height. If some more slowly developing children are to catch up, they either will have to show a sudden leap in development or a longer time period will have to elapse until their development begins to slow down or cease. Children with mental retardation have both a slower pace of development and less complex developmental stages. They cannot be expected to catch up completely, as their development supposedly begins to cease at about the same age as it does for normal children. For premature children a catch-up in length is expected but a catch-up is not expected for children who are short due to a genetic disposition. Children with motor dysfunction might improve with increasing age, but some will continue to have motor problems in adulthood and others may have sub clinical degrees of motor dysfunction (C. Gillberg, 2003). Denckla (2003) postulates that Fog's test and "mirror movements" significantly distinguish children with

hyperactivity from normal controls, i.e. hyperactive children had overflow-movements like younger children, which she attributes to an anomalous maturation of inhibitory function. Over-activity has been shown to decrease with age so that only one in two school-children will meet full criteria for over-activity at 22 years of age (C. Gillberg, 2003). The diagnosis ADHD is difficult to make in young children, as many normal preschool children are more hyperactive and impulsive and have a shorter attention span than most older children, a fact which could support the idea of a maturational-lag. There is also a sex difference in both activity level and attention.

A number of studies of brain anatomy with MRI (Magnetic Resonance Imaging) have been made recently, as described by Castellanos et al (2002) who have shown smaller total brain volume and especially volume reductions in the corpus callosum, the cerebellum and the nucleus caudatus in subjects with ADHD. These volume reductions tend to remain in adult age except in the nucleus caudatus where a catch up is seen.

The theory of maturational lag as a cause of ADHD, i.e. that some children develop slowly but are otherwise normal, was originally influenced by findings of increased slow activity, as younger children have, on the EEG in children with ADHD. Parents and teachers often describe ADHD-children as immature, reminding observers of the behaviour of younger children. If the theory of maturational lag holds true, children with ADHD would eventually have a catch-up and the symptoms would disappear. Recent research by Biederman, Mick & Faraone (2000) have shown that many of the ADHD-symptoms persist to adulthood. Some researchers have described neurophysiological patterns of functioning in ADHD as not resembling normal function among younger individuals. Castellanos et al (2002) have described anatomical findings that persist into adulthood. Still some researchers claim that there might be a subgroup of children with ADHD with a maturational lag with the possibility of catch-up with increasing age. In the present study, objective measures of general biological immaturity like skeletal bone-age, length and height have been used, together with measures of cognitive function, motor function and ADHD-behaviour. Skeletal bone-age has not been used in this context before.

In the present study we have used the concept of immaturity as defined by parents' and teachers' answers to the question: "acts too young for his/her age". This is comparable to the concept used by El Sayed (2002) and Steffenson et al (1999) where parents were asked to rate their child's overall maturity compared to a typical child the same age and to then make an estimation of their child's maturational age.

Children with ADHD had a poorer motor function than the children without ADHD. El Sayed (El-Sayed, 2002) mentions motor dysfunction as a sign of immaturity but has measured the motor function of the subjects only in order to exclude children with neurological disorders and developmental coordination disorder.

The children with ADHD and low cognitive function in combination- were more often scored as immature than any of the other children. The positive and

negative predictive powers for a combination of ADHD diagnosis, poor motor dysfunction and low cognitive function predicting immaturity was found to be very high (86% and 93%). Since it is reasonable to assume that there is a considerable degree of measurement error in these subjective ratings, it seems as if there is not very much predictive power for immaturity left for factors other than ADHD, motor function or cognitive function. Cognitive function has known correlations with ADHD (Hagermann, 2002) and children with low intellectual functioning resemble younger children in their behaviour. Cognitive function as measured by IQ-tests is only briefly mentioned as a measure of immaturity by El Sayed (2002), and the cognitive function of the subjects (measured by WISC) was only determined in order to exclude children with mental retardation from the study. In the unpublished study of 23 children, two of the six children with ADHD had mild mental retardation.

El Sayed (2002) and Steffensson et al (1999) have proposed that there might be two different types of ADHD, one genetically correlated with slow CNS-maturation and postulated to represent a “continuum of normal childhood behaviour with maturational trajectories that are lagging behind but that will catch up”, and another type not correlated with slow maturation but specific to ADHD. In the present study we could not find a distinct subgroup of children with ADHD with immaturity differing from a subgroup with ADHD without signs of immaturity. All (100%) children with ADHD had ratings of immaturity compared to 18% of children without ADHD and 100% of the index children had ratings of immaturity compared to 7% of the control children (one child). El-Sayed’s descriptions of partially different genetic correlations for ADHD and for immaturity according to parents might be explainable by partially separate genetic factors for ADHD, cognitive function and motor function. El-Sayed (2002) and Steffensson et al (1999) argue that children with ADHD have patterns of EEG that are reminiscent of younger children with more low frequency components. J. L. Smith et al., (2004) have analyzed auditory ERP (event related potentials) and have found atypical patterns of early processing in children with ADHD performing a Go/No go task, where the inhibitory processing seemed to be topographically different in location compared to controls. In another analysis of auditory ERP by Johnstone, Barry, & Anderson, (2001), ADHD subjects showed topographic differences from controls across the age range, indicating a qualitatively distinct pattern of brain activation in ADHD. Jonkman et al., (2004) have similarly described atypical patterns in visual ERP in children with ADHD with abnormal selective activation of lateral frontal areas, which might suggest abnormalities in working memory functions. Mostofsky et al (2006) have described decreased contra lateral motor cortex and right parietal activation in children with ADHD during sequential finger tapping, suggesting that children with ADHD have an anomalous development of cortical systems necessary for the execution of patterned movements. These results seem to indicate abnormalities in processing of perceptual information and motor planning in ADHD not easily explainable as only being related to slow maturation.

Biederman, Mick, & Faraone, (2000) have performed a longitudinal study of boys with ADHD that showed that about 40% still had ADHD at 19 years of age. About 70% had at least five of the eight symptoms required for a

diagnosis and about 90% showed evidence of clinically significant impairment (GAF>60), which seems to indicate that most individuals with ADHD continue to have problems. Castellanos et al (2002) have described decreased total brain volume for children and adolescents with ADHD. Developmental trajectories for all brain structures except the caudate nucleus were found to remain roughly parallel for patients and controls showing no tendency of catch-up. A recent study by Shaw et al., (2006) has shown a pattern of cortical thinning in children with ADHD most pronounced in medial and prefrontal and precentral regions. Children with good prognosis when growing up did not have this pattern of prefrontal thinning but had some thinning in the right parietal cortex with normalisation with age. The pattern of cortical thinning seen among children with ADHD did not resemble the pattern among younger normal children, on the contrary younger children have thicker cortex. These findings thus do not support the theory that some children with ADHD have a neurological delay in the normal maturation of the brain. To determine if there is a true "catch-up" in an immature group of children with ADHD, studies are needed where children classified as immature are followed into adulthood.

Limitations: Great caution must be taken when interpreting the results. The time frame of three years might be too short to study a decrease in ADHD symptoms, if the decline in symptoms occurs at a much slower rate than changes for height, weight and skeletal bone-age. In the unpublished study there was a drop-out rate of 50% in the index group. The children whose parents refused participation, were only scored as index children by the teacher's evaluations but not by the parents'. Perhaps this disagreement between teachers and parents could have contributed to a lesser motivation among the parents to participate. There could be a bias so that the older children might have had different means and distribution of important variables when they were the same age as the younger children. To control these kinds of problems a longitudinal rather than a cross-sectional design should be employed. To study if there is a true Catch-up in an immature group of children with ADHD, a study is needed where children with ADHD who are also classified as immature are followed into adulthood.

Conclusion

ADHD symptoms did not correlate with age or with maturity dependent variables. This is not consistent with the view that children with ADHD are normal children with a slow pace of development. Other studies presented above further show that the catch-up in ADHD symptoms when the child grows-up is incomplete, that the brain-volume in adulthood is smaller among individuals with childhood ADHD and that certain neurophysiological patterns deviate from normal younger individuals. The results of the unpublished supplementary study indicate that immaturity ratings by parents and teachers constitute a continuous and not a categorical variable, and that the dimension of immaturity might be difficult to distinguish from degree of ADHD, motor function and cognitive function. The value of the concept of immaturity as defined by parents and teacher ratings can be questioned. Does this concept in any way enrich the field of ADHD research, or might it only lead to confusion?

Paper 4: If motor function is of relevance when studying ADHD, can it be measured in a reliable and valid way?

In this study aspects of reliability and validity of a variant of neurological examination for assessment of so called “soft neurological signs” were examined. Comparisons were made between the ratings for soft signs of four different examiners. The reliability for the total score is shown in table 8 and the reliability of individual items is shown in table 9.

Table 8: Pearson correlations between results of different examiners concerning the total sum of items in the neurological examination.

Pairwise correlations between examiners	All subjects n=35	Subjects with ADHD, n=7	Subjects without ADHD, n=28
examiner 1 and examiner 2	0.921***	0.957**	0.916***
examiner 1 and examiner 3	0.857***	0.943**	0.808***
examiner 1 and examiner 4	0.872***	0.942**	0.821***
examiner 2 and examiner 3	0.833***	0.918**	0.795***
examiner 2 and examiner 4	0.895***	0.946**	0.811***
examiner 3 and examiner 4	0.863***	0.827**	0.807***

* = p<0.05, ** = p<0.01, *** = p<0.001

Table 9: Cohen's kappa, pair-wise comparisons (number of pair-wise combinations of the four examiners, totally twelve with double sided items and six for single item), n=35.

Items	Not enough data	Reliability		
		Bad	Good	Very good
Diadochokinesis, right and left		7	5	
Hopping on one leg, right and left		2	10	
Standing on one leg, right and left			12	
Prechtl choreatic movements, right and left		10	2	
Prechtl athetotic movements, right and left	12			
Prechtl tremor, right and left	12			
Prechtl spooning, right and left		8	2	2
Walking on heels		5	1	
Fogs test		3	3	
Alternating jumps			5	1
Alternating jumps with crossed arm movements		3	3	
Finger opposition		1	4	1

* Bad reliability= kappa<0.40, good reliability = kappa in the range of 0.40 – 0.75, very good reliability = kappa>0.75

Internal consistency was analyzed with Cronbach's alpha with reasonably good consistency (r=0.76). When only the sums of the items diadochokinesis, jumping on one leg and standing on one leg was analyzed a comparable consistency was measured (r=0.75). The test-retest study also showed good reliability (r=0.91). There were modest correlations between the neurological examination for soft signs and the examination by the physical education teacher (r=0.48) and parents' description (r=0.47). The neurological examination was found to have a sensitivity of 0.80 and a specificity of 0.76 in predicting motor problems according to the physical education teacher. The physical education teacher's examination had the strongest correlation with

ADHD-diagnosis, followed by the soft-signs examination, whereas the parents' description had a weak correlation with ADHD. The total sum of the soft-signs examination, the examination by the physical education teacher and the parents' description gave an excellent prediction of ADHD-diagnosis.

In summary the neurological examination studied was found to be a reliable and valid measure of motor function that can be recommended for clinical use. A correlation was found between ADHD and motor dysfunction according to the neurological examination as described by I. C. Gillberg (1985).

Discussion

Motor control and perception problems have been considered to reflect brain dysfunction more reliably than purely behavioural variables like impulsivity or oppositional behaviour. Various neurodevelopmental tests have been used to assess not only gross neurological deviances but also subtle problems often called soft neurological signs (C. Gillberg & Kadesjo, 2003). The terms minor neurological dysfunction or minor neurodevelopmental deviations both abbreviated MND have also been used (C. Gillberg & Kadesjo, 2003). MND has been used in contexts where motor dysfunction has been regarded as a sign of a neurological disorder. The concept of Developmental Coordination Disorder (DCD) was introduced in DSM-III-R 1987 (APA, 1987). DCD is applied if the subject has substantial difficulties in performing daily activities requiring motor coordination, difficulties that significantly interfere with academic achievement or activities of daily living. Different assessment methods for the evaluation of DCD have been developed (C. Gillberg & Kadesjo, 2003). Some tests, like the test used in the present study, have been used by physical education teachers in school settings (Ericsson, 2003). When motor dysfunction is seen as a marker of neurological dysfunction, very subtle deviances not leading to problems in daily activities might nevertheless be of interest in contrast to the DCD concept where the criteria require demonstrating that there are problems in everyday living. In the Nordic countries the concept of deficits in attention, motor control and perception (DAMP) (I. C. Gillberg & C. Gillberg, 1988) has been used to emphasise that problems with motor control and/or perception are important as markers of neurological dysfunction among children with attention deficit disorder. DAMP is nowadays defined as a condition in which Attention Deficit Hyperactivity Disorder (ADHD) and DCD are both present (C. Gillberg & Kadesjo, 2003). Several Swedish studies have shown that about 50% of children with ADHD also meet criteria for DCD and thus fulfil criteria for the diagnosis of DAMP. Children with DAMP have been shown to have poorer outcomes than children with either ADHD only or DCD only (C. Gillberg & Kadesjo, 2003). The concept of DAMP has been criticized by some researchers, and Leung and Connolly even imply that motor functioning is unaffected in patients with ADHD (Leung & Connolly, 1998). A further criticism against the concept of DAMP is that problems with motor coordination are not specific to ADHD. C. Gillberg & Kadesjö (2003) have for example found a strong link between motor control problems and Asperger syndrome. Increased rates of behaviour problems, affective disorders, school adjustment difficulties and social problems have been reported in children with

motor control problems, and clumsy children are reportedly more introverted and have less self-confidence with respect to physical and social skills (C. Gillberg & Kadesjo, 2003). In a study by Erlenmeyer-Kimling et al (2000) a relation was found between schizophrenia-related psychosis in adulthood and childhood deficits in motor skills among the offspring of schizophrenic patients. So called overflow-movements have been studied, e.g. when a child performs the Fog test, and have been found to discriminate hyperactive children from controls (Denckla, 2003).

The reason for the discrepancy in the estimation of degree of motor dysfunction in patients with ADHD could be the result of examining different populations, using different tools of assessment and using methods with poorly examined reliability and validity (Steger et al., 2001). In Sweden, a battery of neurological tests developed by C. Gillberg and his co workers for detecting soft neurological signs (C. Gillberg, 1983), has been used clinically and in several studies. Aspects of reliability and validity of this kind of examination were originally studied by C. Gillberg and his group, but replication is needed.

The results of the present study imply that motor function of the type called “soft signs” can be assessed in a reliable and valid way by using the studied variant of neurological examination. Children with ADHD were found to have more motor dysfunction than children without a diagnosis. Motor function has been shown to correlate strongly with ADHD symptoms and Christopher and Carina Gillberg have formulated the concept of DAMP (Deficits in Attention, Motor control and Perception) (I.C. Gillberg C. Gillberg, 1988) to identify children with a combination of ADHD and motor dysfunction who they believe have a poorer prognosis than children with ADHD without motor dysfunction (C. Gillberg, Hellgren, L., 1996; I. C. Gillberg & C. Gillberg, 1988). The items standing on one leg, hopping on one leg, alternating jumps and finger opposition were found to have the highest degree of interrater reliability. The different parts of the Prechtl’s test had mostly zero answers and thus had a bad resolution. The items in Prechtl’s test can thus be questioned as being useful in detecting so called “soft signs” when examining children with a suspicion of ADHD and/or DCD. Prechtl’s test was developed for examination of children with severe motor dysfunction such as cerebral palsy and might not give usable results when used to examine children with mild to moderate motor dysfunction. When the neurological examination was compared with results from the examination by the physical education teacher, the neurological examination was found to predict motor dysfunction according to the physical education teacher with reasonably good sensitivity and specificity. This is interesting since several items in the examination performed by the physical education teacher remind us of every-day motor performance and sports activities of the kind that usually are discussed when defining the concept of DCD, whereas the items in the neurological examination more nearly define problems of the kind defined as MND (C. Gillberg & Kadesjo, 2003). The findings in the present study imply that there is a reasonably good, although not perfect, association between the two concepts. Since the results of the examination by the physical education teacher and the neurological examination both correlate with ADHD-symptoms but do not correlate perfectly with each other, it seems likely that combining both kinds of

examination will give a better understanding of the child's motor function than performing only one of the examinations.

Limitations: There might be a weakness in the procedure, when video-tapes of neurological examinations are made, tapes that are then viewed by different raters who score the results. The results depend to a certain degree on the quality of the video-tapes. Mostly the quality was estimated as good. There might be a difference between a direct examination and an assessment based on viewing of a video-tape. When doing a direct examination the examiner him/her self gives the instructions to the child. Different examiners might do so in different ways that affect the results. Training raters together would probably improve the inter-rater reliability.

Conclusion

Motor function seems to be of relevance when examining children with ADHD as there is a strong correlation between ADHD and motor dysfunction as described by C. Gillberg (2003). The study shows that motor function can be assessed in a reliable and valid way. Combining the neurological examination with the kind of examination performed by the physical education teacher seems to give a better description of the child's motor functions than does either of the examinations used alone.

CONCLUSIONS AND A HYPOTHESIS:

The present study shows that ADHD symptoms among children have important associations with neurophysiological factors, thereby supporting the assumption of neurobiological correlates of ADHD. A low blood-flow at rest was found in the right frontal lobe. Furthermore two different functional networks, one fronto-temporal network associated with behavioural symptoms and one thalamo-temporo-cerebellar network associated with motor functioning were studied.

The study does not give support to the idea that ADHD symptoms among children are a mere consequence of bad parenting. The finding that pharmacological treatment improves the child's ADHD symptoms and at the same time improves the well-being of the parents and normalizes the family function is also difficult to reconcile with this idea.

The hypothesis that ADHD could constitute a slow pace of development, a maturational lag, among children otherwise quite normal in their development is not supported by this study, as ADHD did not correlate with age and with maturity dependent variables. The concept of immaturity as parents and teachers describe it seems to be a concept hard to interpret. Immaturity had, for instance, a positive correlation with low cognitive function, and low cognitive function does not show much of catch-up with increasing age. Many researchers have described differences in neuroanatomy and neurophysiology in individuals with ADHD that are not comparable with normal findings in younger individuals.

Children with ADHD have motor dysfunction in higher frequency and degree than children without ADHD and assessing motor function is highly relevant as children with a severe degree of ADHD usually have poorer motor function than children with mild degree of ADHD. The study shows that motor dysfunction of mild to moderate degree (so called soft signs) can be examined in a reliable and valid way according to the scheme originally developed by Christopher Gillberg, a scheme that has been much used in Sweden.

A hypothesis formulated from the results is that some children with ADHD have a dysfunction of the cerebellum, temporal lobes and sub cortical areas (basal ganglia and thalamus) correlated with motor dysfunction. According to C. Gillberg & Kadesjo, (2003) children with ADHD and motor dysfunction often have social difficulties of Asperger-type. These children seem to have DAMP according to Gillberg and it seems reasonable that this group of children might have a bad prognosis concerning social functioning and school-achievements. The results give support to the value of performing neurological examinations when diagnosing ADHD. The children with motor dysfunction (DCD) seem to be at greater risk of having a severe and co morbid ADHD and seem to have an especially high risk of having social difficulties of the type seen in Asperger's syndrome. Is there something like a "social ataxia" in a group of children with DAMP who show a deviant functioning in cerebellum, thalamus and basal ganglia? Could this be mediated by difficulties in imitating behaviour, often considered to be primarily a motor function with participation of so called mirror neurons in the frontal and temporal lobes (Iacoboni & Dapretto, 2006) ?

These results point to important interactions between biological factors, like those causing ADHD- on the one hand and social factors, like family interaction, on the other. Further research in these areas seems important.

Appendix I. Neurological examination with determination of “soft signs” according to a scheme developed by C.Gillberg. Items with the scores used.

- Diadochokinesis right and left hand: 0-2 respectively
>10 alternating hand movements/ 10 seconds with smooth movements and deviation of arm from body less than 5 cm required for 0. Jerky movements or deviation of arm from body > 5cm but < 15 cm scored as 1. < 10 alternating hand movements/ 10 seconds or deviation of arm >15 cm scored as 2.
 - Standing on right and left leg: 0-2 respectively
managing >60 seconds, scored as 0, > 10 seconds but with difficulty, unsteadiness, scored as 1, managing < 10 seconds or more than one interruption, scored as 2.
 - Hopping on right and left leg: 0-2 respectively
Hopping 20 times on the same place; < 12 seconds scored as 0. Big movements of arms and body or one interruption, scored as 1. >1 interruption, very jerky movements, not managing to remain in the same place or not being able to lift foot entirely from the floor, scored as 2.
 - Prechtl – choreatic movements (rapid involuntary movements) right and left hand: 0-2 respectively
 - Prechtl – athetotic movements (slow involuntary movements) right and left hand: 0-2 respectively
 - Prechtl – spooning (hyperextension of metacarpo-phalangeal joints and flexion of wrist) right and left hand: 0-2 respectively
 - Prechtl (standing with arms forward with palms of the hands downwards for 20 seconds with eyes closed and tongue protruding from mouth) tremor right and left hand: 0-2 respectively
- Prechtl; No problems standing 20 seconds, scored as 0. Slight difficulties scored as 1. Obviously deviant, scored as 2.
- Walking on heels: 0-2
No problems, scored as 0, more than small symmetric movements of arms or asymmetric arm position, scored as 1, flexion of elbow > 60 degrees or abduction and movements of lips and tongue, scored as 2.
 - Fog’s test (walking on lateral border of feet): 0-2
No problems, scored as 0, more than small symmetric movements of arms or asymmetric arm position, scored as 1, flexion of elbow > 60 degrees or abduction and movements of lips and tongue, scored as 2.
 - Bishop’s test (tracking with a pencil between two quadrates, one inside the other, done with both hands simultaneously): 0-2
< 5 line crossings on paper (drawing on area between the two squares), scored as 0, > 5 line crossings on at least one side but difference between left and right <= 6, scored as 1, difference between number of line-crossings for left and right hand > 6, scored as 2.
 - Alternating jumps with one leg forward the first jump, and then the other, etc: 0-2.
 - Alternating jumps, crossed, with one arm thrown forward the same time as the contra lateral leg is thrown forward, and then the opposite arm and contra lateral leg are thrown forward, etc: 0-2.

- Finger opposition: the thumb is opposed to one at the time of the other fingers, left and right scored together: 0-2.

Appendix II. Items on the MUGI- examination performed by the physical education teacher in the school-study.

- Track of gymnastics
- Imitating movements
- Alternating jumping left-right foot forward
- Walking with toes pointing outwards
- Standing on one leg
- Hopping on one leg
- Skip Jump (jumping two times forward with one foot in front of the other and then changing to keeping the other foot in front of the first and jumping two times forward and then continuing in the same way jumping two times before changing foot).
- Bouncing with a ball
- Throwing and catching a ball

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Sammanfattning på svenska (Swedish summary)

Syftet med avhandlingen har varit att studera olika biologiska och sociala faktorer av betydelse för diagnosen aktivitets- och uppmärksamhetsstörning (ADHD). Den första artikeln behandlar sambandet mellan, å ena sidan neurofysiologiska faktorer i form av regionalt cerebralt blodflöde och EEG, och å andra sidan barnets ADHD-symptom enligt föräldraskattningar, motorisk funktion enligt motorisk neurologisk undersökning samt utvecklingsmässiga avvikelser (så kallade "minor physical anomalies"). Den andra artikeln handlar om bedömningar av familjeinteraktionen i familjer med ett barn med ADHD och hur familjeinteraktionen och föräldrarnas psykiska mående förändras efter tre månaders behandling av barnets ADHD-symptom med amfetamin. Den tredje artikeln handlar om olika mått på omogenhet hos barn och hur dessa relaterar till ADHD-symptom, kognitiv nivå samt motorik. Den fjärde artikeln beskriver en undersökning av reliabiliteten och validiteten vid motorisk-neurologiska undersökningar enligt ett schema utarbetat av Christopher Gillberg och medarbetare i Göteborg, och som använts runtom i landet i samband med utredningar av barn med misstänkt ADHD-problematik.

I den första artikeln beskrivs undersökningar av 30 barn i åldern 6-11 år med diagnosen ADHD. Barnen undersöktes med föräldraskattningar av barnets ADHD-symptom, motorisk-neurologiska undersökningar, undersökning av utvecklingsavvikelser hos barnet (MPA), bestämning av begåvningsnivån genom kognitiv testning, magnetröntgenundersökning av hjärnan, mätning av regionalt cerebralt blodflöde samt EEG-undersökning med kvantitativ frekvensanalys. Inga anatomiska avvikelser från det normala sågs på magnetröntgenundersökningarna. EEG-undersökningarna visade måttligt ökat inslag av långsam aktivitet hos 10 av 26 undersökta barn (4 bortfall). Blodflödesstudien visade ett samband mellan lågt viloblodflöde i höger pannlob och ADHD-symptom enligt föräldrasedömning. Förekomst av utvecklingsmässiga avvikelser hos barnet hade ett samband med lågt blodflöde i pannloberna på båda sidor. Två funktionella nätverk kunde identifieras, ett nätverk omfattande pannloberna och hjässloberna som hade samband med ADHD-symptom och beteendevikelser, och ett annat omfattande lillhjärnan, tinningloberna, thalamus och basala ganglierna som hade samband med motorik och kognitiva förmågor.

Den andra artikeln beskriver undersökningar av 43 barn i åldern 6-12 år med diagnosen ADHD som behandlats med amfetamin. Barnen undersöktes före och efter tre månaders läkemedelsbehandling. Föräldrar och lärare fick skatta barnets beteende och förekomst av ADHD-symptom. Föräldrarna fick skatta familjefunktionen genom att fylla i familjediagnostiska formulär och sitt eget psykiska mående enligt ett formulär. Familjerna videofilmades i samband med olika familjeuppgifter. Dessa undersökningar gjordes om efter tre månaders behandling med amfetamin. De videoinspelade banden skattades av oberoende

skattare med användande av två olika familjediagnostiska instrument. Familjestudien visade att familjerna hade signifikant fler tecken till brister i familjefunktionen jämfört med tidigare undersökta kontrollfamiljer och att familjefunktionen förbättrades signifikant efter att barnet behandlats med amfetamin i tre månader, samtidigt som barnets ADHD-symptom minskade. Föräldrarnas psykiska mående förbättrades också. Detta ger stöd åt tanken att barnets ADHD-symptom utgör en belastning för familjesystemet och att familjefunktionen förbättras då barnets symptom minskar till följd av amfetaminbehandlingen.

Den tredje artikeln (kompletterat med en opublicerad studie) baserar sig på en undersökning av 251 normala skolbarn i åldern 6-9 år. Föräldrar och lärare fick fylla i formulär gällande ADHD-symptom, barnen undersöktes av idrottslärare enligt ett speciellt undersökningsschema (MUGI) och barnens skelettålder bestämdes genom röntgenundersökning. Tjugotre av dessa barn undersöktes närmare med frågor till föräldrar och lärare gällande barnets mogenhet, begåvningsstestning, motorisk-neurologisk undersökning samt anamnes från föräldrar och lärare för att fastställa en eventuell ADHD-diagnos hos barnet. Faktorer som utgör ett mått på allmän biologisk mogenhetsgrad, såsom längd, vikt och skelettålder, uppvisade inte något samband med ADHD-symptom hos barnen. ADHD-symptom, motoriska svårigheter och låg begåvning hade ett samband med föräldrars och lärares skattningar av barnet som omoget. ADHD-symptomen skilde sig inte mycket mellan de tre undersökta åldersgrupperna, medan skelettåldern gjorde det. Dessa resultat talar inte för ett tydligt samband mellan ADHD-symptom och tecken till allmän biologisk omogenhet.

Underlaget till den fjärde artikeln utgörs av 35 barn 5½-11 år gamla med och utan misstänkt ADHD som videofilmats i samband med motorisk-neurologisk undersökning, 20 barn 6-9 år gamla som undersöktes med motorisk-neurologisk undersökning vid två tillfällen med fyra veckor mellan undersökningarna, samt 112 barn 5½-9 år som undersöktes med motorisk-neurologisk undersökning och där föräldrarna intervjuades om barnets motoriska utveckling. De videoinspelade motorisk-neurologiska undersökningarna bedömdes av fyra olika läkare och interbedömarreliabiliteten bestämdes. Test-retest reliabilitet bestämdes utgående från undersökningarna med fyra veckors intervall. Intern konsistens bestämdes utgående från samtliga undersökta barn. Undersökningens validitet skattades genom jämförelse med föräldrabeskrivning av motoriken samt jämförelse med idrottslärares bedömningarna för skolbarnen (med MUGI) där sådana uppgifter fanns. Reliabiliteten och validiteten för denna variant av motorisk-neurologisk undersökning bedömdes som god.

En hypotes utgående från resultaten, är att det finns en subgrupp av barn med ADHD som har mycket utfall på den motorisk-neurologiska undersökningen och som har avvikelser i ett cerebralt nätverk omfattande lillhjärnan, tinningloberna och centrala delar av hjärnan, som motsvarar den grupp som Christopher Gillberg beskrivit som barn med DAMP och som befunnits ha avvikelser gällande bland annat social förmåga med drag av Aspergers syndrom. Denna subgrupp kanske har nedsatt aktivitet i delar av hjärnan som är viktiga för social interaktion (såsom delar av tinningloberna och delar av det

motoriska systemet), så att de har en form av social koordinationsstörning jämte sin motoriska koordinationsstörning.

Det aktuella avhandlingsarbetet visar på viktiga relationsmässiga och biologiska faktorer hos barn med ADHD, med intressanta interaktioner då det gäller ADHD-symptom och familjefunktion. Det finns påvisbara neurofysiologiska avvikelser hos barn med ADHD, dels sådana som har samband med ADHD-symptomens svårighetsgrad, dels sådana som har samband med motoriska och kognitiva svårigheter. ADHD-symptomen kan knappast förklaras endast utgående från föräldrarnas bemötande av barnet. ADHD-symptomen utgör förmodligen inte endast en långsam biologisk utveckling hos vissa barn som somliga föreslagit. Den i vårt land mycket använda metoden för motorisk-neurologiska undersökningar av barn utarbetad av Christopher Gillberg, har i den aktuella studien visat sig ha god reliabilitet och validitet och kan rekommenderas för forskning och kliniskt bruk.