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Brain Maturation, Cognitive Tasks, and Quantitative Electroencephalography: A Study in Children with Attention Deficit Hyperactive Disorder

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To my Parents, Souad Barakat and Mohamed El-Sayed

To Ashraf, Mahinour and Menat-Allah

LIST of PAPERS

This thesis is based on the following six papers, referred to in the text by their Roman numerals (I-VI).

I. Birgitta Steffensson, Jan-Olov Larsson, Ingegärd Fried, Eman El-Sayed, Per-Anders Rydelius, Paul Lichtenstein. Genetic disposition for global maturity: an explanation for genetic effects on parental report on ADHD. *Inter J Behav Develop* 1999, 23(2):357-374

II. Jan-Olov Larsson, Paul Lichtenstein, Ingegärd Fried, Eman El-Sayed, Per-Anders Rydelius. Parents' perception of mental development and behavioral problems in 8-9 year old children. *Acta Pediatrica* 2000, 89:1469-73

III. Eman El-Sayed, Ingrid van't Hooft, Ingegärd Fried, Jan-Olov Larsson, Kerstin Malmberg, Per-Anders Rydelius. Measurements of attention deficits and impulsivity: A Swedish study of the Gordon Diagnostic System. *Acta Pediatrica* 1999, 88:1262-8

IV. Eman El-Sayed, Jan-Olov Larsson, Hans E. Persson, Per-Anders Rydelius. Altered cortical activity in children with attention deficit/hyperactivity disorder during attentional load task. *J Am Acad Child Adolesc Psychiatry* 2002, 41(7):811-819

V. Eman El-Sayed, Jan-Olov Larsson, Hans E. Persson, Elisabeth Berg, Per-Anders Rydelius. Specific QEEG patterns during delay task in children with attention deficit/ hyperactivity disorder. (*Submitted, 2002*)

VI. Eman El-Sayed, Jan-Olov Larsson, Hans E Persson, Paramala J Santosh, Per-Anders Rydelius. "Maturational Lag" hypothesis of ADHD: An update (*Accepted pending revision, Acta Paediatrica, 2002*)

ABBREVIATIONS

ADD	Attention Deficit Disorder
ADHD	Attention Deficit Hyperactivity Disorder
APA	American Psychiatric Association
CE	Commission Errors
CPT	Continuous Performance Task
CR	Correct Responses
DRL	Differential Reinforcement of Low Rates Schedule
DSM	Diagnostic and Statistical Manual of Mental Disorders
DT	Delay Task
DZ	Dizygotic Twin
EEG	Electroencephalography
ER	Efficiency Ratio
ERP	Evoked Related Potentials
GDS	Gordon Diagnostic System
HKD	Hyperkinetic Disorders
ICD	International Classification of Diseases
MBD	Minimal Brain Dysfunction
MRI	Magnetic Resonance Imaging
MRT	Mean Complex Reaction Time
MZ	Monozygotic Twin
QEEG	Quantitative Electroencephalography
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
SPECT	Single Photon Emission Computerized Tomography
VT	Vigilance task
WCST	Wisconsin Card Sorting Test
WHO	World Health Organization
WISC-R	Wechsler Intelligence Scale for Children Revised

CONTENTS

DEFINITIONS OF BASIC CONCEPTS AND TERMINOLOGY USED IN THE PRESENT THESIS

The basic concepts used are defined according to definitions used by Mirsky, 1987; Siegel and Nurcombe, 1996; Kolb and Whishaw, 1998; Mirsky and Duncan, 2001)

Alpha band/rhythm is the EEG frequency of 8-12.5 Hz. Signified by the Greek letter α.

Amplitude of EEG activity is the voltage of EEG waves expressed in microvolts (μV). Measured peak to peak. The EEG power is the square of amplitude.

Arousal is the degree of tonic excitability, which is necessary for all cognitive activity. The reticular formation system, which is originating in the medial portions of the brain stem reticular formation and ascending in the midline and reticular nuclei of the thalamus, has a major role in mediating arousal.

Attention is a complex mental process by which the event, object or idea is selected, located, evaluated and responded to by action or movement. It has been called "the center of human performance."

Automatic processes are executed rapidly, can be accomplished simultaneously with other cognitive processes without interference, are not limited by attentional capacity, and can be unconscious or involuntary. Automatic processes are thought to be either preprogrammed or innate (including the encoding of temporal or spatial relationships, frequency monitoring, and the activation of word meaning) or practiced automatic processes (become automatic with practice).

Beta band/rhythm is the EEG frequency of 13.5 to 40 Hz. Signified by the Greek letter: β.

Consciousness is the awareness of one's own feelings, complex thought processes, and what is happening around one.

Delay aversion is based on the assumption that children are motivated to escape or avoid delay and when children are faced with a choice between immediacy and delay the children choose immediacy.

Directed attention (focus) is selected focusing of attention on one aspect of an event, i.e., without distraction from other events in the environment. Directed attention is supported by structures within the inferior parietal lobule, superior temporal gyrus and parts of corpus striatum.

EEG frequency band is a portion of EEG frequency spectrum, i.e., delta, theta, alpha, beta bands.

Effortful mental processes are slow, serial, demand allocation of attentional capacity, and by definition, are sensitive to motivation and arousal.

Encoding is defined as the comprehension of events. It involves selective attention to one event rather than another and a labeling or interpreting of information in the environment naturally and spontaneously. Encoding is supported by brain structures in and around the hippocampus and amygdala.

Epoch: A period of time in an EEG record. Duration of epochs is determined arbitrarily.

Evoked related potentials (ERPs) represent changes in the electrophysiological activity that can be recorded on the scalp and generated in the brain in response to a stimulus or in association with a movement. ERP components are considered to reflect cognitive processes associated with attention and arousal.

Executive function has been used to cover the actions of planning, inhibiting responses, strategy development and use of anticipatory, goal-directed preparedness to act, flexible sequencing of actions, maintenance of behavioral set, resistance to interference, effortful and flexible organization and mental attention, the temporal ordering of events, and their hierarchical staging into arrangements of goal and sub-goal components (Denckla, 1996; Morris, 1996; Barkley, 2001).

Expectancy helps for preparing and planning to select stimulus and respond in an accurate way.

Fast Activity is the activity of frequency higher than alpha i.e., beta and gamma activity.

Frequency: number of complete cycles of repetitive waves or complexes in 1 second and measured in cycles per second (c/s) or Hertz (Hz).

Functional neuroimaging measures either physiological properties of tissues (metabolism and/or blood flow) and or changes that occur in disease (such as functional magnetic resonance imaging [fMRI], positron emission tomography [PET], single photon emission computerized tomography [SPECT], magnetic encephalography [MEG] and quantitative electroencephalography [QEEG] and event-related potentials [ERP]).

Heritability is the proportion of the total variance that can be ascribed to genetic variations, or in other words, how much proportion of variance is accounted for by genetic variations.

Hz. Abbreviation for hertz. Equivalent: cycles per second (c/s).

Impulsive behavior means (a) responding before instructions are given or before a question is completed, (b) responding without first considering all response options, (c) failing to withhold a motor or cognitive response to an irrelevant or inappropriate stimulus, and (d) acting before considering the consequences of a socially offensive or aggressive behavior.

Impulsive responses are executed with insufficient forethought, planning, or control, and is therefore inaccurate or maladaptive.

Impulsivity might be:

> Dysfunctional impulsivity is defined as the tendency to act with less forethought than do most people which may lead the subject into difficulties ("Often I don't spend enough time thinking over a situation before I act"). Dysfunctional impulsivity includes 1) *Cognitive impulsivity* is distorted judgment of alternative outcomes, resulting in a loss of reward in the long term. 2) *Motor impulsivity* is failure to inhibit behavior, characterized by fast, inaccurate responding.

Functional impulsivity is the tendency to act with little forethought when the situation is optimal ("I am good at taking advantage of unexpected opportunities where you have to do something immediately or lose your chance") (Dickman, 1990).

P300 is a positive peak of the ERP (with a latency of about 300 ms) that is assumed to reflect a phase of post-decision processing and later stage of stimulus selection, which includes the updating of memory.

Perception action cycle refers to a recurrent excitation in a circuit including the prefrontal - executive - cortex and the sensory association cortex. This hypothetical circuit is often looked upon as the basic principle of complex action. The neuroanatomy of the circuit essentially consists of two parallel hierarchies of neural structures, one sensory (perceptual) and one motor (executive) pathway that extend through the entire length of the nerve axis from the spinal cord to the highest cortex of association and the prefrontal cortex. *Perceptual memory* constitutes conceptual, semantic, episodic, polysensory, and phyletic sensory inputs which are related to vision, audition, touch, taste, and olfaction. *Executive memory* includes conceptual outputs, plans, programs, acts, and phyletic motor, which are related to actions, behavior, and language. All these structures and functions are interlinked at all levels by reciprocal connections; feedforward and feedback operate between stages and between sensory motor structures at all levels. During the performance of new or recently acquired behavior, sensory information is processed along the sensory hierarchy. That information is thus translated into action, which is processed down the motor hierarchy to produce changes in the environment. These changes lead to sensory changes, which are processed in the sensory hierarchy and modulate further action, and so on.

Perception refers to immediate awareness or recognition of a sensory impression.

Planning is the capacity to form and execute a plan during delay period.

Quantitative electroencephalography (QEEG) comprises a computerized statistical analysis and topographic mapping of the electroencephalographic activity. The electrical activity is obtained from multiple scalp electrodes and computer processes the data. This enhances the EEG visualization by utilizing graphic display on a color video screen. The data allows

mathematical/statistical-processing procedures including analyses against a normative database.

Reinforcement or reward refers to providing the subject with a reward of some sort whenever he/she makes a correct response to a stimulus.

Response inhibition has been used to refer to three processes: inhibiting the initial prepotent response to an event so as to create a delay in responding; interrupting an ongoing response that is proving ineffective thereby permitting a delay in the decision to continue responding (a sensitivity to error); and protecting the self-directed (executive) responses that will occur within the delay as well as the goal-directed behavior they generate from disruption by competing events and responses.

Selective attention is the capacity to direct attention to a specific external or internal focus.

Self-control is a response (or series of responses) by the individual that functions to alter the probability of their subsequent response to an event and thereby changes the likelihood of a later consequence related to that event, or it is the choice of a delayed, larger reward over a more immediate, smaller one; this ignores the self-directed actions in which the individual must engage to value the delayed over the immediate reward and to pursue that delayed consequence.

Shifting attention involves sequences where there is engagement of attention on a stimulus, then the capacity to disengage from attending to this stimulus and re-engage to a new stimulus. The dorsolateral prefrontal cortex and anterior cingulated gyrus are thought to support this attentional function.

Slow EEG activity: activity of frequency lower than alpha i.e. theta and delta activities.

Stabilized attention is the consistency or stability with which the person can respond to designated "target" stimuli. It is measured by the variance of response times to correctly detected targets in the CPT. It is supported by brainstem reticular formation as well as midline thalamic structures. It supports other elements of attention.

State of regulation refers to the regulation of arousal, effort and activation. The effort system should control and scan the arousal and activation state (If the arousal level is nonoptimal, the effort system can compensate for this. The arousal system is affected by noradrenaline and serotonin (Tucker and Williamson, 1984) and its system is located in the frontolimbic forebrain; the activtaion system is affected by dopamine and acetylcholine and is located in the basal ganglia (Pribram and McGuinness, 1975); and the effort system located in the hippocampus. Motivational factors such as knowledge of results, absence-presence of the experimenter and pay-off influence the effort mechanism (Sergeant et al, 1999; Van der Meere, 1999).

Structural neuroimaging measures anatomic structure (such as radiographs, computed tomography [CT], and magnetic resonance imaging [MRI]).

Sustained attention is the ability to maintain the attention capacity for a period—vigilant attitude—not being disrupted by other stimuli in the environment. This capacity is measured independently in the visual or auditory modalities, and by means of a number of subsets increasing attentional demands such as CPT. This function is supported by brainstem reticular formation as well as midline thalamic structures.

Ten-Twenty system is system of standardized scalp electrode placement recommended by the International Federation of Societies of Electroencephalography and Clinical Neuro-physiology. According to this system, the placement of electrodes is determined by measuring the head from external landmarks and utilizing 10 or 20% of these measurements.

The relation between delay task and the cross-temporal contingencies: Cross-temporal contingencies refer to the performance of temporal structures of action, and thus in establishing temporal order in behavior or reasoning. Cross-temporal contingencies are mediated through the dorsolateral prefrontal cortex and could be between events, stimuli, particular stimuli and particular acts. The best way to study temporal structuring and cross-temporal contingencies is the delayed response task. The delay task is one of the most practical methods used to investigate the neuropsychology and neurophysiology of executive task (Fuster, 1997, 2000).

The relation between the delay task and the working memory is dependant upon the mechanisms we use to hold digits, words, names or other items in memory for a short time. (Fuster, 1997, 2000).

Theta band/rhythm is the frequency band of 4-7.5 Hz. Signified by Greek letter: θ.

Vigilance refers to "the state of maximum physiologic efficiency" i.e., the state of optimal receptivity or alertness. In a psychological context, vigilance involves tasks in which attention is directed to one or more sources of information over varying periods of time without interruption to detect small changes in information being presented (Weinberg and Harper, 1993).

INTRODUCTION

A syndrome characterized by behavioral symptoms of inattention and/or hyperactivity-impulsivity, with onset in childhood and significant impairment in two or more settings is one of the most common conditions in child psychiatry, and, undoubtedly, one of the most controversial. Two main diagnostic concepts and guidelines exist now: AD/HD from the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (APA, 1994, 2000) and the WHO's Hyperkinetic disorders (HKD) from the International Classification of Diseases (ICD-10) (WHO, 1992).

The American Academy of the Child and Adolescent psychiatry (Dulcan, 1997), when publishing practice parameters of ADHD, noted that "the literature on ADHD is voluminous." In spite of this fact, even more relevant from research over the last five years, the explanation of the disorder is still controversial.

Children showing symptoms above the threshold for a diagnosis of ADHD may suffer themselves and are risking to be looked upon as a nuisance for parents and teachers. However, AD/HD-symptoms, i.e. hyperactivity and attention deficits, could improve over time during maturation and development. From this point of view some children with a diagnosis of ADHD could show variants of normal childhood behavior with maturational trajectories that are lagging behind but will catch up. If this is so, ADHD could represent a continuum from normality at one extreme, to a severe disorder, HKD according to ICD-10, or severe ADHD of combined type, at the other extreme.

From conducting an overview of the current opinions, it was found essential to study the relation between brain maturation and ADHD using different measures that might be appropriate when assessing brain maturational trajectories in children with ADHD. From reviewing the literature and from different longitudinal studies on ADHD, we assumed a hypothesis of "maturational lag" to explain the disorder in some children suffering from ADHD. Our assumption is that ADHD symptoms and the biological phenomena associated with the symptoms are not always a disorder per se but may also be due to variations in the rates or styles of cognitive development of attention, impulse control and motor activity. This assumption is based on the fact that brain development (both structure and organization) follows special courses and trajectories throughout childhood and adolescences and is subject to different influences at different times and on the fact that changes overtime are crucial to understanding the nature of clinical problem at different ages. If so ADHD may be a

reflection of what is unacceptable to a specific culture rather than any universally grounded type of brain dysfunction. If this is the case, ADHD symptoms (in some children) may improve and resolve due to a developmental catch-up later in life if there is a supportive environment, or result in a disorder if there is longstanding psychosocial stress. Consequently, such information will be of importance for the planning of preventive and treatment approaches.

AN OVERVIEW OF CURRENT AND OLDER LITERATURE ON BRAIN DAMAGE, MBD, ADD, ADHD AND HKD

The following areas of research are overviewed: (a) Nomenclature and classification systems (b) Components of AD/HD disorder (c) Current theories explaining ADHD (d) "maturational lag hypothesis on ADHD" referring to old and current brain studies on brain development and the concept of maturational trajectories.

HISTORICAL BACKGROUND

ADHD disorder has undergone a great change over the past several decades. In 1902, Still described "a disorder of moral control." However, often referred to as the first description of today's ADHD, Still's description bears more resemblance to conduct disorder and delinquent behavior rather than to ADHD. Levin (1938) reported that only very severe restlessness was linked to lesions of the brain; the milder degrees, comparable with current diagnostic practice, were clinically linked with parenting problems rather than neurological damage.

The concepts of minimal brain damage and dysfunction were used from the 1940s to 1950 (Clements, 1966). As stated by Taylor (Taylor et al, 1987), "This view was never really founded on clinical science as ADHD symptomathology neither being more common in post-encephalitic nor those with MBD showed high rates of neurologically damaging events. Moreover, the majority of children with a diagnosis of ADHD do not show the developmental abnormalities (such as motor delays and language delays) that have been proposed as the validating criteria."

From the 1960s to the 1970s many authors described the behavior resulting from minimal brain dysfunction and not from damage (Rutter, 1982).

Over the last thirty years the syndrome has changed its name from "problems of motor inhibition, hyperactivity" (hyperkinetic reaction to childhood) in Diagnostic and Statistical Manual of Mental Disorders, DSM-II, (APA, 1968) to "problems in attention" (ADD) in DSM III (APA, 1980) to include problems of both "inattention and hyperactivity" in DSM-III R (APA, 1987).

The current DSM-IV (APA, 1994) defines attention deficit-hyperactivity disorder (AD/HD) as a psychiatric disorder involving pervasive symptoms of inattention and/or hyperactivity-impulsivity causing impairments to the children. It is observed in 3-5% of children prior to the age of seven. In community samples the male to female ratio is 3:1, while

among clinically referred cases the ratio is more likely to be 6:1 or even 9:1 (Gaub and Carlson, 1997). Three subtypes of AD/HD are recognized: predominantly inattentive, predominantly hyperactive-impulsive, and a combined subtype. The WHO's Hyperkinetic Disorders (HKD, ICD-10, 1992) does not allow the diagnosis of HKD in the presence of non-externalizing comorbid disorders such as anxiety and depression.

The inclusion criteria of the DSM-IV and the ICD-10 differ. Indeed, both DSM-IV and ICD-10 require that symptoms or impairments to be of a pervasive nature manifesting themselves in more than one setting (both parent and school reports of ADHD symptoms).

Different epidemiological studies have added much complexity to the prevalence of the disorder. The prevalence rate in school aged children is almost 25% for the least restrictive methods for the diagnosis of ADHD to about 1% for the most restrictive methods for the diagnosis of HKD (Swanson et al, 1998; Rydelius, 1999). ADHD is conventionally estimated to occur in 3.0-7.5% of school-age children (Goldman et al, 1998), 5-10% in children and adolescents (Swanson, 1998; Scahill and Schwab-Stone, 2000; Brown et al, 2001). Permissive criteria yield estimates of up to 17% (Barbaresi et al, 2002), and up to 20% of boys in some school systems receive psychostimulants for the treatment of ADHD (LeFever, 1999).

Diagnostic issues are still further complicated by the high levels of comorbidity between ADHD and conduct disorder or affective disorders (Anderson et al, 1987; Biederman et al, 1991; Milberger et al, 1995). On the basis of a review of the literature, Brown and colleagues (2001) found that the conditions most commonly comorbid with ADHD were oppositional defiant disorder (ODD) (33%), conduct disorder (CD) (25%), anxiety disorders (25%), depressive disorders (20%), and learning disabilities (22%).

THE DIFFERENT COMPONENTS OF THE DISORDER

Inattention

There are two main subtypes of ADHD in DSM-IV, one marked by with mainly inattentiveness and the second with overactivity/impulsivity. It is possible to be given the diagnosis of ADHD according to DSM-IV without being inattentive. In the ICD-10, inattentiveness is a necessary requirement for the diagnosis.

The exact criteria for the presence of inattentiveness are very similar in ICD-10 and DSM-IV. Six or more problems need to have persisted for at least six months to a degree that is maladaptive and inconsistent with the child's developmental level.

Overactivity

Overactivity (hyperactivity) means simply an excess of movements. In the DSM-IV, hyperactivity refers to the following activities: leaving a classroom seat when remaining seated is expected; running around when it is inappropriate; talking excessively; having difficulty in playing quietly. Other items include fidgeting with hands or feet and talking excessively where fidgeting and talking are inappropriate at home, school, play, study etc.

In research (such as Porrino et al, 1983; Prendergast et al, 1988; Teicher, 1996) hyperactivity has been looked upon as excess movement and mainly as a mechanical overactivity that could be recorded objectively. This overactivity is increased in ADHD children in most of the situations, including sleep. In a few settings (unstructured free play and lunchroom activities), the activity of the hyperactive children is not significantly different.

Impulsivity

Johanson et al (2002) proposed that the concept of impulsiveness has both a motor and a cognitive component. "Motor impulsiveness" is presently defined as bursts of responses with short inter-response times. This behavior has been shown to emerge in children with ADHD (Sagvolden et al, 1998a, b). "Cognitive impulsiveness" implies that private events like thoughts and plans are dealt with for short sequences of time with rapid shifts, resulting in problems generating and following plans, problems organizing own behavior, and forgetfulness and inefficient use of time (Brandeis et al, 1998; Oosterlaan and Sergeant, 1998; Rubia et al, 1998)

Problems of executive or higher control functions (Barkely et al, 1992) mediated by the frontal lobes have been made responsible for the impulsive features in ADHD. These impulsive features include motor inhibition deficits, prepotent response style, delay aversion, altered reinforcement, poor protection from interference, poor strategic flexibility, poor planning, poor working memory, failure to effectively monitor behavior, and a deficit in cross-temporal contingencies (Barkely, 1997; Fuster, 2000; Rubia et al, 2001; Rubia and Smith, 2001).

Response inhibition was proposed as a result of a complex sequence of neural excitations and inhibitions (Sagvolden and Sergeant, 1998). Poor inhibitory control is thought to underpin ADHD children's dysregulation (Barkley, 1997; Bayliss and Roodenrys, 2000) while delay aversion is the characteristic of the motivational style (Haenlein and Caul, 1987; Johanson et

al, 2002). The delay aversion model is based on the assumption that ADHD behaviors are a functional expression of an underlying motivational style rather than the result of a dysfunction of regulatory mechanism. ADHD children are motivated to escape or avoid aversion (Snouga-Barke et al, 1992 and Snouga-Barke and Taylor, 1992; Sonuga-Barke et al, 1994). Over-rapid responsiveness could be explained by the reward immediacy (i.e., impulsive children were more likely to respond for a small immediate reward than they were when the reward was larger, but delayed) (Rapport, 1986, 1988) or maladaptive and unconditional preference for response (Gordon, 1979).

Altered reinforcement mechanisms and a shorter delay of reinforcement gradient (i.e., the time interval between response and reinforcer is commonly known as the "delay of reinforcement gradient" or simply as the "delay gradient") have been argued to be responsible for features of ADHD (Sagvolden and Sergeant, 1998; Sagvolden et al, 1998; Tripp and Alsop, 1999). Planning is the ability to "look ahead," to construct a plan, and to evaluate and monitor execution of a plan (Goel and Grafman, 1995; Lezak, 1995). A deficit in planning was found in ADHD children (Klorman, et al, 1999).

DIFFERENT THEORIES EXPLAINING THE DISORDER

In response to controversy about the validity of ADHD and the apparent rapid increase in its prevalence in the 1990s, investigators have attempted to formulate different theories to explain the disorder. These theories refer to a neurobiological origin or a psychological origin or from the interaction of environmental and brain development trajectories (the difference in the brain structure and organization throughout childhood which is affected by different influences at different times).

Biological theories involve genetic contribution; several studies of family, adoption and twins have provided evidence that genetic factors contribute to a substantial portion of the phenotypic variance in the expression of ADHD (Thapar et al, 1999). There is a great international effort to identify susceptibility genes for the disorder and associated traits (Thapar, 1998). Many studies published in different countries, using twin design, have shown that ADHD symptom scores whether rated by parent or teacher are highly heritable with most estimates of heritability exceeding 0.70 (Gjone et al, 1996; Eaves et al, 1997; Levy et al, 1997; Smalley, 1997; Tannock, 1998; Neuman et al, 1999; Faraone and Doyle, 2000). Thapar et al (2000) reported that the success of these studies will depend on how well the phenotype is defined, whether ADHD is best considered as a dimension or category and whether parents'

reports of symptoms, teacher reports, or both are required. Twin analysis allows us to examine whether ADHD symptoms rated by parents and those rated by teachers are influenced by a common or separate set of genes and environmental factors (Thapar et al, 2000).

Biological theories include different types of brain dysfunction theories such as frontal lobe hypothesis, temporal lobe involvement, parietal lobe involvement, connective pathways and subcortical structures (see review Bradley and Golden, 2001).

The frontal lobe hypothesis got some support from neuropsychological studies using different psychometric tests (Barkely et al, 1992; Mariani and Barkely, 1997; Seidman et al, 1997) and prefrontal lobe support from (Fuster, 1990). Studies using brain imaging (MRI) studies have also added support to frontal hypothesis (Filipek, 1999; Rubia et al, 1999) and studies using PET also added support to the frontal hypothesis manifesting hypoperfusion in frontal areas (Lou et al, 1984; Lou et al, 1989; Lou, 1996) and low glucose metabolism in anterior frontal regions (Zametkin et al, 1990, 1993).

Studies using psychophysiological measures, such as electroencephalography (EEG) indicated that children with ADHD have a low level of arousal that is related to the prefrontal areas (Hughes and John, 1999). Also, the regulatory system for arousal and motor function is related to the subcortical structures that show dysfunctions in ADHD children (Heilman et al, 1991). More over, others found dysfunction and structural abnormality in the basal ganglia (Hynd et al, 1993; Aylward et al, 1996; Filipek, 1997; Castellanos et al, 1998). Also the caudate nucleus was found to be smaller in ADHD children (Castellanos et al, 1998), while Hynd et al (1993) and Fillipek (1999) found that the left caudate was smaller in ADHD children. Striatum dysfunction and ADHD was the interest of many studies (Castellanos et al, 1996; Filipek et al, 1997; Rubia et al, 1998).

The attention and activity processes are related to the medial aspects of the temporal lobe (Cantwell and Baker, 1991; Millichap, 1997). Parietal lobe theory of ADHD refers to the relation between inattention, hypoarousal and the parietal lobe (Voeller and Heilman, 1988). Furthermore the involvement of right posterior regions of parietal lobe was supported in other studies (Andersen, 1988; Epstein et al, 1997).

Accumulating data indicate that catecholamines, particularly dopamine and norepinephrene, have powerful influences on the working-memory functions of the prefrontal cortex (PFC). Catecholamines may modulate the degree to which the PFC is able to govern the behavior. This susceptibility of the PFC to its neurochemical environment may explain different cognitive functions (Arnsten, 1998). Excess dopaminergic activity in the striatum and/or nucleus accumbens was also suggested to be responsible for hyperactivity, and

possibly poor motor impulse control (Ernst et al, 1998). There is evidence from work in humans and primates that cognitive symptoms, including reduced capacity for delay and reduced working memory function, are mediated by the PFC, and that stimulants may act at D1 and D2 (as well as alpha 2-a noradrenergic receptors) in PFC to optimize or normalize the neurochemical environment. Low tonic stimulation of inhibitory autoreceptors leads to high phasic activity in the nucleus accumbens, and possibly other subcortical sites as well, that results in dysregulated motor and impulse control (Grace, 2001; Ruskin et al, 2001).

Neuropsychological theories attempted to explain ADHD as a disorder of executive or higher control functions. ADHD children lack attentional or strategical flexibility and display poor planning and working memory and fail to control their behavior (Barkley et al, 1992; Clarke et al, 2000). Models of disinhibition, dysregulation of thought and action were proposed (Barkely, 1997; Bayliss and Roodenrys, 2000). A number of models of deficits in the motivational style have been also proposed (Zentall and Zentall, 1983; Haenlein and Caul, 1987; Johansen et al, 2002). The delay aversion model was also proposed where there is dysfunction in motivational style and not dysregulation (Snouga-Barke et al, 1992, 1994, 1996) and choice of imadiacy (Sonuga-Barke et al, 1992). There is also evidence that effortful theory (Borcherding et al, 1988; Ott and Lyman, 1993) or acquired automatic theory (Van der Meere et al, 1999) may underline ADHD symptoms. There is also evidence for the deficit in the state of regulation theory, which includes dysregulation of three energetic systems (arousal, activation, effort) (Van der Meere et al, 1996, 1999; Sergeant et al, 1999; Kuntsi and Stevenson, 2000)

CURRENT STUDIES OF BRAIN DEVELOPMENT USING DEVELOPMENTAL TRAJECTORIES — THEIR INTERACTION WITH ENVIRONMENT AND RELATION TO MENTAL CHARACTERISTICS

ADHD/HKD has been attributed to hypotheses of a maturational lag or developmental delay. According to this concept, referring to brain maturation and development, the symptoms are supposed to be the result of a delay in maturation/development. The ability to catch up with peers has been described to be dependent partly on the number and severity of the initial symptoms. Temperamental vulnerabilities such as high activity level could interact with risk conditions (such as psychosocial stress) and aggravate the disorder (Sandberg, 1996).

An alternative to the concept of developmental delay (indicating pathology) is the concept of maturational rate (indicating a variance of normality). The maturational rate differs

markedly from child to child and it is possible that its velocity cannot be changed except within narrow limits. When the child is not able to keep up with expectations and demands from parents and teachers, the "slow" maturation (expressing itself as a difference in mental age compared to chronological age) can form the basis for stress, hyperactivity, and impulsivity. Thus, a slow maturational rate, although within the normal range, may be looked upon as a risk factor for developing behavior problems and getting a diagnosis of ADHD/HKD.

Development is progressive process from immature and inefficient to mature and efficient structures and functions. Behavioral development is dependent on brain maturation throughout infancy and childhood. There is no single universally agreed upon definition of developmental delay; moreover, the concept of developmental delay is a subjective term, that is based on many factors such as the child's previous developmental pattern, the degree of delay, and the expectations of parents and/or provider. Developmental delay or delayed global maturity involves both children with a reduced speed of development or children with a disability. The children with a reduced speed of development follow different developmental trajectories across ages compared to average children, catching up at a later age with restoration of their developmental functions to a normal level. The prognosis for later psychopathology for these children could be very different from children where the immaturity reflects a disability.

Structural maturation of individual brain regions and their connecting pathways is essential for the development of cognitive, motor, and sensory functions. The development of human brain occurs along a complex systematic schedule determined by genetic and environmental influences (Rubenstein and Rakic, 1999). The neurodevelopment of neurons, neural differentiation and migration, synaptogenesis, synaptic pruning, and myelination follow different timetables across brain regions in early childhood and adolescent and even adulthood (Huttenlocher, 1997; Rakic, 1999). The regional structural modulations, probably reflective of synaptic and dendritic remodeling, are ongoing in the brain throughout adolescence (Huttenlocher and Dabholkar, 1997).

Many researchers have also concluded that both genetic and environmental influences are important for different psychiatric disorders (see for review, Rutter and Silberg, 2002). This means that there is a genetic control on the sensitivity to the different environmental factors (Rutter, 2000). There is apparent relation between ADHD and family dysfunction (Taylor, 1991). Also particular importance of life stressors on the development of ADHD symptoms across ages was found in different studies (Champion et al, 1995). Of great importance also is

the consideration of environment and genetic interplay that underlie ADHD symptoms. The theory of nature/nurture interaction has been proposed and considered in different studies across different decades to be responsible for behavior of ADHD nature (Olsson, 1959, Rutter et al, 1997; McCrae et al, 2000; Rutter and Silberg, 2002).

The behavioral trajectories across ages have been of interest on researchers some years ago; MacFarlane (1954) described the average children from age 21 months to 14 years and studied the relation between development and the behavior. She found that behaviors usually associated with psychiatric diagnoses (for example, with criteria very similar to the DSM criteria for ADHD used today) are more common in boys than in girls and that these behaviors are declining with age. Moreover, the relation between brain maturation, behavioral outcome and educational achievement is obviously complex and undergoes continuous developmental transformations (Olsson, 1959; Fischer and Rose, 1994).

Developmental trends are also known in several of the cognitive aspects of attention (Taylor, 1995; Rebok et al, 1997). The ability to ignore distracting stimuli is found to increase with age (Enns and Brodeur, 1989). Teachers described hyperactivity in an epidemiological study in London as a way in which children can exasperate their teachers (Taylor, 1998).

The maturation in the frontal regions (involved in executive function) reaches a peak at 10.5 years and another peak between 17-21 years. Associations between the stages of brain development and behavior developmental stages of Piaget have been described (Matousek and Petersen 1973; Thatcher, 1991; Hudspeth and Pribram, 1992).

FOLLOW UP STUDIES OF ADHD SYMPTOMS

Some studies have been conducted to understand the natural course of ADHD. Follow-up studies have had controversial reports regarding persistence or remission of ADHD. Some follow-up studies documented that ADHD persists into adolescence and adulthood, however the level of persistence has been inconsistent across studies (Weiss et al, 1985; Barkley et al, 1990a; Mannuzza et al, 1988; 1993; Biederman et al, 1996; Biederman et al, 1998; Elia et al, 1999). Weiss et al (1985) reports that 36% of the children with ADHD had persistence of a full or partial DSM-III ADHD into adulthood, while Mannuzza et al (1993) found a 40% rate of persistence. Barkley et al (1990b) found that 72% of children with ADHD still met the criteria eight years later. Similarly, Biederman (1996) found that 85% of children with ADHD showed persistence of symptoms on a four-year follow-up study. A follow-up of children for ten years from preschool age to 16-17 years of age showed that ADHD children performed

more poorly on attention problems and clumsiness than did controls (Hellgren et al, 1993). Wilens et al (1994) reported that about 30% of persons with ADHD continue to have the diagnosis into adulthood and it seems probable that adults who still have ADHD may represent special cases of the disorder.

The results of the review by Elia et al (1999), which included nine studies that prospectively followed cohorts of children with ADHD until adolescence or early adulthood, indicated that symptoms of attention deficit hyperactivity disorder abated over time, but 22-85% of adolescents and 4-50% of adults who had the disorder in childhood continued to meet the criteria for its diagnosis.

Patterns of remission of ADHD were also inconsistent across different studies; however, recently Keck et al (1998) proposed that the reason for this inconsistency might be highly sensitive to the definition of remission. There are different types of remission that could be syndromatic remission (referring to the loss of full diagnostic status) or symptomatic remission (referring to the loss of partial diagnostic status), and functional remission (referring to the loss of partial diagnostic status plus functional recovery; full recovery) (Hill and Schoener, 1996; Mannuza et al, 1998).

Biederman et al (2000) studied ADHD symptoms over four years following 128 individuals and assessing them five times. The rate of syndromatic remission was 60%. Hill and Schoener (1996) estimated a rate of syndromatic remission of 65-70%. The clinical observation that hyperactivity and impulsivity symptoms tend to decline at a higher rate than inattention symptoms was supported in these two studies.

In summary, reviewing literature of longitudinal studies of ADHD children shows that some children develop well, while others still are having problems later in life. It seems as if the results are dependant on the characteristics of the samples followed. It is not easy to generalize from them and the question on comorbidity is crucial and adds controversy to the presented results.

Recently, MRI studies allowed detailed visualization of volumetric anatomical brain structure. The total brain size increase with age, however, 90-95% of the total adult brain size is already reached by first grade (Giedd et al, 1996; Reiss et al, 1996; Sowell et al, 1999a, b). White and Gray matter follows different developmental paths: Linear age-related increase in the white matter across ages 4 to 22 years (approximately 12.4% increase) (Giedd et al, 1999), and age related non-linear increase in gray matter during childhood followed by decrease through post-adolescent (Giedd et al, 1999; Sowell et al, 1999a, b). These changes in the gray matter were regionally specific, with developmental curves for frontal and parietal lobe

peaking at about age 12 and for the temporal at age 16, whereas through the 20s for the occipital lobe (Giedd et al, 1999).

The corpus callosum, a white-matter structure, continues to develop throughout childhood and adolescence or even into adulthood (Benes et al, 1994; Keshavan et al, 2002). Mylinated axons permit fast propagation of neuronal impulses that are important for normal cognitive and motor development. Myelination is known to occur through adolescence and thought to extend into the third decade (Yakovlev and Lecours, 1967; Giedd et al, 1996; Sowell et al, 1999a). Increase in cerebral cortex size and corpus callosum with age and decrease in signal intensity occur with maturation (Keshavan et al, 2002). It has been found that the size of the anterior region of the corpus callosum (Rostrum) to be small in ADHD children (Giedd et al, 1994; Semrud-Clikeman et al, 1994).

The caudate nucleus abnormality (volume or asymmetry) in ADHD children has been inconsistent between different studies (Baumeister and Hawkins, 2001). There are studies, which state that the caudate nucleus was smaller in ADHD children compared to controls (Filipek et al, 1997) while others stated no such difference (Aylward et al, 1996; Castellanos et al, 1996). There is a lot of conflict in whether the normal caudate is asymmetric or not and whether this asymmetry favors the right (Castellanos et al, 1996) or the left side (Filipek, 1997; Mataro et al, 1997). The basal ganglia, which constitutes both globus pallidus and substantia nigra pars reticularis, was also studied in relation to ADHD children; it was found that the globus pallidus is smaller than controls in ADHD children but these differences were on the left side in Castellanos et al (1996) and in the right side in Aylward et al (1996).

John and associates (1980, 1983) have developed a database of QEEG features obtained from a large sample of normal children between the ages of 6 and 17 years. They used a process called neurometrics to compare these normal children with a large sample of children with learning disorders and neurological disorders. The neurometric QEEG technique (computer assisted) is a sensitive indicator of cortical electrophysiological dysfunction in children and adults with neurological and/or psychiatric disorders (John et al, 1977, 1988). The age-regression QEEG equations developed by this group replicated the earlier work of Matousek and Petersen (1973) have been extensively replicated by others, and have been found to be free of cultural and ethnic bias (Harmony, 1988; Alvarez et al, 1989; Lopes da Silva, 1990). A recent review documents the clinical utility of both conventional and neurometric QEEG in adult and child psychiatric disorders (Hughes and John, 1999).

AIM OF THE THESIS

GENERAL AIM

The aim of this thesis is to study aspects of slow mental maturation in children with ADHD. From an overview of the literature discussing "maturational lag" concept, the aim was also to challenge the current opinions of ADHD as being just a brain disorder. This has been done in the following aspects:

- The association between ADHD and global maturity was tested using a genetic factor as a co-mediator in a study of twins.
- The association between the ADHD and the global maturity was tested using a questionnaire given to the parents "a global maturity parent's scale".
- After checking the Gordon Diagnostic System for use in Sweden, the GDS was used to test attentional and impulse control capacities in Swedish children with ADHD versus controls.
- The GDS was used to study the brain processing activity in children with ADHD and controls using QEEG techniques during attentional load.
- The Delay Task of GDS was used as a "mental stress task" to study the brain processing activity according to QEEG in children with ADHD compared to control children.

SPECIFIC AIMS

STUDY I

The aim of this study was to test the association of ADHD and global maturity using a twin design. There were three sub-aims:

1. To evaluate the importance of the genetic factor for both ADHD, global maturity factor
2. To evaluate the relative importance of genetic and environmental effects for ADHD and the global maturity factor
3. To evaluate the association between ADHD and global maturity

STUDY II

The aim of this study is to investigate how parents' perceptions of maturational status in a nationwide sample of 8-9 year-old children from the Swedish twin register are related to behavioral symptoms according to the Child Behavior Checklist (CBCL) and ADHD using

DSM-III-R criteria. The rationale for the study is that knowledge about parent's ideas about maturity and behavior problems are important from a child psychiatric point of view with respect to how to inform about diagnoses and promote interventions.

STUDY III

The aim of this study was to test if the Gordon Diagnostic System is an appropriate psychometric tool to assess attentional capacities and impulse control in Swedish children across age. The specific questions were:

1) Have Swedish children with ADHD scores on the GDS that are different compared to chronologically age-matched children without ADHD?
2) Does the Swedish children's performance on the GDS tasks resemble that of the children in the American standardization group?
3) How are the GDS test results related to age and gender?

STUDY IV

The aim of the this study was to compare the data of brain information processing using the QEEG technique in children with ADHD and controls at age 6-16 years during an attentional load task. The hypothesis was that children with ADHD should display specific brain activity patterns compared to controls.

STUDY V

QEEG was used to register the nature of neurophysiological brain information processing in children with ADHD compared to controls in during performance of the Delay Task. The assumption was that children with ADHD compared to the controls and performing the DT compared to rest, would display a different electrophysiological pattern in the form of an increase of slower EEG activity compared to rest in different brain regions, especially the frontal region and a decrease of brain activity power in the fast EEG frequency band.

STUDY VI

The aim of this study was to overview past and current literature aiming to study and discuss the "maturational lag" concept, challenging the current opinions of AD/HD as being just a brain disorder.

In this overview the following aspects was discussed: a.) current trends in AD/HD research; b.) reports on the persistence and remission of ADHD symptoms over time; (c.) studies on children's maturational trajectories referring to brain development and mental

characteristics; d.) the relationship of maturation to AD/HD vs. HKD, and to discuss the hypothesis that ADHD sometimes represents variants of normal maturational trajectories.

MEASURES USED IN THE THESIS

THE TWIN DESIGN (USED IN STUDY I)

The twin design analysis

The twin design gives possibilities to examine the extent to which traits and disorders are heritable, as well as to estimate the contribution of shared and non-shared environmental influences. The monozygotic twins (MZ) are genetically identical, whereas the dizygotic twins (DZ) share on average 50% of their segregating genes. MZ twins will be more similar than DZ assuming that MZ and DZ twins share environment to the same extent.

In the study, two types of analyses were used:

1) **The intraclass correlation** that represents the proportion of total variance that is due to variance between pairs (i.e., the intraclass correlation is the most direct estimates for heritability). Intraclass correlations analysis is suitable to evaluate the importance of the genetic factor for both ADHD and global maturity factor. The intraclass correlations depend on two rules:
    - If the genetic factor is important for ADHD scores, then the intraclass correlations of MZ should be higher than DZ .
    - If the genetic factor is important for Global maturity scores then the intraclass correlations of MZ should be higher than DZ .

2) **Model-fitting analysis** that helps to estimate the relative importance of genetic and environmental both for ADHD and Global maturity i.e., to cover the second and third specific aim in this study. There are two types of model fitting:

a. *Univariante model fitting* analyses estimates the magnitude of genetic and environmental effects for ADHD and Global maturity per se and it is an approach to resolve the sources of variation in twin data.

In the univariate model fitting, the variance in the phenotype is assumed to be due to three effects: The genetic and environmental effects are not measured directly and are referred to as latent variables (depicted by circles). Additive genetic (A), shared (common) environment (C), and non-shared environment (E), while, a= genetic loading, c = shared environmental loading, and e = non-shared environmental loading. While the ADHD and Global maturity in each twin pair are observed variables (depicted by circles) (Fig 1, **Study I**).

The phenotype of one of the twins in a pair can be symbolized as--Twin 1= a* A1+c*C1. The correlation between latent factors (genetic and environmental effects) are set to fixed values according to theoretical expectation and the model can be represented by the following equations: *The variance* = $a^2 + c^2 + e^2$; *Cov (MZ)* = $a^2 + c^2$; *Cov (DZ)* = $0.5 * a^2 + c^2$

b. *Bivariate model fitting* analysis to explore how genetic and environmental influences contributes to co-variation between global maturity and ADHD.

The model decomposes the variance in ADHD into: 1) Variance in common with the global maturity (A1, C1, E1); 2) Variance unique to ADHD (A2, C2, E2).

The standardized path coefficients from the model can be used to estimate how correlation between ADHD and global maturity is mediated.

The estimated phenotypic correlation between ADHD and Global maturity can be computed as r = (a_{11} * a_{21}) + (c_{11} * c_{21}) + (e_{11}* e_{21}) i.e., r = (Genetic) + (shared environment) + (non shared environment) where, the genetic, shared environmental, and non-shared environmental pathways for ADHD in common with global maturity indicate the extent to which the same sets of genes or environments are important for the two measures.

THE GLOBAL MATURITY AND BEHAVIOR SCALES

THE GLOBAL MATURITY SCALE (USED IN STUDIES I, AND II)

Background

Reviewing literature for a methodology where the global maturity of the child could be estimated by questionnaires given to the parents gave the following result: Parental estimates provide a good indication of their child's developmental status (Heriot and Schmickel, 1967; Saxon, 1975; Coplan, 1982; Keshavan and Narayanan, 1983).

Glascoe and Sandler (1995) reported that parents could provide a single, global age-estimate (how old does your child seem to you to act, overall) that had high levels of sensitivity in identifying children with likely developmental problems. Much effort has been expended in attempting to identify factors associated with greater or lesser parental accuracy. No such definitive identification has been made, although there has been some evidence that maternal education (Ewert and Green, 1957) sex of the child (Tew et al, 1974), presence of physical disability (Ewert and Green 1957; Keshavan and Narayanan, 1983) and the child's

developmental level or adaptive skills (Heriot and Schmickel, 1967) influence maternal accuracy.

Age estimates by parents could be elicited quickly, and parents, regardless of differences in levels of education and parenting experience, were equally able to provide estimates that identified children with difficulties, a finding consistent with other research on parents' age estimates (; Glascoe and Sandler, 1995; Pulsifer et al, 1994; Glascoe et al, 1991; Glascoe and Maclean, 1990; Glascoe, 1991; Glascoe, 1989).

Parental estimates validity to obtain accurate developmental information was confirmed in different studies and the questions, when asked appropriately, will avoid parental inhibition or distortions and give a valid picture of the child's developmental functioning (Carey, 1982; Pulsifer et al, 1994). Similarly, adolescents have been studied by asking about their views about their subjective age (Galambos et al, 1999). Therefore, the low age estimate in a particular domain should not be taken literally but rather as a need to explore further the nature of a child's apparent difficulties (e.g., whether the patient hears well or has adequate language, motor, behavioral self-control, or cognitive skills).

Parents global maturity scale

The parents' global maturity scale consists of two questions (Table 1). The first question was a five-graded scale with the alternatives very immature, somewhat immature, average, somewhat mature and very mature. In the second question the parents were asked to rate the child's maturational age in comparison with his chronological age. The maturity age was subtracted from the chronological age (if it is 0 then there is no difference, if it is positive then the estimated is older than the chronological age, if negative then the child is younger than what it is chronologically). The two variables were standardized (z-scores with a standard deviation of 1). The child's global maturity score was given as the sum of the results of the two variables (mean 0.0, range –3.6-3.7). Then the correlation quotient between the two variables of the first and the second question of global maturity was calculated to see if they are correlated or not. The correlation quotient between the two variables was 0.75 (N.B.: if it is one, they are most highly correlated).

The operational definition of immaturity in the present study was the parent describing the child as either according to A or B or both A and B:

Table 1. The short questionnaire to the parent(s) about the child's maturational age

1	Consider the overall maturity of your child (interests, habits and behavior). Compared to a typical child of the same age, how mature is your child?	Percentage of answer
□	Very mature	5.3%
□	Somewhat mature	20.2%),
□	Average	60.4%
□	Somewhat immature	13.2%
□	Very immature	0.9%
2	What is your view about the maturational age of your child (without thinking about the actual age)? The child is---years of age (your estimation of the maturational age).	

Boys have significantly higher means for maturity (boys = .21, girls = .18), indicating that boys are more immature than girls (t=4.92, p=.000).

Furthermore, in order to study if the global maturity parents' scale is measuring mental or physical maturity, the child's "global maturity" is correlated to the developmental milestones questionnaire also completed by parents. The Spearman Correlation Coefficient results were, as birth weight (Spearman Correlation Coefficient=0.19), age at walking (0.10), age at teething (dentition) (0.06), ability to handle scissors (0.38), and the ability to interpret a watch (0.24). These correlations values support that global maturity scale measures mental rather than physical aspects of maturation.

BEHAVIOR SCALES

THE ADHD BEHAVIOR SCALES (USED IN STUDIES I, AND II)

When the study began, DSM-IV was not introduced. The parents completed a questionnaire including 14 symptoms for ADHD according to DSM-III-R (1987) in "Yes" or "No" alternatives. (Table 1, **Study I, II**). For the calculations, "yes" was scored as 1 and "no" as 0 and then summed up in a total score. Due to a skewed distribution, the logarithm of the total score was used. A questionnaire-based diagnosis of ADHD was assigned if the parents reported eight or more symptoms according to the DSM criteria. ADHD (bivariate variable) was analyzed as the dependent variable with the maturity variable, gender and SES as the independent variables using logistic regression. Boys have significantly higher means (.83) for ADHD than girls (.68) (t=4.35, p=.000).

CBCL QUESTIONNAIRE (USED IN STUDY II)

The parents completed the Swedish version of the Child Behavior Checklist (CBCL) which includes the grouping of syndromes includes internalizing (withdrawn; somatic complaints; anxious and depressed), externalizing (delinquent behavior; aggressive behavior) and the total behavior problems score (Achenbach, 1991). Because the raw CBCL score were in a skewed distribution they were converted to logarithmic form prior to the statistical analyses.

THE GORDON DIAGNOSTIC SYSTEM (USED IN STUDIES III, IV, AND V)

To measure attention and impulsivity – A background

Compared to rating scales, objective laboratory measures play a potentially important role in assessing different aspects of attention and impulsivity. The application of computer technology to psychometric tests has received great interest as it is fast, easy, and flexible and data can be stored in cases of follow up studies (Du Paul et al, 1992; Gordon, 1993; Berger, 1994).

Continuous Performance Tests (CPTs), such as the Conners' Continuous Performance Test (Conners and MHS Staff, 1995), the Gordon Diagnostic System (GDS; Gordon and Mettelman, 1987), the Test of Variables of Attention Continuous Performance Test (TOVA; Greenberg and Dupuy, 1993), and the Mean Complex Reaction Time (MRT) by Frisk (1991) are among the used measures of attention and impulsivity in children and adults with ADHD (Newcorn et al, 1989; Barkley and Grodzinsky, 1994; Gordon et al, 1996).

CPT was originally developed to assess possible brain damage (Rosvold et al, 1956). In a common CPT paradigm, subjects are required to observe a screen for a period of 9 to 15 minutes, while a series of stimuli (typically letters or numbers) are rapidly presented. The subject is asked to respond to a target stimulus, or a pair of stimuli in sequence, by immediately pressing a button (Barkley, 1991). It has been proposed that such tasks measure the child's ability to pay attention under conditions requiring self-control (Gordon et al, 1996). There is some support for the use of CPTs in clinical practice to assess attention problems (Halperin et al, 1988; Aylward et al, 1990; Barkley et al, 1990a; Corkum and Siegel, 1993; Barkley and Grodzinsky, 1994; Inoue et al, 1998). Some researchers, however, have not found agreement between CPT measures and rating scale scores in children with ADHD (DuPaul et al, 1992).

Among those laboratory objective tests that have been used to assess impulsivity in ADHD children are the Matching Familiar Figures Test (MFFT; Kagan, 1965), Porteus Mazes (Palkes et al, 1968), Continuous Performance Test (Losier et al, 1996), Stroop Color Word Interference Test (Barkley et al, 1992), Draw-A-Line Slowly and Draw-A-Line Fast tests (Levy and Hobbes, 1979), and the competitive game developed by Atkins (Atkins et al, 1993).

Recently, Monteresso and Ainslie (1999) discussed the assessment of impulsivity. Two main procedures exist, the "Delay of Reward" paradigm and the "DRL" paradigm (differential reinforcement of low rate behavior). In the "Delay of Reward" paradigm, the subject chooses between two rewards (large or small), According to Ho et al (1998), the "Delay of Reward" paradigm is based upon a hypothesis of a deficient tolerance to wait for gratification/reward (a steep temporal discount rate). The DRL paradigm, on the other hand, is supposed to be dependant upon an inability to inhibit or to delay voluntary behavior (poor inhibitory control). The inefficient response of hyperactive children in DRL tasks could be explained either by inability to withhold response during the reinforced interval or inability to discriminate and remember that length of the time interval to be rewarded (Sonuga-Barke et al, 1998). The performance of children in such tasks is affected by the motivational factors such as knowledge of results, absence-presence of the experimenter and pay-off, and the influence of the effort mechanism (Sanders, 1983; Van der Meere, 1996).

For the following reasons, the Gordon Diagnostic System (GDS) was found to be a suitable tool to assess inattention and impulsivity in children with ADHD and controls across ages:

1. The Gordon Diagnostic System (GDS) has ten different tasks including the vigilance task and the delay task.
2. It was standardized among more than 1,400 American children and also proved effective also among Swedish children.
3. It is easily portable with a built-in computer that will not be affected by the change of software over the years.
4. It takes only about 20 minutes to perform both the vigilance and delay tasks.
5. It is easily administered and can be connected to equipment for neurophysiological measures such as QEEG without muscular artifacts.
6. The performance in the tasks is influenced by the age of the subject.

Vigilance Task (used In studies III, and IV)

The vigilance task (VT) of the GDS is a variant of the CPT, which, is a popular component in the assessment of impairment in sustained attention and impulsive behavior in children with ADHD (Barkley et al, 1990a, Barkley 1991; Kail, 1991). It requires the subject to respond to a target stimulus (visual stimuli) of a sequence of numbers "1-9" on a screen and to refrain from responding to other non-target stimulus (to test the child's ability to sustain attention for nine minutes).

Each digit appears for 200 milliseconds and is presented at a rate of one per second (Gordon and Mettelman, 1987). The rate of presentation of the stimulus is very important for the ADHD children insofar as it affects the activation state and regulation state (i.e., the child regulates his inhibition control by regulation of his activation state according to the rate of presentation of stimuli) (Van der Meere et al, 1999). The rapid rate of presentation of events activates the ADHD children and lets them perform poorly, so it is better to decrease the rate of presentation of stimuli (Douglas, 1983; Van der Meere et al, 1995). The absence or presence of the experimenter usually affects children's performance in such tests; in that absence of the experimenter will decrease the performance of the ADHD children (Power, 1992; Klinberg et al, 1997). Three scores are calculated; correct responses (CR), the number of targets missed (omissions), and the number of the incorrect responses to non-target stimuli (commission errors) (CE).

The delay Task (used In studies III, and V)

The Delay Task (DT) is based upon DRL paradigm (Skinner, 1938), which measures the ability of impulse control, inhibition control, strategic planning, motivational effect, sense of time and readiness to respond. Gordon (1979) developed a Gordon's DT version where the response has to be withheld unsignalled for 6 seconds and the reward only given when the 6 seconds have elapsed.

This test requires the child to inhibit responding in order to earn a point. The child is instructed to press a button, wait, and then press the button again. When he/she refrains from responding for at least six seconds, a light flashes and a numeric counter records the increments. When the child responds before the interval elapses, the timer resets and no point is recorded. The GDS Delay Task generates the "Efficiency Ratio" (ER) score, which represents the proportion of correct responses. The microprocessor calculates these scores for the entire eight minutes test as well as at two-minute intervals.

Hyperactive children have been shown to respond prematurely under these reinforcement conditions more often than controls and to perform inefficiently (Gordon, 1979, McClure and Gordon, 1984, Schahar and Logan, 1990; Gordon et al, 1996). DT Scores correlate with other behavior-based measures of ADHD symptoms (Gordon, 1979; McClure and Gordon, 1984; El-Sayed, 1999) and seem to detect the combined effects of medication and cognitive intervention on impulsivity (Hall and Kataria, 1992).

QUANTITATIVE ELECTROENCEPHALOGRAPHIC TECHNIQUES (USED IN STUDIES IV, AND V)

Background

Reviewing literature, we searched for a possible method to assess brain information processing capacities in ADHD and controls across ages. There are different brain imaging methods, either structural or functional imaging that permitting repeated assessment of the developing human brain. Structural imaging measures anatomic structure (such as radiographs, CT, and MRI). Functional imaging measures physiological properties of tissues (metabolism and/or blood flow) and/or changes that occur in disease (such as, fMRI, PET, SPECT, MEG and QEEG, and ERPs.

Of all the imaging modalities, the electrophysiological assessments (EEG, QEEG and ERP) were considered the most practical of these methods. They use relatively simple, inexpensive, noninvasive tools that are capable of quantitatively assessing both resting and evoked brain activity with sensitivity and temporal resolution that is superior to those of any other imaging method.

Physiological basis

EEG primarily reflects the extra-cellular current flows associated with the summated fluctuations of excitatory and inhibitory postsynaptic potentials in synchronously activated, vertically-oriented pyramidal cells of the upper layers of the cerebral cortex. Research on the origins of rhythmic electrical brain activity in the various frequency bands indicates that anatomically complex homeostatic systems regulate the EEG. Brainstem, thalamic, and cortical processes involving large neuronal populations mediate this regulation, using all the major neurotransmitters (Nuwer, 1997).

Pacesetter neurons distributed throughout the thalamus normally oscillate synchronously in the 7.5-12.5-Hz frequency range. Efferent projections globally distributed across the cortex

produce the rhythmic electrical activity known as the alpha rhythm, which dominates the EEG of an alert healthy person at rest. Nucleus reticularis can hyperpolarize the cell membranes of the thalamic neurons by gamma-amino butyric acid (GABA) release, slowing the dominant alpha rhythm into the lower theta range (3.5-7.5 Hz). Slow delta activity (1.5-3.5 Hz) is believed to originate in oscillator neurons in deep cortical layers and in the thalamus, normally inhibited by input from the ascending reticular activating system in the midbrain (Pedley and Traub, 1990; Hughes and John, 1999).

Two different but interconnected neural systems are argued to be involved in the generation of EEG within the theta and alpha frequency bands where theta activity appears to be generated within the septal-hippocampal pathway, whereas the alpha frequency involves thalamocortical and cortical-cortical circuitry (Lopes da Silva, 1996; Steriade et al, 1990). Within the theta generating septal-hippocampal pathway, the septal nucleus and the nucleus accumbens receive inhibitory modulation through dopaminergic innervation from the ventral tegmental area, via dopamine D2 receptors (DeBoer and Abercrombie, 1996; Ikarashi et al, 1997). Thus, theta excess can occur with an overactivation of the septal-hippocampal pathway or secondarily via disinhibition from negative dopaminergic regulation (Russell et al, 1995).

Excess alpha activity could be produced from the thalamocortical pathway, which receives positive modulation from the midbrain reticular formation via acetylcholine, and negative regulation through the nucleus reticularis of the thalamus via gamma-aminobutyric acid, with further modulation via the dopaminergic striatal/nigral system. Then, disregulation of this system can lead to an alpha excess by 1) hyperactivation of the thalamus that may be secondary to overstimulation of the midbrain reticular formation due to decreased modulation via the dopaminergic nigral system, or 2) hypoactivation of the prefrontal cortex and a resulting disinhibition from nucleus reticularis. Thus, both theta and alpha activity excess might result from low dopamine levels.

The faster activity in the beta band (12.5-20 Hz) is believed to reflect corticocortical and thalamocortical transactions related to specific information processing (Hughes and John, 1999). When the mesencephalic reticular formation is activated, the nucleus reticularis becomes inhibited by cholinergic and serotonergic mediation. The thalamic nuclei get released from the inhibitory effect of the nucleus reticularis so the EEG activity becomes rapid. This fast activity increases and the flow of information becomes rapid between thalamus and cortex (Pedley and Traub, 1990).

Niedermeyer and Naidu (1998) argues that the physiological basis of EEG activity in different frequency bands may be correlated to their neurophysiological model of ADHD emphasizing prefrontal, frontal, and striatal and thalamic interconnections.

QEEG Procedure

In **Study IV**, QEEG was recorded during two different recording conditions: 1.) resting state (R), eyes open with visual fixation on a small object for at least 10 minutes, and 2.) performance of the Vigilance Task (VT) of the Gordon version of the Continuous Performance Test (Gordon and Mettelman, 1988).

In **Study V**, QEEG was recorded during two different recording conditions: 1.) resting state (R), eyes open with visual fixation on a small object for at least 10 minutes, and 2.) performance of the Delay Task (DT) of the Gordon version of the Continuous Performance Test (Gordon and Mettelman, 1988).

In **Studies IV, and V,** the EEG signals were bandpass-filtered (1-30 Hz-6dB/octave), fed into a personal computer, then collected and analyzed with a 17-channel Brain Atlas IV apparatus (Bio-Logic System Corporation). The power spectrum was averaged from all epochs without artefacts to obtain the average power spectrum for all the 17 electrode positions ranging from 0.01 to 30.0 Hz with a resolution of 0.5 Hz. The average power spectrum for the EEG frequencies between 0.00 and 30.0 Hz was calculated for these epochs by means of the Fast Fourier Transform (FFT). The Bio-Logic Brain Atlas IV calculated a topographic frequency map for each ADHD subject and control. Numerical data of the FFT maps were kept for subsequent statistical analyses. The total power contained in the frequency bands—theta (4-7.5 Hz), alpha (8-12.5 Hz), and beta (beta-1 = 13-16.5 Hz; beta-2 = 17-30 Hz)—were determined.

In **Study IV**, ADHD and control group comparisons were made for the different recording conditions (R, VT) in absolute and relative EEG power spectrum of the electrodes sites (F3, F4, F7, F8, P3, P4, T3, T4, T5, T6) in theta, alpha, beta 1, and beta 2 frequency bands.

In **Study V**, ADHD and control group comparisons were made for the different recording conditions (R, DT) in relative EEG power spectrum of the electrodes sites (F3, F4, F7, F8, P3, P4, T3, T4, T5, T6) in theta, alpha, beta 1, and beta 2 frequency bands.

QEEG data analysis

The EEG data were collected using the Biological Brain Atlas program and then transformed to ASCI format for use in statistical programs to running different statistical calculations. The absolute power was converted by using the logarithmic transformation. The relative power was calculated as a percentage of total power (absolute power for a given band /total absolute power in all four bands x 100% = RPP). The RPP data were converted by using the logarithmic transformation log (RPP/100-RPP) to achieve an approximate Gaussian transformation (John et al, 1980).

STATISTICAL ANALYSIS

STUDY IV

Comparisons between the ADHD and control group were made for the different recording conditions (VT, open eyes) in absolute and relative EEG power spectrum of frontal region electrodes (F3, F4, F7, F8), temporal region (T3, T4, T5, T6) and parietal region (P3, P4) in different frequency bands (theta, alpha, beta 1 and beta 2).

The strategy in the analyses was to perform four separate four-way repeated measure ANOVAs (Davidson et al, 2000; Kirk, 1995) on the logarithms of the theta, alpha and beta 1 and beta 2 powers. The absolute and the relative power in each band in F3, F4, F7, F8, T3, T4, T5, T6, P3, P4 were used as dependent variables. *Condition* (open eyes, VT), *region* (five regions F3/F4, F7/F8, T3/T4, T5/T6, P3/P4, and *hemisphere* (two sides) as the within subjects factors and *group* as between-subjects factors. A four-way interaction would be expected. If the four-way interaction was not significant, three-way and two-way interactions were checked. If the interaction with factor group was significant, we focused on the between-group comparisons at fixed levels of the other factor(s) (in the interaction term). In each group per se (ADHD group and control), appropriate comparisons between the within factor levels were performed. For these post-hoc comparisons we set the significance level to $\alpha = 0.05$ (Cobb, 1998). In case of significant interactions, simple effects tests were performed, i.e. effects of one factor holding one or several factors fixed. The group effects in the ANOVA models were also adjusted for the covariates *age* and *gender*.

STUDY V

Relative power was calculated as a percentage of total power (absolute power for a given band /total absolute power in all four bands x 100% = RPP). As the main objective was to compare the children with ADHD with the controls in regard to the difference in DT performance compared with baseline (rest), we calculated the relative power of DT minus baseline (rest) condition for each frequency band. All analyses were then based on these differences since our focus was on the changes in activity (the reaction) between DT and rest.

The strategy in the analyses was to perform separate three way repeated measure ANOVAs (Kirk, 1995; Davidson et al, 2000) on the relative power difference variables (DT minus Rest) of the theta, alpha and beta 1 and beta 2 power. The difference variables (DT minus Rest) of the relative power in each band in F7, F8, F3, F4, T3, T4, T5, T6, P3, P4 were

used as dependent variables. *Region* [Five regions F7/F8, F3/F4, T3/T4, T5/T6, P3/P4, and *hemisphere* (two sides) were the within-subjects factors and *group* was between-subjects factor. Then we calculated the least square means of the difference variables (DT minus Rest) between the ADHD group and the control group. The 95% confidence intervals for the difference between DT and rest in different EEG frequency bands for each group were calculated. If "zero" was not included in the confidence interval, a significant difference between the tasks was found.

THE STUDY GROUP AND THE CONTROLS

STUDY I

The subjects were 1,480 pairs of twins born in Sweden between April 1985 and December 1986 (aged 8-9 years) who were identified through the population-based Swedish Twin Registry (Cederlöf and Lorich, 1978). The response rate was 75% (n=1106). The sample was divided into five subgroups: MZ girls (n=164), DZ girls (n=201), MZ boys (n=181), DZ boys (n=185) and DZ unlike sex (n=317). Both pair twins were analyzed (i.e., the twin design was used).

STUDY II

A sample from the Swedish Twin-Registery of 8-9 year-old children (n=1079) was randomly selected (525 boys and 554 girls) with only one child of each pair. In this study, no twin design was used and the children were looked upon as a representative of cohort of Swedish 8-9 year-olds. The sample studied includes 339 monozygotic twins, 685 dizygotic, and 55 undetermined zygotic.

STUDY III

A clinical sample including 61 boys and 10 girls (mean age: 10.5 years, range 6-16.9 years) who had the diagnosis of ADHD combined type (DSM-IV) was compared to a control sample of 65 boys and 23 girls (mean age 10.2 years, range 6-16.9 years) where neither parents nor teachers had reported existing behavioral problems or mental disorders.

STUDIES IV, AND V

A clinical sample (not on medication) of 31 boys and 5 girls with ADHD and a mean age of 10.51(2.6 SD) years was selected from a child and adolescent psychiatric unit (specialized to do neuropsychiatric assessments) in Stockholm, Sweden. All children met DSM-IV criteria for severe ADHD of the combined type, also meeting the criteria for HKD according to ICD-10. Children from the corresponding sex and age group were accepted as controls when neither parents, teachers, school nurses, psychologists nor school doctors reported them as having learning disabilities, behavioral problems and/or mental disorders. The control group consisted of 46 boys and 17 girls with a mean age of 10.03 ± 2.2 SD years.

RESULTS

STUDY I

When analyzing the DSM-III-R based ADHD symptoms questionnaire, boys showed significantly higher means (0.83) than girls (0.68) ($t = 4.35$, $p = 0.000$). Regarding the global maturity questionnaire boys also showed higher means for maturity than girls (boys = 0.21, girls = 0.18). This indicates that boys are more immature than girls ($t = 4.92$, $p = 0.000$).

Regarding the first aim of this study, to evaluate the importance of a genetic factor for ADHD, the intraclass correlations showed that the twin similarity was higher among MZ than DZ which means that a genetic factor is important. Similarly, the twin similarity was higher of MZ than DZ regarding global maturity, which indicates that the genetic factor was important for mediating global maturity.

Univariant analysis was used to evaluate the importance of the genetic factor and environmental effects for ADHD and global maturity. For ADHD, the genetic influences (heritability) were higher for girls (68%) than for boys (35%), while the influence of shared environment was higher for boys than for girls. For global maturity in girls the heritability (43%) and shared environment (37%) contribute to almost the same extent. For boys, the genetic effect (heritability) is very high (91%), whereas the shared environment is estimated to (0 %) and thus not contributing to maturity in boys.

To evaluate the association between ADHD and global maturity, bivariate analysis was used to investigate how much of the variance was unique to ADHD and how much was in common with global maturity. As there were significant sex differences in the etiology of ADHD and maturity, the bivariate modeling was conducted considering girls, and boys separately. The correlation between ADHD and maturity was estimated to 0.18 for girls (completely due to the genetic pathway) and 0.26 for boys (primarily to the genetic pathway).

In summary, the results of **Study I**, showed that there are at least two pathways through which genetic effects can influence ADHD, one through predisposition for maturational lag (supporting the main hypothesis) and one unique to ADHD.

STUDY II

When analyzing the CBCL-scores, it was found that “somatic” complaints and being "anxious and depressed" were more common among girls, while, attention problems, delinquent behavior, and aggressive behavior were more common among boys. In the grouping of syndromes, and as expected, girls had more internalizing symptoms while boys had more

externalizing symptoms. (Table 1, **Study II**). Of 1,079 children, 7% of the boys and 3.9% of the girls fulfilled the criteria for ADHD (p=0.03).

The parents' perceptions of their children's maturational status in relation to the indices of behavior problems according to CBCL were statistically related in the following areas: somatic complaints, being anxious and depressed, social problems, thought problems, attention problems, delinquent behavior and aggressive behavior. Statistically significant relations were found between the maturity factor and the CBCL grouping of syndromes (internalizing, externalizing) and the total behavior problems score. The range for the adjusted R-square was 0.02-0.14, highest for social problems (0.13) and attention problems (0.14) (Table 2, **Study II**). The parents' perceptions of their children's maturational status in relation to ADHD were statistically related ($p<0.001$, beta coeff=0.5, SE=0.1, z=4.7, n=492, pseudo R2=0.12).

In summary, the results of Study II support the main assumption of an association between ADHD and expressions of immaturity as estimated by the parents. Maybe the most clinically important relationships are the links between the maturity factor and a.) social and attention problems according to CBCL and b.) ADHD-symptoms according the checklist based on the DMS-III-R.

STUDY III

The aim was to assess if the GDS could be an appropriate tool to be used as an objective measure to assess attention problems (VT) and impulsive control capacities (DT) in Swedish children with ADHD and controls across ages.

The clinical sample showed significantly lower ER means (which indicates impulsivity) and lower CR means (which indicates inability to sustain attention) than both the control sample and the American Gordon standardization group in all age groups except 8-9.9 years for CR. The clinical sample had significantly higher CE means (which indicates impulsivity) compared with the two other groups, with the exception of the clinical versus the control sample in age groups 6-7.9 and 10-11.9 years. The ER, CR, and CE means of the control sample showed no significant differences compared with the American Gordon standardization group with some exception (which indicates that our control could be representative of a non referred sample (Table 2**, Study III**). When analyzing the rated GDS scores (abnormal/borderline/normal). The clinical sample compared to the control sample showed the following percentage of abnormality (63%: 14% for ER ($p<0.001$), 61%: 17% for CE ($p<0.001$); and 62%: 10% for CR ($p<0.001$). (Table 3**, Study III**).

When estimating the values of the GDS (ER, CE, and CR) to predict if a child was in the clinical sample or the control sample (all age groups together), the following areas was under the ROC-curve: 0.72 (ER), 0.73 (CE) and 0.72 (CR) When analyzing the ROC-curve areas in each age group, an age-related tendency was found (e.g. 0.90 for CR in 6-7.9 year-old children compared to 0.73 in the age group 12-16.9 years (Table 4, **Study III**). However, these differences in ROC-areas between the age groups were not statistically significant.

The sensitivities of the GDS results using cutoff points to give the best accuracy of the test when comparing the differences between the clinical and control samples were 59.2 (ER), 50.7 (CE) and 49.3(CR). The corresponding specificities were 81.3 (ER), 84.9 (CE) and 87.2 (CR) (Table 5, **Study III**).

When analyzing the GDS results in relation to age and gender, the bivariate analyses between the GDS test results and the child's age showed the following correlation coefficients (Spearman) in the clinical sample 0.20 (ER), -0.44 (CE) and 0.48 (CR) and in the control sample 0.46 (ER), -0.69 (CE) and 0.56 (CR). The multivariate analyses showed statistically significant associations between the GDS results (ER, CE and CR) and age when controlling for the sample group (clinical or control sample) and gender (Table 6, **Study III**). The multivariate analyses showed statistically significant associations between the GDS results (ER, CE, CR) and the sample group (clinical or control samples) for age but not for gender. In summary, the Gordon Diagnostic System was found to be an appropriate tool and test device for the purposes of the study.

STUDY IV

The aim was to study if children with ADHD compared to controls had different EEG frequency patterns (of a more immature type) during concentration when performing the GDS Vigilance Task.

Absolute theta activity during VT was increased in children with ADHD compared to the controls in relation to condition and hemisphere, especially in the frontal region [(F3, F4), (F7, F8)] ($p < .01$) (Fig. 1 A, B).

The ADHD group showed significantly greater absolute alpha activity compared to controls in F7 during VT ($p < .05$) (Fig. 1 C, D). With respect to absolute beta activity (Fig. 1 E, F, G, H study IV), there was significant two-way group x region interaction in absolute beta 1 activity (Fig 3 E, F) [$F (3;270) = 3.24$, $p = .022$]. There were no significant regional differences or interactions in absolute beta 2.

The ADHD group showed a significantly decreased relative alpha activity compared with controls, during open eyes condition in the left and the right hemispheres across the frontal, parietal, and temporal regions [(F3, F7, P3, T3, T5), (F4, P4, T4, T6) ($p < .05$ and $p < .001$ respectively)] (Fig 2 C, D). The ADHD group also showed a significantly decreased relative alpha power (Fig 2 C, D) compared with controls during VT in the left and the right hemisphere across the frontal, parietal, temporal regions [(F3, F7, P3, T3, T5), (F4, P4, T4, T6)] ($p < .01$ and $p< .05$ respectively). The ADHD group showed a significantly decreased beta-1 (Fig 2 E, F) power compared with controls during VT and open eyes conditions across all regions and hemispheres ($p < .001$).

The ADHD group showed a significantly decreased relative beta-2 activity (Fig.1 G, H) compared with controls during VT and open eyes conditions in the left and the right hemisphere across all regions but more significantly in the frontal region ($p < .001$).

No significant condition difference between VT and open eyes with respect to fast activity of beta-1, and beta-2 was found in the ADHD children or the controls.

A hemispheric difference was found in controls who showed significantly more activity in right hemisphere compared to left hemisphere in absolute and relative alpha power in both conditions ($p< .001$, $p< .01$, respectively). On the other hand, the ADHD group showed no significant difference between the right and left hemisphere at any frequency band in both conditions.

In summary, our hypothesis that children with ADHD compared to controls during an attentional load task would display a different pattern of frontal, parietal and temporal brain activation indicating immaturity was partially supported. The children with ADHD showed a decreased brain activity with more theta power, which might be interpreted as an indication of maturational lag as this slow activity pattern usually been found in younger children.

Fig. 1 Comparison of the means (and confidence intervals) of the absolute power for the ADHD □ and the controls ▲groups in all frequency bands in relation to condition (R = rest with open eyes; VT = vigilance task) and hemisphere. A, B theta power. C, D alpha power. E, F Beta-1 power. G, H Beta-2 power.

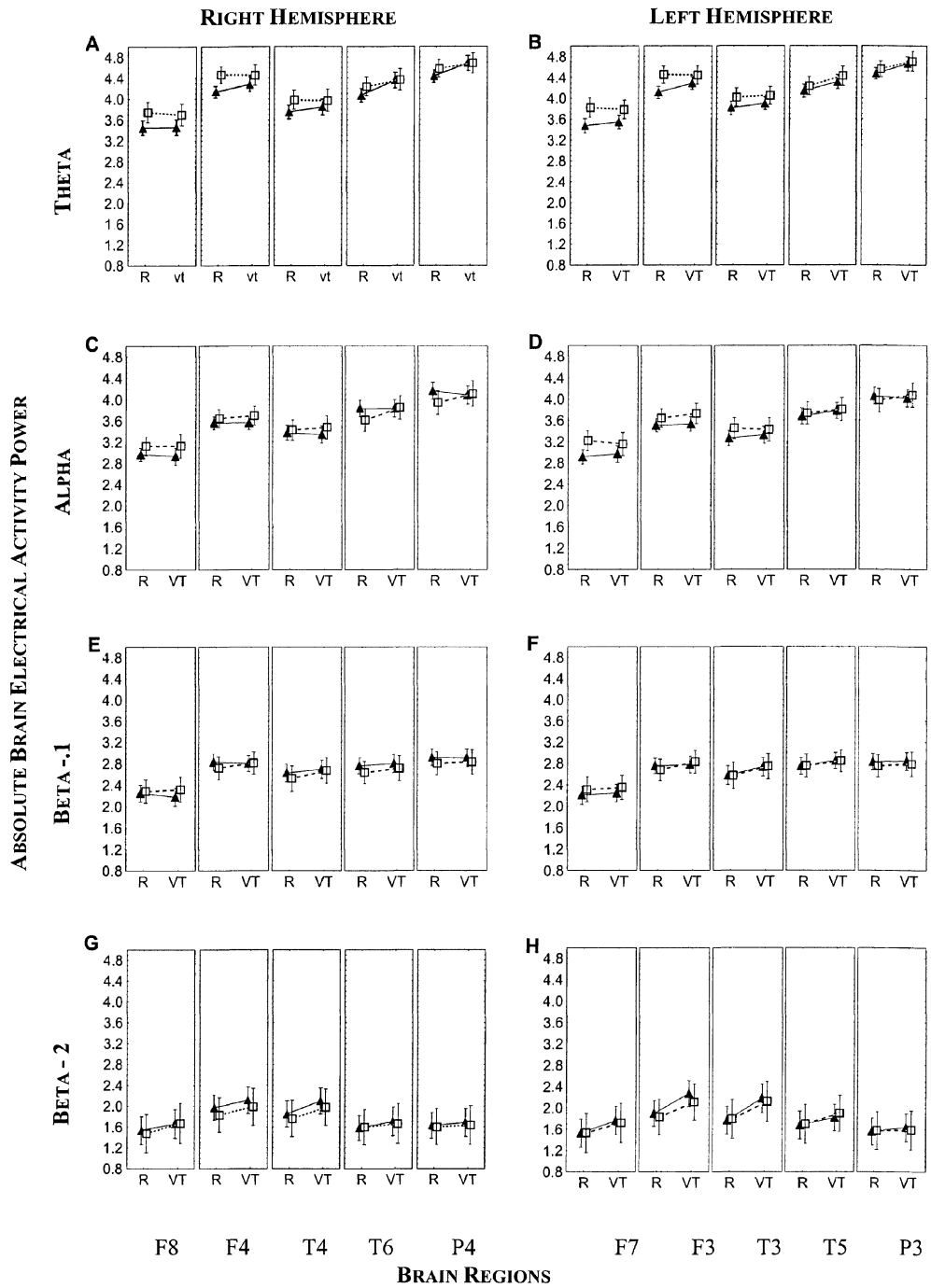
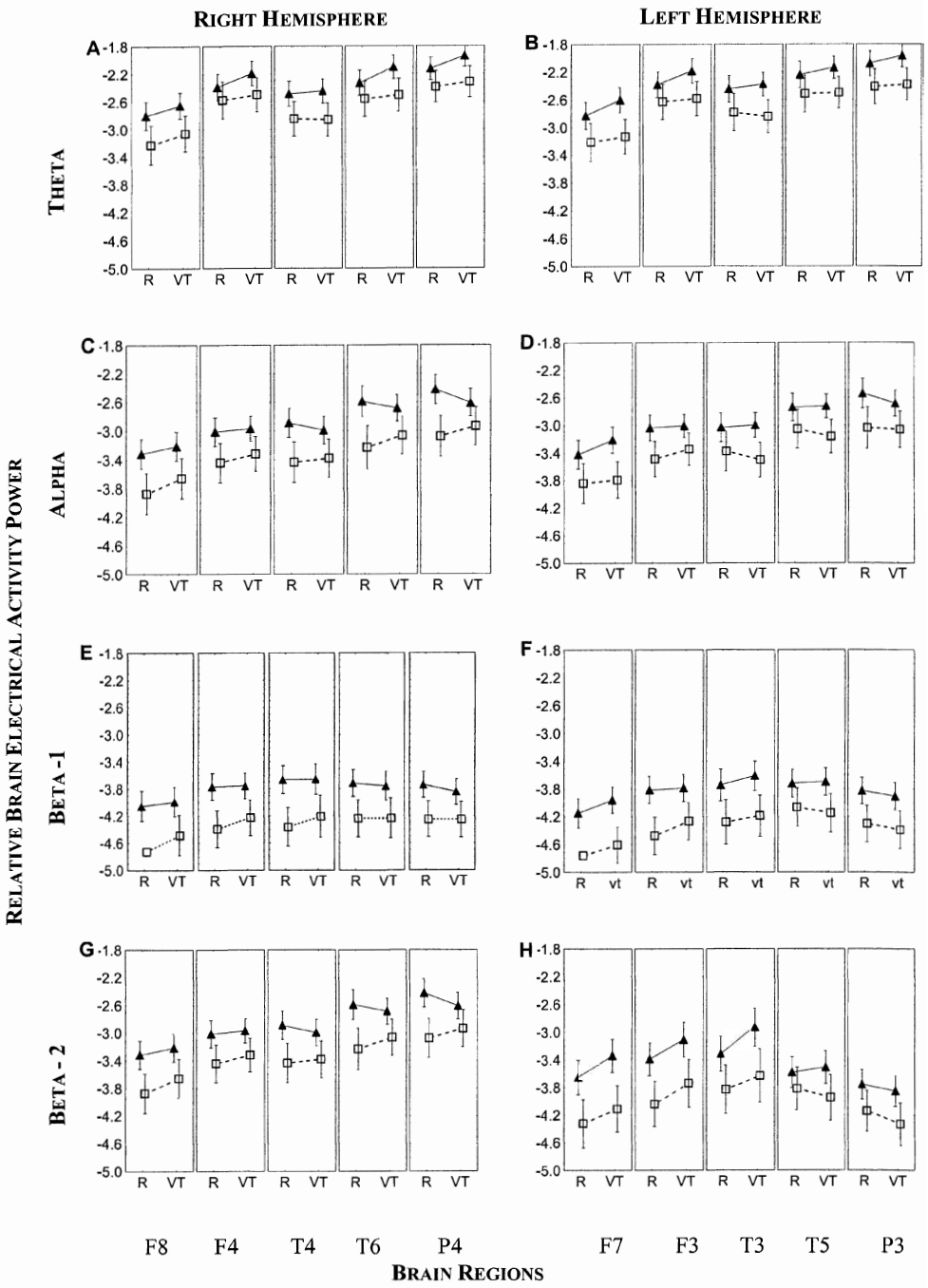


Fig. 2 Comparison of the means (and confidence intervals) of the relative power for the ADHD □ and the controls ▲groups in all frequency bands in relation to condition (R = rest with open eyes; VT = vigilance task) and hemisphere. A, B theta power. C, D alpha power. E, F Beta-1 power. G, H Beta-2 power



STUDY V

The aim was to study if children with ADHD compared to controls had different EEG frequency patterns especially in the frontal regions (and of a more immature type) during the mental stress performing the GDS Delay Task.

The overall between group (ADHD/control) comparisons were statistically significant for each frequency band, i.e. for the theta frequency band: [$F(1.90)=7.13$, $p = 0.009$], the alpha band: [$F(1.90)= 13.137$, $p < 0.001$] and for beta-1 and beta-2: [$F(1.90)=13.31$, $p < 0.001$, $F(1.90)=6.7$, $p = 0.012$ respectively].

Generally, the ADHD group showed an increase in the relative power difference (DT minus rest) in all frequency bands in some brain regions, especially in the frontal region with a positive confidence interval in 10 out of 40 electrode sites. The controls manifested a significant decrease in the relative power difference (DT minus rest) in all frequency bands in some brain regions, and especially in the frontal region—they evinced negative confidence intervals in 19 out of 40 electrode sites (Table 1, **Study V**; Fig 3).

In the relative theta activity band (Table 1, **Study V;** Fig 3), the children with ADHD displayed an increased theta brain activity during DT in 3 out of 10 electrodes (F7, F8, P3). In contrast, the controls showed a reaction of decreasing the slow theta activity during DT in 3 of 10 electrodes (F4, T3, T4). In the remaining electrodes no significant differences were observed.

In the relative alpha activity band (Table 1, **Study V**; Fig 3), the children with ADHD had an increased alpha activity during DT in one electrode out of 10 electrodes (F7); the controls displayed a decrease in alpha power in DT in 9 of 10 electrodes (F8, F4, T3, T4, T5, T6, P3, P4).

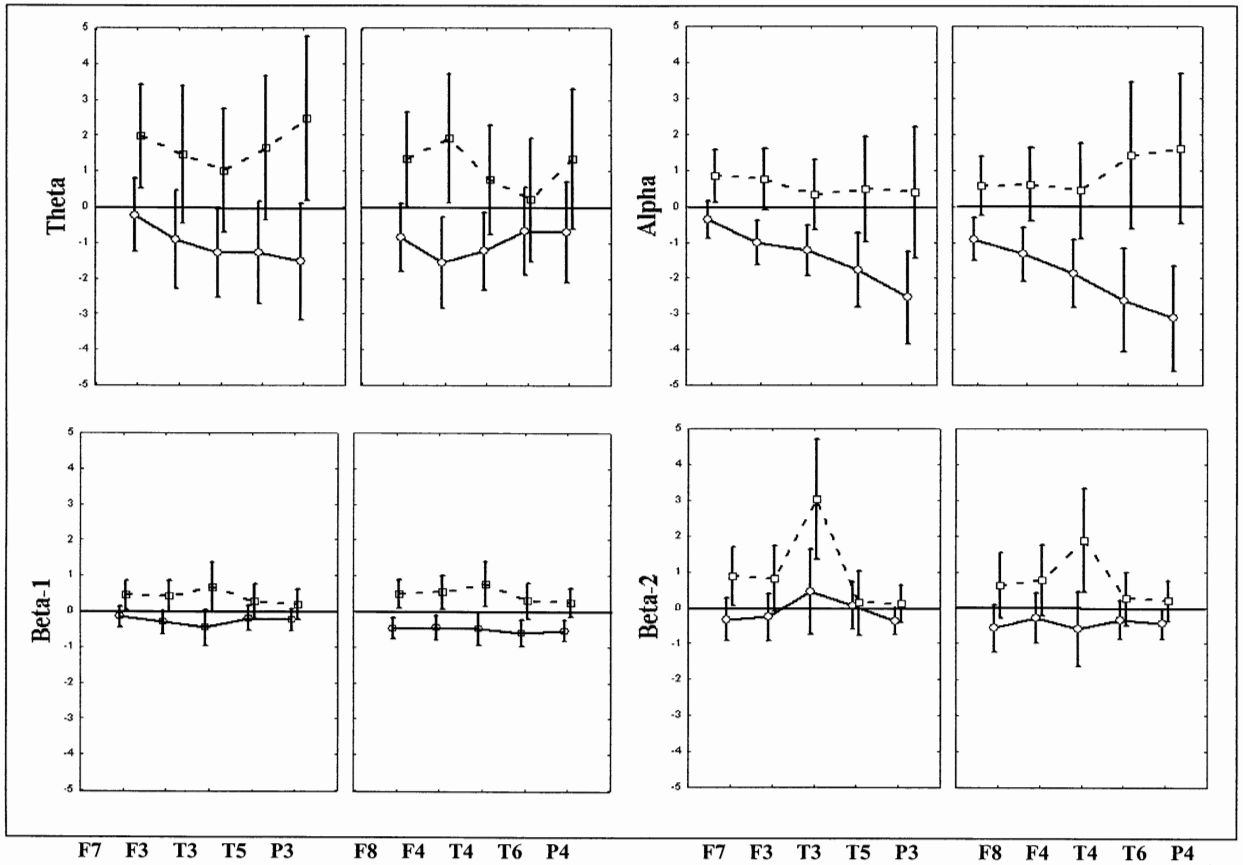
In the relative beta-1 activity band (Table 1, **Study V**; Fig 3), the children with ADHD had an increase in power in 4 out of 10 electrodes (F7, F8, F4, T4), The controls showed a reaction of beta activity decrease during DT compared to rest in 5 of 10 electrodes (F8, F3, F4, T4, P4).

In the relative beta-2 activity band (Table 1, **Study V**; Fig 3), the children with ADHD showed an increased power in 2 out of 10 electrodes (F7, T4), the controls had decreases in power in 2 of 10 electrodes (P3, P4).

In summary, the assumption that children with ADHD compared to controls would display a different electrophysiological reaction during DT as compared to rest was confirmed. The assumption that children with ADHD would display different reactions in the frontal region was also confirmed. Post-hoc contrasts between ADHD children and controls

were carried out for the frontal region (F3, F4, F7, F8) (Table 2, **Study V**). The differences in reaction between children with ADHD and controls were statistically significant in all frequency bands in all frontal electrodes, single electrodes, and combinations of electrodes, with the lowest p-values appearing in beta-1 (Table 2, **Study V**). The slow EEG activity patterns in the children with ADHD resemble those of younger children studied longitudinally. It is possible that these patterns represent "maturational lag" that may under certain conditions catch up. However, follows up studies are needed to verify this assumption.

Figure 3. Least square means and confidence intervals of the relative brain activity power in all frequency bands band difference between DT and rest in AD/HD group and controls.



In an exploratory analysis, we calculated the least square means and the 95% confidence intervals for the difference between DT and rest in different EEG frequency bands for each group. If "zero" was not included in the confidence interval, a significant difference between the tasks was found.

DISCUSSION

ADHD/HKD is a childhood-onset, clinically heterogeneous disorder of inattention, hyperactivity and impulsivity. Its impact on society is enormous in terms of its financial cost, stress to families, adverse academic and vocational outcomes, and negative effects on self-esteem (Barkley, 1998). For these reasons, discussions of the etiology of ADHD have serious implications. Recent research on ADHD/HKD has focused upon the biological basis at the molecular and the neurophysiological levels of the brain (Swanson et al, 1998; Tannock, 1998). Definable genetic causes and brain dysfunctions are discussed, but still there is no clear biological marker of ADHD. It is also unclear whether the disorder is unique or merely one end of the continuum of age appropriate behavior (NIH, 1998; Carey, 1999)

The human brain is really undeveloped at birth. The brain's structure and organization change profoundly from birth to adulthood and seems to be subject to different influences at different times. Food, vitamins, perceptual stimuli and emotional support are among the factors involved in brain development. >From this point of view, the overall hypothesis of this study is that ADHD is highly related to brain maturation and global maturity.

The influences of nature and nurture in the determination of the individual brain structures are not independent from each other. Genes operate through environmental influences, including stressors or hazards (Rutter et al, 1999). The genetic control of the brain's structure and development displays asymmetries in the brain's functional organization, and genes are supposed to strongly control a broad anatomical band encompassing frontal and sensorimotor cortex.

The aim of **Study I** was to investigate upon the association between ADHD and global maturity using a twin-design and information from the parents on their children's level of maturity (a questionnaire for parents concerning the children's global maturity) and their behavior according to CBCL (Achenbach, 1991) and the occurrence of ADHD symptoms according to DSM-III-R (APA, 1987).

A twin design makes it possible to study to which degree heredity is involved for understanding behavior, and the extent to which individual differences can be attributed to genetic or environmental factors. The findings indicated that genetic and environmental factors are important both for ADHD symptoms and for global maturity and that global maturity mediated part of the genetic effects for ADHD.

The findings of the importance of genetic factors for the ADHD is in agreement with the results of other twin studies (ADHD symptoms scores rated by parents or teachers) in the US

(Goodman and Stevenson, 1989; Gillis et al, 1992; Edelbrock et al, 1995; Eaves et al, 1997; Sherman et al, 1997), in the UK (Thapar et al, 1995; Thapar, 1998), in Norway (Gjone et al, 1996), and in Australia (Levy et al, 1997).

However, there is a lot of controversy surrounding the interpretation of results from twin studies of ADHD (Levy et al, 1997; Thapar, 2000). One example is whether ADHD should be considered a dimension or a category and whether parent reports of symptoms, teacher reports or both are required. The dimensional view sees ADHD as a continuous trait and might explain the apparent genetic heterogeneity of the disorder. Stevenson (1992) and Levy et al (1997) studied ADHD comorbid with CD. Their findings indicate that this subtype is a more severe clinical variant of ADHD, and may even be a separate category as a genetically based persistent form of ADHD.

The findings of **Study I** also showed that shared environmental effects are important for understanding ADHD. These results are in agreement with other studies showing that psychosocial stress and socioeconomic factors are of importance for mediating ADHD (Larsson et al, 1996; Biederman et al, 2002). Parental and family factors were found to play an important role in development of behavioral problems as ADHD also affecting its outcome (Nigg and Hinshaw, 1998). Psychosocial treatment of ADHD was found to be helpful (Pelham et al, 1998).

Although the family dysfunction may perhaps not initiate ADHD, it could still lead to the development persisting impairments and conduct disorder in vulnerable ADHD cases (Beiderman et al, 1996; Silberg et al, 1996; Woodward et al, 1997). There is also evidence for shared genetic effects on hyperactivity and conduct problems, both when hyperactivity has been considered as a continuous dimension (Silberg et al, 1996; Nadder et al, 1998) and as an "extreme" group (Kuntsi & Stevenson, 2000).

The genetic brain maps studies by Thompson et al (2001) indicate how genes determine individual differences in the brain's way of working. The results may shed light on the heritability of cognitive and genetic liability for behavior and add support to the understanding of how genetic factors, environment and behavior are interacting with each other. Advances in molecular genetics (Fischer et al, 2002) showed that ADHD is unlikely to be explained by a single major-gene effect, and that a number of allelic variants at a number of risk loci may exist.

From **Study I** and from other genetic studies it seems reasonable to conclude in similarity to Taylor (1999) who reported, "the genetic contribution is strong, but it is important to remember that a strong genetic contribution does not imply determinism. Genetic influences

are expressed through interaction with environment, and it is still through environmental changes that treatment advances are likely to be made."

The influences of maturational rate on behavior are crucial when studying children's normal psychological development and in clinical situations when assessing children's behavioral symptoms. Some behavioral disturbances could, more or less directly, be caused by a slow developmental rate. MacFarlane (1954) studied changes in behavior during average children's development and showed that an ADHD behavior (with criteria very similar to the DSM criteria for ADHD used today) were more common in boys than in girls and were changing over time. Wolff argued (1976) that the higher incidence of behavioral disturbances in boys might be caused, at least in part, by their relatively slower maturation. Frisk (1991, 1999) reported that children with developmental delays seem to have an increased prevalence of psychiatric problems with symptoms of aggression, hyperactivity, withdrawal and social maladjustment. The importance the child's developmental functional level, mental age and behavior is also stressed in the DSM-IV manual (APA, 1994, 2000).

From these different views we assumed that problems with inattention, impulsivity, poor inhibition control and hyperactivity could partly be explained from variations in the rates, styles or trajectories of mental development of these functions, sometimes leading to a chronic impairment. The assessment of mental age and the global maturity level became of special interest.

In **Study II**, an association was found between parental-reported immaturity and behavioral problems, indicating that expressions of immaturity are associated with ADHD and other behavioral problems in young children. There were statistically significant relationships between the parents' characterization of their children as being immature and high scores in the Child Behavior Checklist grouping of syndromes (internalizing, externalizing, total behavior problems score) as well as between immaturity and ADHD symptoms according to DSM-III-R. The findings that parent overall age estimates provide a sensitive and specific indicator of global developmental status are in line with other studies (Heriot and Schmickel, 1967; Coplan, 1982; Pulsifer et al, 1994; Glascoe and Sandler, 1995; Glascoe, 2000; Galambos et al, 1999; Larsson et al, 2002).

The findings in **Studies I and II** are dependant on rating scales. However, while such scales may be sensitive and accurate, the results of rating scales should not be taken blindly. There are some limitations in using parents' scales such as rater bias, expectancy and halo effects (Barkley et al, 1988; Abikoff et al, 1993).

The results from **Studies I and II** led to an interest to study the measurement of attentional and impulse control problems using objective psychometric tests.

The psychological mechanisms that underlie ADHD/HKD have proved very difficult to identify. Numerous studies have reported on poorer performance from children with ADHD/HKD on various tasks (for reviews, see Pennington et al, 1996; Sergeant et al, 1999; Kuntsi and Stevenson, 2000, Kuntsi et al, 2001). Investigators have unsuccessfully attempted to formulate a single theory of ADHD (Sonuga-Barke, 2002) that would facilitate the development of an objective diagnostic test. These single-cause theories have appealed to psychological constructs such as the inhibition hypothesis (Quay, 1988, 1997; Barkley, 1997), the hypothesis on dysfunctional regulation of arousal/activation (Sergeant et al, 1999), the hypothesis on slow mode of information processing (Tannock, 1998), the hypothesis on delay aversion (Sonuga-Barke, 2002) and the hypothesis on deficits in retaining a sequence of events in working memory and deficits in sense of time or temporal continuity (Barkley, 1997).

Objective laboratory measures play a potentially important role in assessing different aspects of attention and impulsivity. CPT has been used to measure the ability to sustain attention under conditions requiring self-control (Newcorn et al, 1989; Barkley and Grodzinsky, 1994; Gordon et al, 1996). The two main ways to assess the degree of impulsivity are the "Delay of Reward" paradigm and the "DRL" (differential reinforcement of low rate behavior) paradigm (Monterosso and Ainslie, 1999).

In S**tudy III** we used the CPT version of GDS, VT and DT version of GDS to assess both sustained attention problems under self-control and impulse control problems respectively in children with ADHD and controls.

These two tasks test the brain's executive function including both (input) retrospective elements (sensory or re-sensing, visual in this task) and (output) prospective (preparatory motor) elements (Goldman-Rakic, 1995; Fuster, 1997) and requires interference control for its effective performance. The accurate performance of these two tasks (vigilance and delay task) requires an arising mental module for sensing the hypothetical future from the experienced past. This serves to generate the private or mental representations (combination of numbers, flash) that bridge the cross temporal elements within a contingency arrangement (event-response-outcome) being crucial for self-control toward the future (D'Esposito et al, 1997).

The lateral prefrontal cortex is supposed to mediate information (through working memory and preparatory set) when a person is performing these two tasks and is supposed to

be the neural substrate for the cognitive functions supporting the temporal organization of behavior (Fuster, 2001).

In **Study III**, the ADHD group compared to the controls showed more omission errors, reflecting less ability to sustain attention in the VT task and more commission errors (extraneous button presses), reflecting impairment in impulse control during the DT. The results are in agreement with other studies using the GDS to compare children with and without ADHD (Gordon, 1979; Gordon and Mettelman, 1987; Gordon et al, 1989; Bauermiester et al, 1990; Aylward et al, 1997; Mayes et al, 2001).

The GDS scores were not associated with gender but strongly associated with age, especially in the control sample. The accuracy of the GDS referring a specific child to either of the samples was, as expected, not impressive, which was in accordance with other studies such as Gordon (1993) and Fischer et al (1995).

The findings of **Study III** support the main hypothesis of a slower maturational rate in ADHD children compared to the control children. The GDS scores were highly correlated with age with better a performance among the older children. Although a prospective longitudinal follow up is needed to study if there will be a catch up, the obvious age variation of GDS scores in relation to chronological age in the ADHD group is an indication of the relevance of the maturational lag hypothesis.

A number of structural brain imaging studies have manifested structural differences in children with ADHD compared to controls. The brain was 5% smaller in children with ADHD compared to age-matched controls (Castellanos, 1996; Filipek et al, 1997): The right frontal lobe was found to be smaller in some subjects with ADHD (Hynd et al, 1990; Castellanos et al, 1996). The cerebellum (especially the posterior inferior cerebeller vermis volume) was found to be smaller in ADHD boys (Berquin, et al, 1998; Mostofsky et al, 1998; Castellanos, 1996, 2001). Functional brain imaging studies have observed decrease metabolic function in adults (Zametkin et al, 1990) and in adolescents with ADHD (Zametkin et al, 1993; Ernst et al, 1998); circulatory differences were found between children with ADHD and same age peers (Amen et al, 1993; O'Tuama and Treves, 1993; Sieg et al, 1995). Neuroimaging studies have also supported the hypothesis of the importance of the frontostriatal circuitry in understanding the neurological basis of ADHD (Zametkin et al, 1998; Rubia et al, 1999).

Functional neuroimaging technology studies during task performance have shown differences between ADHD and controls. Hyperactive children showed, during the stop task, less brain activity in the right inferior prefrontal cortex and left caudate nucleus and in right

frontal during delay task (Rubia et al, 1999) and during nonverbal working memory tasks (delay task responses) (D'Esposito et al, 1997).

The limitations of pediatric neuroimaging research, the inconsistent findings and the controversy about normality vs. deviance of different brain anatomical regions and the possible asymmetry between the right and the left parts of the brain (still unproved) were discussed by Ernst (1999) and Santosh (2000).

Several research teams have reported on the reliability and validity issues of QEEG-based measures for ADHD. Chabot and Serfontein (1996) and Chabot et al (1996) demonstrated the ability of a discriminant function analysis of certain QEEG characteristics (e.g., absolute power, relative power, coherence between pairs of electrodes, and power asymmetry) to distinguish individuals with ADHD from nonclinical control and patients with learning disabilities with test sensitivity and specificity rates greater than 87%. Lubar et al (1996) and Mann et al (1992) when examining electrophysiological power and power ratios at specific cortical locations reported on QEEG findings that differentiated patients with ADHD from a matched control group. Recently, Monastra et al (1999) manifested an increase in the theta/beta power ratio obtained from a single vertex recording with eyes open in a group of children with ADHD and its subtypes and reported a sensitivity of 86% and a specificity of 98%. In 2001, Monastra et al reported that the sensitivity of the QEEG-derived attentional index (theta/beta power ratio) was 90% and the specificity was 94%.

From QEEG studies there are three models explaining ADHD, including the maturational lag model, which means that the pattern of QEEG found in the children with ADHD would be normal at a younger age (Chabot et al (1996). Another electrophysiological model is the developmental deviation model (i.e., score not normal at any age), which was presented by Chabot and Serfontien in 1996. A pattern of "hyperarousal" in the frontal region has also been suggested as a neurological subtype found in patients with ADHD (Chabot and Serfontien, 1996).

Many studies indicate that EEG, especially alpha and theta frequency bands, is sensitive to the type and quality of the cognitive task being used (Davidson et al 1990; Gevins et al 1997; Petersen et al 1998; Harmony et al 2001).

From reviewing different EEG studies, it was found that EEG techniques are sensitive to brain maturation. Although the results presented are inconsistent and further studies are needed, the QEEG technique was chosen for the cross sectional S**tudies IV and V** in order to study brain activities during concentration and the provocation of impulsivity in children with

ADHD and controls. The data collected will form the basis for future follow-up studies of the same children across ages.

According to a study design suggested by Gevins et al (1987) and Smith et al (1999) we have measured brain activity power in different frequency bands using QEEG while children with ADHD and controls were performing cognitive tasks (VT **[Study IV]** and DT **[Study V]** according to the GDS).

In **Study IV**, comparisons of the cross sectional data of QEEG activity in children with ADHD and controls at age 6-16 years were done. The hypothesis was that children with ADHD would display specific differences in the patterns of frontal, temporal and parietal brain activation (enhanced slow cortical activity and decreased fast activity, mainly in the right hemisphere) during the attentional load task compared to controls.

The absolute theta activity during attentional load task was increased in children with ADHD compared to the controls, especially in the frontal region. These findings are consistent with other QEEG studies (Satterfield et al, 1972; Defrance et al, 1996; Bresnahan et al, 1999; Lazzaro et al, 1999; Chabot et al, 2001). Some studies have interpreted the presence of increased slow activity as a maturational lag (Mann et al, 1992; Matsuura et al, 1993; Lazzaro et al, 1998) or as pathological deviations from normal brain activity development (Chabot and Serfontein, 1996). In other studies, the increased slow activity has been interpreted as evidence for a state of low CNS cortical arousal due to dysfunction in subcortical centers in ADHD children.

The children with ADHD showed a significantly decreased alpha power compared with controls across the frontal, parietal and temporal regions during VT, which were in accordance with the results from Callaway et al (1983), Fernandez et al (1995) and Clarke et al (1998, 2001a, 2001b). Decreased alpha activity was interpreted as an impaired development of the neuromotor system and as a delayed maturation of the brain (Matsuura, 1993; Schmid et al 1997). The children with ADHD in **Study IV** showed a decreased beta activity during VT performance, which is consistent with the results of studies by Callaway et al (1983), Mann et al (1992) and Kuperman et al (1996). These results of a decreased fast activity could be explained within the context of neurodevelopmental delay or a problem with arousal adjustment (Satterfield et al, 1984).

In **Study V**, a comparison of the cross sectional data of QEEG activity in children with ADHD and controls at age 6-16 years was done during the performance of DT (delay response task). The assumption that children with ADHD compared to controls would display a different electrophysiological reaction (DT minus rest) during DT was confirmed.

Children with ADHD showed increasing theta brain activity during DT. The findings are in accordance with the results from Mann et al (1992) who during reading and drawing tasks, found significant differences between ADHD subjects and controls in baseline condition, from Sasaki et al (1996) who investigated upon the attentive state during a mental task and from Frennandez et al (1995) and from Gundel and Wilson (1992) who studied brain activity during arithmetic problems. An increase in theta baseline activity has been regarded as an electrophysiological marker of cerebral dysfunction in different childhood disorders, such as learning disabilities (Lubar et al, 1985) and in hyperactivity (Wilker et al, 1970).

The controls showed a reaction of decreasing the slow theta activity during DT which is in parallel with Posner´s results (1995), but in disagreement with the results by Slobounov et al (2000). The controls also displayed a decrease in alpha power during DT, which is in accordance to the findings of Altenmüller et al (1989), verbal mental task, of Rosler et al (1995), memory encoding, and of Harmony et al (1999) investigating upon a calculation task.

The ADHD group showed increased beta activity during DT. This increase in beta activity might be looked upon as a state of hyperarousal. In agreement with our findings of possible hyperarousal in the ADHD group in **Study V**, Clarke et al (2001c, 2001d) and Chabot and Serfontein (1996) also found an increase in beta amplitude, which was interpreted as the result of comorbidity with emotional disturbances. On the other hand, a hypothesis of hypoarousal in ADHD children has been supported from different neurophysiological studies where a decrease in beta activity was found (Callaway et al, 1983; Mann et al, 1992; Matsuura et al, 1993; Lazzaro et al, 1998).

From the EEG reactions in the children with ADHD during DT it could be argued that children suffering from ADHD experience problems in cerebral processing when performing a mentally demanding task during a restricted time. However, the cerebral processing underlying the EEG reactions to the mental stress should be further studied.

Since the slow EEG activity patterns in the children with ADHD (in **studies IV and V**) resemble those of younger children studied longitudinally (John et al, 1980; Benninger et al, 1984; Gasser et al, 1988a, b; Hudspeth and Pribram, 1992; Bresnahan et al, 1999), it is possible that these patterns do represent a "maturational lag" which under certain conditions may catch up. Follows up studies are needed to verify this assumption.

From the findings of **Studies I, II, III, IV and V,** it was found reasonable to discuss and consider the "maturational lag hypothesis" of ADHD.

The aim of **Study VI** was to overview the literature on ADHD, the different biological and developmental studies of ADHD children that have been run and to discuss the concept of

maturation vs. ADHD, challenging the current opinions of ADHD as being just a brain disorder; may be ADHD sometimes represents variants of normal maturational trajectories.

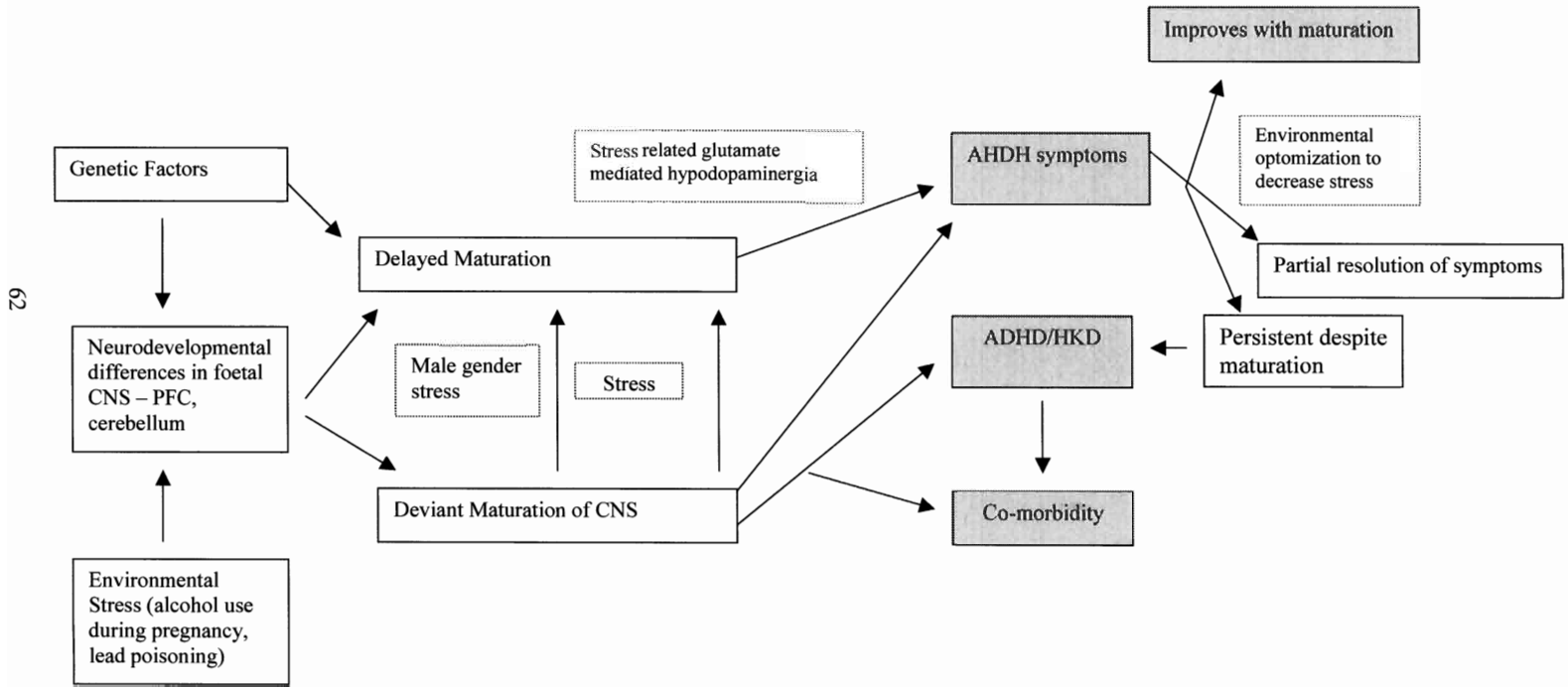
The overview of old and current literature covers the following aspects, a.) current trends in ADHD research; b.) reports on the persistence and remission of AD/HD symptoms over time; c.) studies on children's maturational trajectories referring to brain development and mental characteristics; d.) the relationship of maturation to ADHD vs. HKD.

The overview shows that there are different groups of children showing similar behavior with inattention, hyperactivity and impulsivity, but due to different reasons. AD/HD could represent a continuum from normality at one extreme to a severe disorder, HKD, or severe ADHD of combined type—at the other extreme.

ADHD symptoms per se do not necessarily lead to major behavioral problems later in life. Studies that report on ADHD children with persistent disorders included samples of children with a wide range of additional problems such as learning disabilities, environmental mental disadvantages and neurological abnormalities. Thus, despite hyperactivity being a predisposing factor to developing conduct problems, it is difficult to draw conclusions on whether the primary symptoms of childhood hyperactivity, inattention and impulsivity, or the additional behavioral problems, such as conduct disturbance, predict later psychiatric or social problems.

It is possible that a genetically determined "slow maturation speed" plays a greater role (or a different role) in the etiology of ADHD across the continuum mentioned above. It is possible that the dimensions of hyperactivity impulsivity and inattention may have differing maturational trajectories. It seems reasonable to assume that within the group of children showing ADHD/HKD, there is a subgroup with severe symptoms having a true disorder or showing extreme vulnerability to environmental factors. A model of how to understand the complexity and the different outcomes of ADHD is presented in (Fig 4).

Fig 4. Possible mechanisms involved in aetiology of ADHD



CONCLUSION

The aim of the thesis was to study the hypothesis that some children with ADHD may show the symptoms due to a slow speed of mental maturation with the possibility of a catch-up.

- In Study I, the association between ADHD and global maturity was tested using a twin design. The results showed different pathways through which genetic effects may influence the behavior pattern in children with ADHD. Among boys, there are at least two different genetic pathways to explain ADHD, one through predisposition for maturational lag and one specific to ADHD. A different pathway may explain ADHD in girls.
- In Study II, the relationship between behavior, ADHD symptoms and maturity was studied using a questionnaire (a global maturity parent's scale) given to the parents. Relationships were found between the maturity factor and the CBCL grouping of syndromes (internalizing, externalizing, total behavior problems score) as well as between the maturity factor and ADHD. From the parents' point of view the behavior problems in their children may be related to maturity.
- In Study III, a computerized tool (the Gordon Diagnostic System, GDS) was used to test concentration and impulse control comparing children with ADHD and controls. Differences were found between ADHD children and age-matched control children in each age group. The GDS scores were highly correlated with age with better a performance among the older children, which could support the relevance of the maturational lag hypothesis.
- In Study IV, a possible immature brain processing during concentration was studied comparing children with ADHD and controls. QEEG techniques were used when the children performed the Vigilance Task of GDS. Compared to controls children with ADHD displayed specific differences in the pattern of frontal, temporal, and parietal brain activation. They had an enhanced slow cortical activity and decreased fast activity similar to younger children. These findings indicate a different arousal level in children with ADHD, which could be due to a delay in functional cortical maturation.
- In Study V, impulsivity, brain processing and possible immaturity were studied. The same children with ADHD and controls as in study IV performed the Delay Task of GDS during registration of QEEG. In similarity to the results of study IV children with ADHD displayed different electrophysiological reactions, which may indicate

that they, like younger children, have problems in cerebral processing when performing a mentally demanding task during a restricted time.

- In Study VI, the "maturational lag" concept ADHD was discussed over viewing previous and current ADHD-literature. The overview shows that maturity and developmental aspects are important factors to be included in studies of ADHD. A slow speed in mental development may be of importance for the treatment and prognosis of ADHD.

The overall results support the view, that some children with ADHD could represent a continuum of normal childhood behavior with maturational trajectories that are lagging behind but that will catch up. The recently presented prospective and longitudinal imaging study presented by Gogtay et al (2002) showing that the trajectories of brain development of normal children and children with ADHD tend to meet after the age of 20 years is also supporting such a view.

If fulfilling the present criteria of ADHD according to DSM-IV, a child is assigned the diagnosis of a psychiatric disorder. This seems reasonable referring to children with impairments due to severe symptoms of the combined type or to children fulfilling the criteria of HKD according to ICD-10.

But, the DSM criteria of ADHD may be over-inclusive. Symptoms similar to ADHD are sometimes caused by psychosocial stress. The current findings support the idea that the symptoms could also be the final consequences of a common pathway from a genetically determined developmental delay/maturational lag where the difference between the chronological age and mental age is the crucial factor to understand the pathology.

May be, vulnerable children showing symptoms of ADHD are unable to compete with schoolmates and friends of the same chronological ages? Compared to average children, they are more sensitive to negative psychosocial factors and will benefit from special considerations. Whether they should be looked upon as being impaired, genetically vulnerable or just looked upon, as normal but needing time is more a debate of semantics.

However, if a substantial proportion of children are having ADHD symptoms caused by maturational lag or stress in the environment, the timing of the diagnostic assessment must be questioned. When is it appropriate for a child to get a categorical diagnosis? If the symptoms are changing over time, it seems essential for parents, schoolteachers and others not to look upon them as merely being disordered but to adjust to their difficulties and to support them according to their mental age and not to their chronological age during development. If not,

and exposed to negative psychosocial or environmental factors, they may face the risk to develop persistent ADHD, with or without co morbidity. From this point of view, Olsson's statement from 1959 on a good outcome despite a slow maturational speed still seems relevant: "Those who surprise us seem to take a longer time to travel a given road, but that road has been kept open by parents and teachers who felt it worthwhile."

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