Global Assessment of Attention Deficit Hyperactivity Disorder

Examining Objective Measures of Hyperactivity, Impulsivity and Inattention in Adults

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Hanna Edebol
To the Edebol Family - Enthusiasm, Dedication, Energy, Belief, Optimism and Loyalty!
Doctoral Dissertation

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Hanna Edebol, Department of Psychology, Karlstad University, Sweden.

Abstract

The aim of this thesis is to examine objective laboratory measures of Attention Deficit Hyperactivity Disorder (ADHD) in adult persons and to develop measures for diagnosis and treatment using a psychometric instrument called the Quantified Behavior Test Plus. The instrument objectively quantifies cardinal symptom manifestations in adult ADHD using motion tracking devices and continuous performance testing. Papers I-IV suggest that ADHD predisposes adult persons to perform poorer on continuous performance tasks and to have higher levels of motor activity while performing these tasks as compared to other clinical as well as non-clinical groups. Performance by adults with ADHD is normalized following stimulant treatment and measures of response to treatment and remission are suggested.

Paper I concludes that the psychometric instrument needs to be calibrated with regard to adult ADHD and emphasizes the importance of a composite measure for the disorder. Paper II generates two new measures, the Weighed Core Symptom scale (WCS) - a composite measure of adult ADHD ranging from 0 to 100, and Prediction of ADHD (PADHD) - a categorical variable of diagnostic status with good predictive power. A majority of participants with ADHD has low points on WCS (indicating high levels of symptoms) and a majority of non-ADHD normative participants has high points on WCS (indicating low levels of symptoms). Paper III examines WCS and PADHD among clinical groups with shared symptoms vis-à-vis ADHD. Here, participants with ADHD present higher level of symptoms than other clinical participants with bipolar II disorder, borderline personality disorder, participants with disconfirmed ADHD and even higher levels of symptoms than non-clinical participants. In Paper IV, the measures are proposed as indications of response to treatment and remission after titration with stimulant treatment and WCS indicates response to small changes in dose level.

The major findings of the present thesis may be summarized as the construction of two new objective measures for ADHD in adult persons with practical implications for diagnosis and...
treatment. Hyperactivity is the most specific marker for ADHD in both men and women, followed by the cognitive markers of inattention and impulsivity. PADHD and WCS may not replace a thorough neuropsychiatric assessment and further studies that promote diagnostic subtype stratification are suggested. Future studies may want to consider these measures in outcome-based investigations of treatment efficacy as well in the study of neuropsychological endophenotypes. Practical implications include clinical strategies to enhance objectivity during assessment, optimizing beneficial effects of treatment, attaining remission as well as improving the quality of life for adults with ADHD.

**Keywords:** Attention Deficit Hyperactivity Disorder, Objective measures, Adults, Psychometrics, Diagnosis, Treatment
Doktorsavhandling

Global Bedömning av Aktivitets- och Uppmärksamhetsstörning: Objektiva Mätningar av Hyperaktivitet, Impulsivitet och Ouppmärksamhet hos Vuxna Personer

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Sammanfattning

Syftet med avhandlingen är att undersöka objektiva mätningar av aktivitets- och uppmärksamhetsstörning (ADHD) hos vuxna personer samt att utveckla kliniska mätinstrument för diagnost och behandling med hjälp av det psykometriska instrumentet Quantified Behavior Test Plus. Instrumentet registrerar och kvantifierar kardinalsymptomen vid ADHD med hjälp av en rörelsekamera samt ett datoriserat test. Resultaten av studierna (Paper I-IV) visar att vuxna personer med ADHD har svårare att vara uppmärksamma och genererar högre grader av motorisk aktivitet under testet i jämförelse med andra kliniska samt icke-kliniska grupper. Kardinalsymptomen vid ADHD normaliseras till följd av behandling med centralstimulerande läkemedel och nya mätinstrument av respons och remission vid medicinsk behandling föreslås.

Den första studien (Paper I) konstaterar att testet behöver kalibreras gentemot ADHD och utvecklandet av ett kompositmått föreslås. Den andra studien (Paper II) utvecklar två nya mätinstrument som kallas WCS (Weighed Core Symptom scale) - ett kompositmått som anger graden av ADHD-symptom på en skala från 0 till 100, samt PADHD (Prediction of ADHD) - en kategorisk variabel som anger diagnostisk status och som har goda prediktiva värden. De flesta personer med ADHD har låga värden på skalan vilket indikerar höga nivåer av symptom och de flesta personer utan ADHD har höga värden på skalan vilket indikerar låga eller obefintliga nivåer av symptom. I den tredje studien (Paper III) undersöks de nya mätinstrumentens förmåga att särskilja ADHD från andra psykiatriska diagnoser. WCS och PADHD särskiljer vuxna med ADHD från deltagare med bipolär sjukdom typ två, emotionellt instabil personlighetsstörning, deltagare som blivit utredda för ADHD men inte fått diagosen samt från icke-kliniska deltagare. I den fjärde studien (Paper IV) mäter instrumenten graden av respons under medicinsk behandling samt indikerar remission efter titrering med centralstimulerande läkemedel och WCS indikerar respons vid små förändringar i dosnivå.
Slutsasterna som man kan dra från den här avhandlingen är att två mer objektiva mätinstrument har utvecklats för att mäta ADHD hos vuxna personer med praktiska implikationer för diagnos och behandling. Hyperaktivitet i form av motorisk aktivitet är den starkaste markören för ADHD hos både män och kvinnor följt av kognitiva mått på ouppmärksamhet och impulsivitet. Vid diagnos och behandling behöver resultaten från mätinstrumenten sättas i relation till annan klinisk information, instrumenten ersätter inte en omfattande utredning och fördjupade analyser av instrumentens tillförlitlighet i relation till diagnostiska subtyper rekommenderas. Framtida studier kan exempelvis använda dessa mätinstrument i syfte att öka objektiviteten vid utvärderingar av behandlingsresultat samt för att studera ärftliga indikationer vid ADHD. Praktiska implikationer av studierna är ökad objektivitet under kliniska utredningar samt metoder för att optimera positiva effekter av behandling, uppnå remission samt förbättra livskvaliteten för vuxna personer med ADHD.

*Nyckelord: Aktivitets- och uppmärksamhetsstörning, ADHD, Mätning, Psykometri, Diagnos, Behandling*
This thesis is based on the following four papers, which will be referred to in the text by their Roman numerals:


III Edebol, H., Helldin, L., & Norlander, T. (2012). *Objective measures of behavior manifestations in adult ADHD and differentiation from participants with Bipolar II disorder, Borderline personality disorder, participants with disconfirmed ADHD as well as Normative participants*. Manuscript in press at Clinical Practice and Epidemiology in Mental Health.

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Contents

1. INTRODUCTION .................................................................................................................. 12
  1.1 Background .................................................................................................................. 12
    1.1.1 Historical perspectives ......................................................................................... 12
    1.1.2 Contemporary perspectives ............................................................................... 15
    1.1.3 Clinical perspectives ......................................................................................... 23
    1.1.4 The Continuous Performance Test Paradigm .................................................... 44
    1.1.5 Clinical applications of Continuous Performance Tests ............................... 50
    1.1.6 Psychometric properties of Continuous Performance Tests ....................... 67
    1.1.7 Objective measures of hyperactivity in adults ............................................. 74
  1.2 Theoretical perspectives ............................................................................................... 87
    1.2.1 Introduction ....................................................................................................... 87
    1.2.2 Response inhibition deficit ............................................................................... 87
    1.2.3 Working memory impairment ......................................................................... 93
    1.2.4 The cognitive-energetic model ....................................................................... 95
    1.2.5 Delay aversion hypothesis .............................................................................. 99
    1.2.6 Dopamine hypofunctioning .......................................................................... 104

2. THE PRESENT INVESTIGATION ......................................................................................... 107
  2.1 Introduction .................................................................................................................. 107
  2.2 Paper I. In Search for an Objective Measure of Hyperactivity, Impulsivity and
  Inattentive Adult Attention Deficit Hyperactivity Disorder .................................... 107
    2.2.1 Aim .................................................................................................................... 107
    2.2.2 Design ............................................................................................................... 107
    2.2.3 Instruments ....................................................................................................... 108
    2.2.4 Procedure .......................................................................................................... 108
    2.2.5 Statistics ............................................................................................................ 109
    2.2.6 Results ............................................................................................................... 110
  2.3 Paper II. Composite Measure of Adult Attention Deficit Hyperactivity
  Disorder ............................................................................................................................. 110
    2.3.1 Aim .................................................................................................................... 110
    2.3.2 Design ............................................................................................................... 110
    2.3.3 Instruments ....................................................................................................... 111
    2.3.4 Procedure .......................................................................................................... 112
    2.3.5 Statistics ............................................................................................................ 113
    2.3.6 Results ............................................................................................................... 114
  2.4 Paper III. Objective measures of behavior manifestations in adult ADHD and
  differentiation from other clinical groups ...................................................................... 114
    2.4.1 Aim .................................................................................................................... 114
    2.4.2 Design ............................................................................................................... 115
    2.4.3 Instruments ....................................................................................................... 115
    2.4.4 Procedure .......................................................................................................... 116
    2.4.5 Statistics ............................................................................................................ 118
    2.4.6 Results ............................................................................................................... 119
2.5 **Paper IV.** The Weighed Core Symptoms scale and Prediction of ADHD in adults, objective measures of remission and response to treatment with methylphenidate. 120

2.5.1 **Aim** ........................................................................................................ 120
2.5.2 **Design** .................................................................................................... 120
2.5.3 **Instruments** ............................................................................................ 121
2.5.4 **Procedure** .............................................................................................. 123
2.5.5 **Statistics** ............................................................................................... 125
2.5.6 **Results** ................................................................................................... 125

3. **GENERAL DISCUSSION** ........................................................................... 127
3.1 **Introduction** ............................................................................................... 127
3.2 **Theoretical accounts** ................................................................................ 128
3.3 **Empirically derived measures for the clinical practice** ............................... 140

4. **CONCLUSIONS** ........................................................................................ 151

5. **REFERENCES** ............................................................................................. 152

PAPER I
PAPER II
PAPER III
PAPER IV
1. INTRODUCTION

1.1 Background

1.1.1 Historical perspectives

For centuries now there have been descriptions of ADHD in the belles’ letters as well as in the scientific literature. One of the earliest examples originates from late eighteenth century when Sir Alexander Crichton (1763-1856) being the court physician of Tsar Alexander I of Russia describes in two volumes (1798) on the “Inquiry into the nature and origin of mental derangement: comprehending a concise system of the physiology and pathology of the human mind and a history of the passions and their effects”, a certain state of “mental restlessness” characterized by “the incapacity of attending with a necessary degree of constancy to any one object” that “when born with a person it becomes evident at a very early period of life” and “what is very fortunate, it is generally diminished with age” (as cited in Palmer & Finger, 2001, p. 68-69). Another example comes from nineteenth century fictive writer Mark Twain (1835-1910) who in 1891 translates Die Geschichte Vom Zappel-Philip (1848) into The story of Fidgety Philip derived from a collection of stories originally created by German psychiatrist and poet Dr. Heinrich Hoffman in the lack of suitable goodnight stories for his 3-year old son, and it goes like this “Let me see if Philip can, Be a little gentleman, Let me see if he is able, To sit still for once at table, Thus Papa bade Phil behave, And Mamma looked very grave. But fidgety Phil, He won’t sit still, He wriggles, And giggles, And then, I declare, Swings backwards and forwards, And tilts up his chair, Just like any rocking-horse- “Philip! I am getting cross!” (Hoffman, 2010, p. 10).

Later on, England’s first professor of child medicine and British pediatrician, Sir George Fredrick Still (1868-1941) presents in The Lancet (Still, 1902) a series of lectures known as the “Goulstonian Lectures” concerning some abnormal psychical conditions in children including severe disturbances in self-regulation, inhibition and sustained attention, excessive passions and the lack of moral control. About the same time (1906), Swedish writer and teacher Selma Lagerlöf (1858-1940), publishes her beloved fictive story on The wonderful
adventures of Nils, whose first chapters presents emblematic imageries of ADHD behavior in that the young lad Nils who is left unattended by his parents who are going to church is unable to stay alert while reading the Holy Gospel but instead his “chief delight was to eat and sleep, and after that he liked best to make mischief” (Lagerlöf, 1906, p. 1). Nils however escapes the situation by using his creative abilities to encounter the Swedish folklore landscape on the wings of a wild-goose named Akka who takes him on a courageous journey heartening good will and mental development.

In the 20th century, emerging empirical traditions of psychology and medicine provides scientifically derived terminologies for ADHD characterized by rapidly changing research paradigms and conceptualizations epitomized by improvements in diagnostic classifications, treatment interventions and study designs. In retrospect of the past century there have been three main perspectives of the disorder from scientific quarters, (1) etiological (e.g. minimal brain dysfunction), (2) behavioral (e.g. hyperkinesis disorder), and (3) cognitive (e.g. attention deficit disorder). So for example, the concept of Minimal Brain Damage evolves in the 20s (Ehrenfest, 1926) and is typical for the scientific era’s dominant view of organic brain pathologies being the etiological cause of disruptive behavior disorders and a certain organic drivenness (Kahn & Cohen, 1934), strengthened also by the recognition of similarities between hyperactive children and the behaviors of primates with frontal lobe lesions, even though evidence for such a hypothetical view was scarce. Cases of children without brain pathology but with disruptive behaviors led researcher in the 60s to develop instead the term Minimal Brain Dysfunction (Bax & MacKeith, 1963) in order to reflect the neurological mechanisms underlying behavioral symptoms of perception, attention, memory, impulse and motor control. Due to the weak evidence and vague definitions of the term however, it was thrust aside during the 80s in favor of more explicit labels referring to observable and measurable behavior deficits in children, including for example dyslexia, learning disabilities, hyperactivity, and language disorders. Researchers then elaborated on the causal mechanisms by emphasizing elements of psycho-social environment and childhood rearing capacities as implicated in the term hyperkinetic reaction of childhood (American Psychiatric Association, 1968) initiated also by objective verifications of hyperactive behavior and a widespread view of psychophysiological symptoms being outgrown by the reach of adolescence: “the disorder is characterized by overactivity, restlessness, distractibility, and short attention span, especially in young children; the behavior usually diminishes by adolescence” (American Psychiatric Association, 1968, p. 50).
Subsequent editions of the diagnostic manual (American Psychiatric Association, 1980, 1987, 2000) originate from atheoretical perspectives with regard to etiology but were constructed instead via field trials of descriptive and manifest behavior symptoms that was strengthened by empirical validity of the concept and its separation from other disorders. In the 70s, cognitive models penetrated scientific thinking by means of experimental procedures performed by Douglas and colleagues (1972) in which hyperactive children were repeatedly found to have substantial difficulties on measures of cognitive vigilance and sustained attention using Continuous Performance Tests (CPT). Follow-up study methodologies (Mendelson, Johnson, & Stewart, 1971) revealed that cognitive deficits of attention and impulsivity persisted into adolescence and the term *attention deficit disorder* with or without hyperactivity was coined using core symptom of inattention, impulsivity and hyperactivity (American Psychiatric Association, 1980). At this time, Scandinavian countries introduced the concept *Deficits of Attention, Motor control and Perception*, i.e. DAMP (Gillberg, 1987), which has been used in Scandinavia parallel to ADHD when describing a somewhat broader definition of the concept including also motor and perceptual difficulties.

A more recent concept of ADHD was first introduced in the late 80s (DSM-III-R) when key symptoms of hyperactivity and restlessness were again postulated for classification of the disorder and the previously dominating attention taxonomy turned into a diagnostic subtype. About this time, pioneers (Brown & Borden, 1986; Clampit & Pirkle, 1983; Thorley, 1984) in the field of adult ADHD increasingly noted that symptoms associated with the disorder persisted into adolescence and was associated with amplified risks of additional psychiatric disorders and the idea that ADHD was not merely a childhood disorder was introduced. Following the same assumption for classification as the abovementioned edition, the latest version of the manual (American Psychiatric Association, 2000) conceptualizes ADHD using core symptoms of (1) hyperactivity, (2) impulsivity, and (3) inattention, distributed in two categories of attention and activity that are summarized using the following diagnostic subtypes, (1) predominantly inattentive, (2) predominantly hyperactive-impulsive, and (3) combined type. Using the current clinical definition within a developmental life-course perspective, assuming retrospectively the onset of symptoms in childhood, adults are now frequently being included into the ongoing conceptual evolution of ADHD.
1.1.2 Contemporary perspectives on adult ADHD

Essentially nothing was known about Attention Deficit Hyperactivity Disorder (ADHD) in adults until the standard widely accepted diagnostic criterions presented in the 80s (American Psychiatric Association, 1980, 1987) stimulated research that in the past 30 years have been facilitating considerable clinical and scientific interest on the topic. Today ADHD is recognized as a developmental childhood-onset chronic disorder affecting about 5 % of the adult population, more so in males than females as mirrored in a gender ratio of roughly 4:1 in community samples, and it is associated with clinically significant impairments and substantial risks. The present chapter briefly reviews a selection of recent studies on the developmental course and outcome of the disorder as well as key contemporary conceptualizations of ADHD from psychological, neuropsychological, neurobiological and clinical perspectives.

Development course
ADHD is a developmental disorder with strong evidence confirming its persistence into adulthood even though the extent of this persistence has been challenging to evaluate. There is now good consensus that the same features of childhood ADHD occur also in adults with the disorder when behavioral traits are being evaluated from developmental and dimensional rather than age-fixed and categorical perspectives. Prevalence in the adult general population commonly ranges from 4 to 5 % (Kessler et al., 2006, 2007) which makes ADHD one of the most commonly occurring adult psychiatric disorders and studies have found 16.4 % of adults meeting subthreshold criteria (Faraone & Biederman, 2005). When defined in symptomatic (maintenance of partial diagnostic status) rather than syndromatic terms (maintenance of full diagnostic status), approximately two thirds of children continue to have the disorder as adults (Barkley, Fischer, Smallish, & Fletcher, 2002; Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1998; Wilens et al., 2009). Studying fixed and age-relevant criteras using psychometric techniques, the persistence is 46 and 66 % respectively (Barkley et al., 2002). In a longitudinal study, Biederman and colleagues (2000) found 38 % of children with syndromatic persistence, 72 % with symptomatic persistence and 90 % with clinically significant impairments at the age of 19. In a review study (Faraone, Biederman, & Mick, 2006), the portion of full syndromatic persisters at age 25 was 15 % but an additional 50 % was in partial remission. Documented childhood predictors of adult ADHD are for example
symptom severity, presence of all core symptoms, higher rates of comorbidity and especially depression, anxiety and conduct disorders as well as psychosocial problems, familial loading of ADHD and parental psychopathology (Biederman et al., 1996; Lara et al., 2009). It is suggested that the more persistent forms of ADHD have higher familial loading, including increased rates among parents, siblings and off-springs compared to less persistent forms (Faraone, Biederman, & Monuteaux, 2000).

Notably, there is a contradiction between the current conceptualization of ADHD and the criteria used for diagnosis. Despite ADHD being age-relative and defined with regard to levels of developmentally inappropriate symptoms (please see section 1.1.3 on diagnostic criterias), the current diagnostic threshold are fixed across all ages which makes ADHD statistically rarer with age. Decreasing ADHD over time may indeed reveal measurement problems as well as spontaneous remission of symptoms resulting from cerebral maturation (Barkley, 1997). Symptom decline as a true function of age are reflected in longitudinal studies of children (Biederman et al., 2000), adolescents and adults (Faraone et al., 2006) in which symptoms of hyperactivity and impulsivity tend to involve more age-related modifications than symptoms of inattention. However, the entire core symptom spectra was frequently self-reported and highly correlated with independent observers of adult patients attending an ADHD clinic (Downey, Stetson, Pomerleau, & Giordani, 1997), and other studies of adult populations are consistent with these findings (Biederman et al., 1993; Murphy & Barkley, 1996). Many authors (Barkley et al., 2002; Biederman et al., 2000; Faraone et al., 2006) suggest that the current diagnostic criterias are not sensitive enough for the clinically significant impairments that are frequently recognized among adults with persistent ADHD core symptoms. The current DSM-V work-group (DSM Taskforce, 2012) suggests that ADHD be referred to as a neuro-developmental disorder with stronger focus on developmentally inappropriate and age-relevant descriptions of behavior.

**Developmental outcome**

Similar to their childhood counterparts, adults with the disorder are consistently found to have elevated risks of developing comorbid psychiatric disorders and severe functional impairments in major areas of life. Academic and employment impairments have been carefully evaluated with regard to normal and clinical control populations and the childhood diagnosis of ADHD. Robust findings include for example more frequent job changes, greater
likelihood of quitting or being fired from job, lower rates of professional employment, fewer years of education, lower occupational achievement, lower socio-economic status, history of poorer educational performance and more school disciplinary actions taken against them, learning disabilities in college, lower grade point average and academic underachievement (Barkley, Fischer, Smallish, & Fletcher 2006a; Biederman et al., 2006a; Weiss & Hechtman, 1993). Social outcome in adult ADHD are broadly related to the same problems seen in child ADHD as well, including for example higher risks of severe psychosocial impairments such as greater social skills and interaction problems, psychological maladjustment, higher rates of divorces and multiple marriages, immaturity, fewer social acquaintances and friends, more problems keeping friends and more dating partners as compared to controls (Murphy, Barkley, & Bush, 2002). Also, there have been frequent assessments of risk-factors regarding motor vehicle driving habits in young adults with ADHD. Reports reveal no deficits in driving comprehension although there are poorer driving habits, higher rates of speeding tickets, crashes, suspended licenses, increased likelihood of driving without a license, more impulsive errors and poorer rule adjustment with reference to controls (Barkley et al., 2006a; Biederman et al., 2006a; Fischer, Barkley, Smallish, & Fletcher, 2007; Weiss et al., 1993).

Parallel to ADHD children, adults with the disorder are more likely to face amplified risks of lifetime coexisting psychopathology and nearly double at risk for injuries requiring medical attention (Merrill, Lyon, Baker, & Green, 2009) as reviewed in the light of non-affected controls. ADHD has associations with major physical health problems such as obesity (Cortese & Morcillo Penalver, 2010) and health economic studies suggest that the disorder inflicts higher total societal economic burden in the form of health care expenditures and loss of productivity compared to non-ADHD controls (Hodgkins, Montejano, Sasané, & Huse, 2011). More importantly, except from the financial costs of illness, ADHD is associated with severe social and quality-of life- costs, suicide attempts and suicide (Impey & Heun, 2012). McGough and colleagues (2005) found 87 and 56 % of adult subjects with ADHD having one or at least one psychiatric disorder respectively as compared to 64 % and 27 % of non-ADHD subjects. Furthermore, when comparing clinic-referred ADHD adults, non-referred ADHD adults and non-ADHD adults (Biederman et al., 1993), ADHD was associated with higher rates of greater disruptive behavior, mood, anxiety, substance/drug use, and antisocial disorders as well as earlier onset of major depression, dysthymia, oppositional defiant disorder and conduct disorder. ADHD increases the risk for depression and combining them severely raises the risk for diabetes, hypertension, asthma, irritable bowel syndrome, bipolar
disorder, anxiety, alcohol abuse, and other substance abuse compared to those with ADHD alone (Hodgkins et al., 2011). Similar features of the disorder are found in both genders (Biederman, Faraone, Monuteaux, Bober, & Cadogen, 2004a) but rates of mood and anxiety disorders are, as in the general psychiatric population, somewhat more common in female subjects (Bijl, Ravelli, & van Zessen, 1998). When comparing patterns of psychiatric comorbidity across the three subgroups of ADHD in 149 adult subjects (Millstein, Wilens, Biederman, & Spencer, 1997), the combined subtype was associated with greater likelihood of developing oppositional defiant disorder, bipolar disorder and substance use disorder while the predominantly hyperactive and impulsive subtype was more likely so than the inattentive subtype to have obsessive compulsive disorder and posttraumatic stress disorder, which altogether strengthens implications of diagnostic subtypes. Patterns of psychopathology and psycho-social functioning in adults with ADHD are analogous with those found in children with the disorder, the level of associated problems is even higher among adults, regardless of gender and corresponds well to current conceptualizations of the disorder as deficits of impulsivity, hyperactivity, inattention and the overall reduction of self-regulation.

**Etiological aspects**

Cumulated research on behavioral, neurological and molecular levels presents evidence for the strong genetic inheritance of ADHD as well as environmental contributions to variations in symptom presentation. The particular developmental mechanisms that underlie genetic associations and the pathways through which genetic and other factors interact and play a part over time is not fully understood. It is likely that susceptibility for ADHD is mediated by the effect of several genes, or phenotypic characteristics of small effects, that interact with each other and with the environment. Cumulated research suggests that ADHD is a pervasive, highly heritable and polygenetic disorder.

One of the best verified etiologies for ADHD is heritability and it has been carefully investigated in family-, twin-, adoption-, segregation-, and molecular studies. So for example, double-blind, controlled, large-scale family studies (Biederman et al., 1992; Larsson, Anckarsäter, Råstam, Chang, & Lichtenstein, 2012; McMuffin, Riley, & Plomin, 2001; Willcutt, Pennington, & DeFries, 2000) of both pediatrically and psychiatrically referred groups with ADHD consistently supports the notion that ADHD loads high on heritability, suggesting strong genetic etiologies for the disorder and actually, ADHD is one of the most
recognized genetic-based psychiatric disorders. However, even though ADHD is among the most heritable phenotypes with main genetic effects, this is not the same as to say that the genetic effects are predetermined or cannot be affected via interactions with environmental factors. Epigenetic studies (Haynes & Silver, 2011) put forth that except from the structural DNA, we also carry information that are regulatory and involves what genes are expressed and not. When lasting genetic expressions are inherited between cell generations, the change is called epigenetic and involves huge implications for human development that are not neglectable for an etiological understanding of ADHD. For example, experiences and exposures during early development in the utero as well as during childhood and later on are influencing both the onset and development of ADHD genetic expressions into behaviors (Nigg, 2012). The implications of recent epigenetic findings for neuro-developmental disorders like ADHD are still unwinded and interpretation of research conducted to date requires open and curious minds.

Research to date report that biological relatives to probands with ADHD display higher rates of the disorder than would be expected from biological base rates, parents has a 2- to 8 fold increased risk of the disorder (Faraone & Biederman., 1998), probability rates in off-springs are 57 % (Biederman et al., 1992), the prevalence of ADHD in siblings are 31 % (Sprich, Biederman, Harding, Mundy, & Faraone, 2000), and the overall heritability estimate is often found around .80 (Faraone & Biederman, 1994a, 1994b). Biological relatives also perform poorer on standardized measures of attention and impulsivity, i. e., Continuous Performance Tests, as compared to controls and unaffected relatives (Kollins et al., 2008; McLoughlin et al., 2011) and they also produce higher levels of motor activity (Wood, Asherson, Rijsdijk, & Kuntsi, 2009). A recent study addressing the categorical versus dimensional nature of ADHD traits among all Swedish twins born between 1992 and 2000 (Larsson et al., 2012), found a strong heritability estimate around .60 for both the extreme and the substreshold variations of ADHD symptoms. The authors suggest that ADHD are the quantitative extreme of genetic and environmental factors operating dimensionally in the distribution of all three core symptoms. The study found that ADHD was a higher order trait with the same etiological factors involved for all three core symptoms which stress the need for dimensional measures of factors involved in the transition from milder to more severe forms of ADHD along with behavioral manifestations. Interestingly, the study did not find any evidence for gender differences in the heritability estimates. Willcutt et als (2000) twin study also indicated that hyperactive/impulsive and inattentive symptoms make-up two separate but correlated
dimensions. They found that the most extreme inattentive scores were highly heritable whether or not the proband exhibited extreme forms of hyperactive/impulsive symptoms. Heritability of the hyperactive/impulsive symptoms on the other hand increased as a function of the number of inattentive symptoms presented by the proband. This suggests that there may be different etiological causes underlying hyperactive/impulsive behavior in individuals with and without additional inattention. Molecular and biobehavioral data suggest that genes play an important role for the etiology of the disorder but the fact that heritability rates are less than 1.0 (100%) in most of these studies also implies that environmental and especially non-shared environmental features play a part for the disorder. Examples of risk factors during pregnancy are exposure to drugs such as alcohol and nicotine, maternal stress and high blood pressure, premature birth and low birth weight (Grizenko et al., 2012; Nomura, Marks, & Halperin, 2010), and postnatal risk factors are severe early social deprivation such as that of Romanian orphanages (Stevens et al., 2008). The impact of environmental factors are probably also mediated by genetic factors.

The rapidly evolving research field of neuroimaging, neurocognitive and neurophysiological studies suggests that brain abnormalities and dysfunctions of for example dopaminergic and noradrenergic systems underlie behavioral core symptoms of ADHD but the exact pathophysiology is not fully understood. Substantial scientific findings points at frontal lobe dysfunctions and brain abnormalities in adult and young ADHD as compared to non-affected controls. So for example, fronto-striatal dysfunction and increased dopamine transporter density in the striatum have been found (Krause, 2008; Spencer et al., 2007). Studies with magnetic resonance imaging (MRI), have found evidence for reduced volumes in especially the right hemisphere of frontal cortex, in corpus callosum, and in subcortical structures such as the basal ganglia and cerebellum (Castellanos, 2002; Makris et al., 2007; Seidman et al., 2006). In their beautiful study, Castellanos and colleagues (2002) reported smaller and age-persistent volumes of all cerebral and cerebellar areas under investigation (except the caudate) for both male and female subjects. Also, white matter volumes have been found at reduced levels in prefrontal cortex and corpus callosum in ADHD (Filipek et al., 1997). Cumulated findings to date suggest that neural dysfunctions seen in ADHD are likely to involve several brain regions or circuits rather than a few key isolated parts of the brain. Three regions are often mentioned in the literature including the frontal areas of Anterior Cingulate Cortex, ACC (Bush et al., 1999), Lateral Prefrontal Cortex, PFC (Rubia, Smith, Brammer, Toone, & Taylor, 2005), Inferior Frontal Cortex, IFC (Rubia et al., 2005) and Orbital Frontal Cortex,
OFC (Hesslinger et al., 2002). The frontal regions seem to be important for cognitive control, regulation of behavior, to sort out distractors, allocate attention, hold task-relevant information online and evaluate reward contingencies. A second region that is often mentioned includes the striatum, i.e., caudate, putamen and ventral striatum (Castellanos et al., 2002) and/or basal ganglia and they are often discussed in relation to prefrontal regions because of the dense neural connections between these areas. Striatal connections provide signals to prefrontal areas related to cognitive control such as updating working memory, and informing about the (dys-) regularities of events. A third region is the cerebellum which has decreased volumes and reduced activation in ADHD (Castellanos et al., 2002) and are involved in expecting and detecting stimulus as well as in the timing of stimulus.

Less neural activity are found in the right mesial PFC and in the right inferior PFC in adolescents with ADHD as compared to controls during neuropsychological performance of impulse inhibition (Rubia et al., 1999). Zametkin et al. (1990) used PET in adults with ADHD and found reduced glucose metabolism in both premotor and prefrontal cortex during task performance of executive functioning which was not found in controls, and others have been able to replicate this finding (Schweitzer et al., 2000). Using the PET technique in another study, Ernst et al. (1998) found dopaminergic hypoactivity in the prefrontal cortex, and especially in the medial and left prefrontal areas. Notably, Ernst’s study found significant gender interactions in that lower ratio of function were found in male brains for both control and patient groups. Furthermore, using fMRI during cognitive task (i.e., stroop), adults with ADHD failed to trigger the anterior cingulate activation which is a region of importance for attentional networks (Bush et al., 1999) and differences in brain functioning have been documented in more recent studies of adults with ADHD and controls as well (Makris et al., 2007, 2008; Paloyelis, Mehta, Kuntsi, & Asherson, 2007; Suskauer et al., 2008). So, neuroimaging findings implicate both reduced volumes and dysfunctions in especially frontal brain areas involved in catecholaminergic regulation of motor control and attention which is consistent with genetic and psychopharmacological findings. Therapeutic dosages of stimulants such as methylphenidate block the reuptake of dopamine and norepinephrine in neurons and increases release of these transmitters into the synaptic cleft, a process that has been demonstrated to have beneficial therapeutic effects on ADHD core symptoms in children (Wolraich et al., 2001), adolescents (Schachter, Pham, King, Langford, & Moher, 2001) and adults (Biederman et al., 2006b).
Another approach to understand developmental mechanisms in the pathogenesis of ADHD has been in terms of molecular genetics which indicate both positive findings and non-replications. Molecular research has primarily focused on the functional candidate gene approach, which attempts to localize specific genes that increase vulnerability for ADHD, and the linkage analysis approach, which allow screening of broad sections in the genome to identify regions of increased susceptibility for the disorder. The candidate gene approach has mainly focused on encoding proteins involved in dopaminergic and adrenergic pathways which correspond to findings of pharmacological (Biederman et al., 2006b; Wolraich et al., 2001) and neuroimaging studies (Castellanos, 2002; Castellanos et al., 2002). Only a tiny part of the genetic contribution to the disease has been identified using the candidate gene approach and the genome wide association studies have not been able to identify significant associations for ADHD (Franke, Neale, & Faraone, 2009; Neale et al., 2010). Recently however, a neurodevelopmental protein network involved in directed neurite outgrowth was found in convergence of five published genome-wide associations (Poelmans, Pauls, Buitelaar, & Franke, 2011) and suggests further clues to the candidate gene approach for ADHD. The candidate genes with best verification are all catecholaminergic genes including dopamine receptors (DRD4 and DRD5), dopamine transporters (DAT1) and serotonin transporters (5-HTT), serotonin receptor (HTR1B) and a special protein called SNAP-25 of importance for neurotransmitter release (Faraone et al., 2005b; Li, Sham, Owen, & He, 2006).

The dopamine D4 receptor of the DRD4 gene acts on both norepinephrine and dopamine agonists and is widespread in the frontal-subcortical regions involved in ADHD. One variant of the exon III repeat polymorphism in the DRD4 (7-repeat allele) that mediates response to dopamine has been suggested to play a part in cognitive and emotional functioning and is associated with ADHD in both children and adults (Faraone, Doyle, Mick, & Biederman, 2001). The gene has been widely replicated with an estimated odds ratio of 1.16-1.45 in pooled and meta-analysis data (Faraone et al., 2005b) but it is found in far from all subjects with ADHD. The 7-repeat allele form of the DRD4 gene has also been related to higher impulsivity and activity levels during neuropsychological test performance of children with ADHD (Langley et al., 2004). There have been other studies of DRD4 polymorphism as well but they have been less conclusive (Barr et al., 2001; Kustanovich et al., 2003). Another dopamine receptor gene, DRD5, was found to be associated with ADHD in the first entire genome wide scan for genetic locations involved in the disorder (Fisher et al., 2002) and in meta-analysis (Li et al., 2006).
A dopamine transporter gene known as SLC6A3 or DAT1 has been widely studied in ADHD since methylphenidate inhibits the dopamine transporter and increases the amount and duration of dopamine in the synapses and produces therapeutic effects on ADHD symptoms (Faraone et al., 2005b). The 48 bp Variable Number of Tandem Repeats (VNTR) polymorphism in the SLC6A3 has been associated with sustained attention in children (Loo et al., 2003), and the 40 bp 10-repeat allele is correlated with higher production of the dopamine transporter and over-represented in children with ADHD (Curran et al., 2001; Faraone, et al., 2005b; Fuke et al., 2001). However, although the SLC6A3 is the best studied gene in childhood ADHD it has been studied in a few studies with regard to adult ADHD (Barkley, Smith, Fischer, & Navia, 2006b; Franke et al., 2008) and results suggest that the effect of this genotype may increase with rising age. Since SLC6A3 is mainly expressed in the striatum and not in the prefrontal cortex, it is theorized to influence striatum-related functions, i.e. delay aversion, to a higher extent than for example prefrontal executive functions. In animal studies, decreased function of this dopamine transporter has resulted in hyperactivity and impulsivity (Giros, Jaber, Jones, Wightman, & Caron, 1996), but the modes of actions caused by this gene in ADHD and especially in adult ADHD remain unclear. Other genes of interest encode the serotonin (5-HT) transporter (SLC6A4) and the serotonin receptor 5HT1B (HTR1B). Several polymorphisms have been studied for this gene and especially the 480-bp allele which has been reported to have small but significant associations to ADHD, with an estimated odds ratio of 1.13 (Faraone et al., 2005b). In summary, by means of molecular, neurobiological and behavioral studies during the past decades, ADHD has been increasingly known as a pervasive, highly heritable and polygenetic developmental disorder but the particular developmental mechanisms that underlie genetic associations and the pathways through which genetic and other factors interact and play a part over time is far from fully understood.

1.1.3 Clinical perspectives on ADHD

Definition of ADHD

From clinical perspectives, ADHD is a disorder that encompasses a triad of core symptoms including inattention, impulsivity and hyperactivity. The diagnosis is currently defined in terms of operationalized cognitive impairments (inattention, forgetfulness, distractibility) and behavioral manifestations (hyperactivity, impulsivity, fidgeting) that are synthesized by means of diagnostic subtypes currently outlined in the fourth edition of the Diagnostic and
Statistical Manual of Mental Disorders-IV (DSM-IV-TR; American Psychiatric Association, 2000):

“A. Either (1) or (2):
(1) Six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

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

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

Hyperactivity
(a) often fidgets with hands or feet or squirms in seat
(b) often leaves seat in classroom or in other situations in which remaining seated is expected
(c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
(d) often has difficulty playing or engaging in leisure activities quietly
(e) is often “on the go” or often acts as if “driven by a motor”
(f) often talks excessively

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

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

Code based on type:
314.01 Attention-Deficit/Hyperactivity Disorder, Combined Type: if both Criteria A1 and A2 are met for the past 6 months.
314.00 Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type: if Criterion A1 is met but Criterion A2 is not met for the past 6 months.
314.01 Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive-Impulsive Type: if Criterion A2 is met but Criterion A1 is not met for the past 6 months.

Coding note: For individuals (especially adolescents and adults) who have symptoms that no longer meet full criteria, “In Partial Remission” should be specified” (DSM-IV-RV; American Psychiatric Association, 2000, pp. 47-49).
Clinical assessment of adult ADHD

ADHD is recognized as a well-established mental health disorder that affects both children and adults. However, there are both professionals and folks in the general public that are unsure about the significance, necessity, components and positive outcome of diagnosing and treating ADHD in adulthood despite substantial research that provide legitimate answers to these questions. Perhaps the reason for a hesitant perspective is associated with the long-time historical view of ADHD as a childhood disorder, stigma associated with diagnosis and treatment, problems with implementing research into everyday practice, different perspectives on knowledge and the traditional separation from child and adult psychiatry (Kooij et al., 2010). Nevertheless, from clinical and empirical points of view, ADHD is a valid and meaningful diagnosis that often inflicts lifelong significant impairment in adults, currently associated with underdiagnosis and approximately 90% of adults with ADHD are untreated (Culpepper & Mattingly, 2010). There are however effective treatment alternatives available which are very encouraging given the large proportion of the world’s population directly affected by the disorder, approximately 15 million adults in the US and almost half a million in Sweden for example.

Today, increasing numbers of adult persons are seeking professional help for ADHD and its associated impairments and there is a great need for reliable assessment tools. Even though some patients may self-refer if they suspect that their symptoms may be related to ADHD and they are worried about the impact on their daily life, other patients will not recognize the symptoms and associate them with ADHD. Adults with undetected ADHD may not consider the diagnosis since the onset is often in early childhood and they assume that their behavior is normal, an assumption that may present a bias before and during an assessment since many tools are subjective self-ratings covering degrees of experienced impairment. A common screening tool is the Adult ADHD Self-Report Scale (Kessler et al., 2005b) but about a third of adults with ADHD do not screen positive on ASRS and it may therefore not be sufficient to rule-out the disorder (Culpepper & Mattingly, 2010). The clinical assessment includes data-collection and decision-making on quantities and qualities relating to psychopathology, functional impairments, duration, intensity, and differential diagnosis. The clinical assessment is based on both anamnestic and current clinical information in order to evaluate adult behavior with regard to diagnostic criterions of ADHD. Specifications regarding childhood onset may be evaluated retrospectively using anamnestic interviews, behavior rating scales,
parents’ narratives, school and clinical records. The present life-situation may be evaluated using clinical interviews, behavior checklists and psychometric techniques for assessment of psychopathology and functional impairment. Depending on the symptoms profile, ADHD will be diagnosed using one of the three diagnostic subtypes in which the combined subtype is the most common, about 2.5 percent of adults has this form and about 1.3 percent has the predominantly inattentive subtype while the predominantly hyperactive/impulsive subtype is the least common found in only about 0.9 percent of adults (Murphy & Barkley, 1996).

Diagnosing ADHD in adults requires careful consideration of differential diagnoses since core symptoms are shared with other psychiatric disorders including for example mood, conduct, substance use and personality disorders which may also exist as comorbid psychiatric disorder (Pary et al., 2002; Searight, Burke, & Rotnne, 2000). Noteworthy is that ADHD exist in about 10-20 % of the general population with mental health problems, clinical populations with substance abuse and personality disorders are especially prone to have ADHD and about 40 % of persons found in the forensic psychiatry have ADHD (Foreman, Foreman, Prendergast, & Minty, 2001; Ginsberg, Hirvikoski, & Lindefors, 2010). Two diagnoses with especial significance for differential diagnosis are borderline personality disorder and bipolar II disorder as these affective disorders presents a number of the core symptoms associated with ADHD. Bipolar disorders for example often include the attention symptom domain such as low attention span, forgetfulness and distractibility as well as the activity symptom domain with increased psychomotor activity, impulsive and intrusive behaviors as well as affective symptoms of irritability, emotional lability and tantrum outbursts which may be found in ADHD as well (Giedd, 2000; Kent & Craddock, 2003). With regard to ADHD, borderline personality disorder particularly includes the core symptom of impulsivity and this symptom significantly contributes to the severity of the disorder. Impulsivity may result in behaviors of overactivity such as motor impulsiveness, restlessness and inner stress, as well as poor cognitive, emotional and interpersonal control in both ADHD and borderline and thus the clinical presentation of the two disorders may resemble each other (Speranza et al., 2011). It is widely recognized that behaviors of ADHD are demanding to discriminate from overlapping and co-existing psychiatric conditions when the assessments are based on qualitative and unstandardized tools alone and measures that allow for quantification may be helpful in terms of both assessing symptom severity and discerning diagnoses (Murphy & Adler, 2004; Woods, Lovejoy, & Ball, 2002).
There is no omnipotent neurobiological or neuropsychological test to identify adult ADHD but instead best practice include multiple sources of information (e.g., close relatives, spouse, employers, friends, coworkers, and the patient) along with an integrative perspective (e.g., clinical interviews, family history, behavioral rating scales and neuropsychological tests) (Kooij et al., 2010). ADHD is sometimes assessed by means of clinical information alone such as interviews and behavioral check-lists, but this leaves clinicians heavily dependent upon subjective observations made by themselves and others. Multiple sources of clinical data-collection with complementing objective psychometric techniques are one strategy to potentially minimize sources of error, subjective predisposition, to increase inter-rater reliability and enhance credibility (Culpepper & Mattingly, 2010). Behavioral measures are in line with the current clinical perspectives of ADHD and allow quantification of symptom severity and validation of subjective behavior ratings made by patients and family members.

From empirical scientific quarters and by means of literature reviews (Epstein, Johnson, Varia, & Conners, 2001) of adult ADHD using recent neuropsychological, electrophysiological and neuroimaging perspectives, heavier weight on performance based assessments has been suggested for clinical and research methodologies (Doyle et al., 2005b; Frazier, Demaree, & Youngstorm, 2004), including empirically derived and age sensitive neuropsychological/neurobiological tests and behavioral measures that potentially differentiate ADHD from other psychiatric disorders with shared symptoms vis-à-vis ADHD.

Most research on neuropsychological and other assessment tools has built upon studies of children by generalizing and applying findings to adult conditions and this appears to work well for some assessment, e.g., rating scales, and treatment strategies (Krause, Dresel, Krause, Kung, & Tatsch, 2000; Levin et al., 2006). However, translation of neuropsychological findings from childhood literature upon adult ADHD has not been as straightforward as the aforementioned and from cross-sectional neuropsychological data it appears that deficits may be altered during the course of life (Barkley et al., 2006b; Biederman et al., 2000; Brocki, Tillman, & Bohlin 2010; Seidman, Biederman, Weber, Hatch, & Faraone, 1998a). There is indeed a lack of consensus regarding as to which neuropsychological deficits exist in both children and adults with ADHD and how to best operationalize and measure them. Numerous of neuropsychological domains have been suggested for adult ADHD, including for example vigilance, motor inhibition, attention, working memory, verbal learning, problem solving, planning, reaction time and its variation, abnormal arousal and other executive functions. In their review of 35 studies on the subject,
Woods and colleagues (2002) found that most of the studies (92%) reported significant differences between adult ADHD and healthy controls on at least one measure of executive function or attention, and that the most reliable measures were the Stroop task (1935) which is supposed to measure response inhibition and/or poor selective attention, a test of verbal letter fluency, the auditory-verbal learning and Continuous Performance Tests, which was most often reported by means of omission errors, commission errors and summary scores. Another meta-analytic review (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005) of 83 studies with neuropsychological measures found the strongest and most consistent effect sizes for CPT omission errors, which is related to inattention, and the Stop Signal Reaction Time test (SSRT) which is related to impulsivity. Consistent with these findings is Hervey and colleagues (2004) meta-analytic review of 33 studies in which the highest effects sizes were found for Continuous Performance Test omission errors (0.76) and the Paced Auditory Serial-Addition Task, i.e., PASAT (0.83), which assesses the capacity and rate of information processing as well as sustained and divided attention. In general, the overall results of these meta-analyses support the notion that adult ADHD is associated with weaknesses in executive functions but that weaknesses in executive functions is not necessary nor sufficient enough to identify all cases of adult ADHD. The results are also complicated by methodological limitations such as variation in sampling procedures and testing domains, as well as the challenge of validating and interpreting measures of the broad and general construct of executive functions in relation to adult ADHD. For a comprehensive review on executive functioning and development in ADHD please see Brocki (2007). It is complex to interpret in what way poor performance on neurocognitive tasks may explain underlying neurocognitive deficits in ADHD. Several theories have been postulated to account for poor performance but they have generally been developed with regard to the childhood presentation of deficits. It is not until recently that adult performance deficits were theoretically targeted by generalizing and examining previous findings into adult cases of the disorder. Some of the theories that have been put forth concern attentional deficits, poor response inhibition, altered motivational and arousal states, working memory impairments, deficient extinction processes and delayed reward gratification. For a closer look into these matters please see the theoretical section.
**ADHD core symptom endophenotypes**

As a psychiatric diagnosis, ADHD is assumed to reflect the extreme of underlying dimensional traits continuously distributed in the general population but there is a large gap between ADHD behaviors (phenotype) and candidate genes (genotype). In order to bridge this gap and aid in the genetic studies of ADHD including investigating more genetically homogenous clinical subtypes as well as validate neurocognitive measures of the disorder, there have been a number of attempts to validate endophenotypes for ADHD during the past two decades. The term endophenotype was originally proposed for psychiatric genetic research by Gottesman and Gould (2003) as an underlying, heritable, vulnerability trait that is thought to increase liability of development of a disorder. The trait, or construct of traits, can be measured at a cognitive or biological level with a better proxy of the biological etiology of the clinical disorder as compared to looking only at behavioral symptoms (Rommelse et al., 2008a). Consequently, endophenotypes are thought to be more directly influenced by genetic underpinnings than the manifest symptoms that they in turn underpin, and are also hypothesized to form an intermediate link between the genotype and the phenotype of an individual. One important assumption is that an endophenotype is less genetically complex than the disorder it underlies and also influenced by fewer genetic and environmental risk factors than the disorder as a whole which would increase the statistical power to detect the effects of individual genes (Rommelse et al., 2008a). There have been several attempts to define criterias for an endophenotype and the most commonly occurring in neurocognitive literature are that: it should be associated with the disorder, have good psychometric properties, be present in relatives to persons with the disorder to a higher extent than randomly selected persons from the general population, it should correlate between biological family-members and it should at least partly arise from the same heritability factors that also influence the phenotype (Waldman, 2005). Endophenotypes should preferably be investigated with different approaches using for example neurocognitive, electrophysiological and neuroimaging methods in order to clarify etiological causal pathways of the disorder (Gottesman et al., 2003).

In the search for neurocognitive endophenotypes for ADHD, researchers have been especially concerned with the broader construct of executive dysfunctions which have been fruitful using constructs such as working memory, planning, inhibition and set shifting (Kuntsi et al., 2006; Rommelse et al., 2008b; Shur-Fen Gau & Shang, 2010), reaction time variability.
(Castellanos & Tannock, 2002), sustained attention (Willcutt et al., 2005) and visuospatial attention (Nigg, Swanson, & Hinshaw, 1997). Empirical support for impairments in similar neurocognitive tasks have also been found for non-affected relatives to children with ADHD, including for instance executive functions during the stop task, attentional set shifting, time reproduction (Rommelse et al., 2008a, 2008b; Seidman, Biederman, Monuteaux, Weber, & Faraone, 2000), attentional control (Slaats-Willemse, Swaab-Barneveld, de Sonneville, & Buitelaar, 2007) and response inhibition (Slaats-Willemse, Swaab-Barneveld, de Sonneville, van der Meulen, & Buitelaar, 2003), which strengthens the validity of these measures as potential neurocognitive endophenotypes for ADHD. However, the results seems to be dependent upon the specific task under study as well as the manipulation of the task and there have also been reports of no conclusive evidence for impaired executive functions in relatives to children with ADHD (Nigg, Blaskey, Stawicki, & Sachek, 2004; Seidman et al., 2000) while not all measures within the executive functioning domain have been examined with regard to non-affected relatives.

Research conducted with larger twin samples has been fruitful for the area of cognitive endophenotypes for ADHD even though a majority of these participants do not have the disorder. Heritability estimates for working memory have been found in the range of 43 to 49 % (Ando, Ono, & Wright, 2001), the Wisconsin card sorting test endurance errors produced heritability estimates in the range of 37-46 % (Anokhin, Heath, & Ralano, 2003), and response interference estimates was 49 % (Stins, van Baal, Polderman, Verhulst, & Boomsa, 2004). Cognitive-experimental tasks such as the Go/No-Go task (a measure of especially response inhibition) has been investigated as a plausible endophenotype for ADHD in samples of children, adolescents and young adults (Alexander et al., 2008; Kuntsi, Andreou, Ma, Börger, & van der Meere, 2005; Rommelse, et al., 2008b) and results generally support these measures as being reliable and valid tools to investigate individual differences. Kuntsi and colleagues (2006) investigated four-hundred 7- to 9- year old twin pairs on tasks measuring inhibition, reaction time, working memory and delay aversion to find moderate degrees of heritability for the mean reaction time (.38 to .54), reaction time variability (.10 to .35), working memory performance using digit span backwards (.36), inhibition as measured with commission errors (.18) but the heritability estimate of response inhibition was higher for faster go/no-go condition (.38). As the authors point out (Kuntsi et al., 2006), heritability estimates may have been underestimated as the genetic heritability is limited by test-retest reliability which is commonly overlooked in cognitive endophenotype research but may have
serious implications on data, and the authors suggest that by creating composite scores, reliability and heritability estimates will improve since the error term may be accounted for. Such undertakings may also serve more valid examinations of the link between task performance and underlying neurocognitive deficits.

One way to see it, is that studies in the cognitive area may be more or less focused into “higher-order” cognitive processes impaired in ADHD where the executive functions play a major role, while other studies are more concerned with “lower-order” cognitive functions such as those requiring effortful control, motivation, state regulation, activation and arousal as well as the ability to allocate cognitive resources rather than the cognitive resources per se (Sergeant, 2005). An index of the latter has sometimes been the mean reaction time and reaction time variability and even though these measures has been replicated many times for ADHD (Castellanos & Tannock, 2002; Kuntsi, Stevenson, Oosterlaan, & Sonuga-Barke, 2001; Oosterlaan, Logan, & Sergeant, 1998) and it seems representative for ADHD participants in general, other studies claim that it is not a universal impairment in ADHD (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005b). In their study, Nigg and colleagues reported a general lack of heterogeneity in performance such that only about 35-50 % of the combined-type ADHD at different research sites showed deficits on reaction time variability and other commonly used measures of inhibition, processing speed, set shifting and interference control. Poor negative predictive power have been reported for neurocognitive measures in other studies as well (Doyle, Biederman, Seidman, Reske-Nielsen, & Faraone, 2005a; Hinshaw, Carte, Sarni, Treuting, & Zupan, 2002). One distinguishing feature of ADHD in the cognitive domain has been a lack of universal impairments which is not surprising given the heterogeneous phenotypic and potential genetic character of the disorder and the neuropsychological variability studied by for example Nigg et al. (2005b) and Sonuga-Barke and colleagues (2002) which have also laid the ground for suggestions concerning a dual-pathway model of ADHD (Sonuga-Barke, 2002). A common finding is that most participants are impaired on at least one measure which has led researchers (Rommelse et al., 2008a) to propose more of composite measures and constructs of endophenotypes in order to enhance positive predictive power. The Go/No-Go paradigm is expected to tap sustained attention and response control which may be interpreted as executive functions but also modulated by motivational- and state-regulatory processes, and it has been studied among children in search for endophenotypes for ADHD. Uebel and colleagues (2010) had 205 children with ADHD from 6 to 18 years of age and their non-affected siblings as well as controls to perform
the Go/No-Go paradigm with three conditions where the speed varied. The percentage of false alarms, omission errors and reaction time variability decreased with increased age while reaction time were faster for older children and the performance differences between the three conditions was smaller with increased age. They concluded that reaction-time variability and accuracy parameters such as omission errors and false alarms could be useful neuropsychological endophenotypes for ADHD and also independent of gender. With their results springing from a broad range of ages, this study illustrated that it remains unclear whether the results may be generalized to adulthood since performance improves with age which suggests further considerations of developmental aspects in the study of endophenotypes for ADHD.

Except from cognitive deficits, several studies have found that, similar to their affected siblings, non-affected children and adults have difficulties with stability of motor control (Slatts-Willemsen, de Sonneville, Swaab-Barneveld, & Buitelaar, 2005), problems with motor and response variability (Andreou et al., 2007; Bidwell, Willcutt, DeFries, & Pennington, 2007; Rommelse et al., 2008c), and impairments in the precision of motor control (Rommelse et al., 2007a, 2007b), as measured with computerized and other laboratory tasks of motor performance. Rommelse and colleagues (2008a) found that many of the neuropsychological tasks of cognition, i.e., the Stop task, shifting attentional set, and time reproduction as well as motor tasks such as pursuit, tracking, and motor timing correlated more strongly between siblings and children with ADHD than ADHD itself. Their results thus support these measures as potential endophenotypes as they are more strongly associated with the disease genetic factors than the phenotype which also makes them a potentially more powerful detector of genes involved in the disorder. Rommelse and colleagues have especially been investigating motor output deficits as a marker for ADHD with hypothesized familiality such that motor problems might be genetically related to the risk for developing ADHD (Rommelse et al., 2007a, 2007b, 2008c). With a motor timing task subjects were instructed to press a button with their preferred index finger when they thought a 1-second time interval had passed and the variability of motor timing was clearly associated with ADHD, present in non-affected siblings and correlated within families. When motor output was indexed in terms of under-versus-overproduction they found no strong support for impairments and correlations in the families however. This suggests that it is the variability in response pattern rather than a specific response pattern that would be a successful endophenotype for ADHD.
In line with the studies by Rommelse and colleagues, Wood and colleagues (2009) investigated actigraphy data during cognitive performance using measures of intensity as well as number of movements from waist and leg plus the intra-individual variability on these measures for 116 ADHD combined-type probands aged 6-18, their siblings and control siblings. The magnitude of movements and the intra-individual variability data from actigraphs demonstrated significant shared familial vulnerability for an ADHD diagnosis. The authors suggested that these two measures may be suitable candidates for future molecular genetic studies seeking to identify polymorphisms associated with the risk for ADHD. Actigraphy data on hyperactivity have also showed significant moderate heritability in a general population sample with 463 twin pairs producing an estimated heritability of 36% (Wood, Saudino, Rogers, Asherson, & Kuntsi, 2007) as well as good reliability in discriminating between ADHD and controls with a specificity of 75% (Inoue et al., 1998). Other studies have reported similar heritability estimates of 40% in both childhood twin pairs (Saudino & Eaton, 1995) and adult twin pairs (Spinath, Wolf, Angleitner, Borkenau, & Riemann, 2002). Wood and colleagues (Wood, Kuntsi, Asherson, & Saudino, 2008) also demonstrated that measures at the aggregated level, using four loci and 12 tasks provided more reliable data than the individual task measures and actigraphs was suggested as an additional source of information in studies that aim to improve phenotype definition for activity levels and ADHD. More genetic associations with actigraphy data has been reported for the DRD4 risk allele and increased activity among children with ADHD (Langley et al., 2004). In general, actigraphy data that accounts for the magnitude in addition to the number of movements seems to be reliable measures of activity level and heritability of this ADHD trait.

Another closely related branch here is the study of electrophysiological measures such as event-related spatial-temporal waves during for example CPT- performance. Here, McLoughlin and colleagues (McLoughlin et al., 2010) made testing with 21 male adults with current and childhood ADHD combined type as well as controls during two cued CPTs. The results were a pattern of altered cognitive-electrophysiological processing previously found in children with ADHD and reflected in weaker orienting attention to cues. There were also signs of weaker cognitive preparation and inhibitory processing without for example significant group differences in the number of commission errors which reflect the potential of electrophysiological measures. Interestingly, the authors speculated that the correlation between cues and inhibitory processes resulted from reduced allocation of resources to cued stimulus and reduced expectancy for Go/No-Go stimulus. This is theoretically interesting
since this would suggest that motivational and arousal processes underpin inhibitory deficits, rather than the reverse and another study have found similar results for females with ADHD (Valko et al., 2009). Altogether it is interesting that the CPT triggered these deficits even though the overt manifestation also seemed to depend upon the specific characteristics of the test employed. More specifically, the CPT-test with flankers (distractors) made the underlying deficits into manifest performance deficits to a higher extent than the test without flankers. It was also interesting that the findings were in line with previous reports of childhood ADHD and thus possibly reflected a developmentally stable profile marker. Another study (Alexander et al., 2008) investigated event-related spatio-temporal potentials with EEG in participants with ADHD aged 6-18 years ($N = 175$, $M = 12.29$, $SD = 3.08$). They performed an auditory task and a CPT with special focus on non-targets, i.e., impulsivity. Results identified associations between less levels of low frequency wave activity and CPT-impulsivity as well as associations with behavioral ratings of hyperactivity and impulsivity. The wave activity was also normalized following stimulant treatment. This suggests that the CPT test successfully triggered explicit behavior related to ADHD that was also confirmed by measurements of direct brain waves and behavior ratings. Using fMRI in a similar design (Tamm, Menon, Ringel, & Reiss, 2004) with 10 adolescent boys diagnosed with ADHD combined type and controls, the ADHD group made significantly more errors of omission and commission as well as showed marked abnormalities in brain activation during response inhibition including hypoactivation of the anterior/mid-cingulate cortex and motor areas as well as hyperactivation of the left temporal gyrus which was suggested to reflect core deficits of response and task switching abilities in the ADHD group.

Event-related potentials were used by Bekker and colleagues (2005) during the stop signal task in 24 adults with ADHD combined type and controls. ADHD participants’ performance was associated with smaller stop-event related potentials but absence of larger early responses in the auditory cortex when stop signals resulted in successful stops relative to failed stops which signified decreased attention in ADHD. Depue et al. (2010) had a sample of 31 adult participants with ADHD and 21 controls in which they performed optimized Voxel-Based Morphometry (VBM) to assess grey matter volumes and behavioral measures of CPT and the stop-signal test. ADHD participants exhibited slower processing speed, reduced response inhibition and increased response variability which correlated significantly with reduced grey matter volumes in the right inferior frontal gyrus. These and other studies suggest morphometric differences that are related to disruptions in behavioral performance tasks and
future studies will hopefully shed further light on the persistence of these deficits from a developmental perspective as well as various causal pathways that influence development and the great variability of performance deficits seen in many studies. To sum up, both cognitive-experimental and electrophysiological measures of for example executive functions, state regulation and sustained attention seems like fruitful candidate endophenotypes for ADHD and they often co-vari. Studies of motor output have also provided promising endophenotypes. Moreover, performance variability and heterogeneity has generally been characteristic of this research domain as both children and adults with ADHD seem to be marked by their variation in performance. It is often not clear what neurocognitive processes underlie performances on particular tasks or the implication of manipulating experimental tasks from a theoretical point of view. More studies are needed and especially to investigate deficits among unaffected relatives to patients with ADHD and to what extent shared genetic influences account for the correlation between neurocognitive processes and behavior manifestations in order to better understand multiple causal and developmental pathways of the disorder.

Remission of ADHD

Remission is a clinical concept first introduced by researchers at the University of Pittsburg in the study of Major Depressive Disorder (MDD) during the late 80s (Frank et al., 1991). Since then, the concept has been applied onto a number of psychiatric disorders in order to provide a rationale for the study and application of objective, measurable and clinically interpretable therapeutic end-points. Definitions have traditionally been refined and validated for psychotic and affective disorders using rating scores and finite time periods (McIntyre, Fallu, & Konarski, 2006). An example is bipolar disorder- for which a full syndromatic remission (loss of full diagnostic status) is defined as eight consecutive weeks of not meeting criteria for manic, depressive or mixed states according to DSM-IV. Symptomatic remission (loss of partial diagnostic status) is defined with minimal or no symptoms on specific rating scales also for eight weeks, and finally functional or full remission (loss of partial diagnostic status and full functional recovery) is defined as the return to premorbid functioning for at least eight weeks (McIntyre et al., 2006).
A closely related concept is response which is defined as improvements in symptoms as a result of treatment and for MDD it was usually operationalized as a 25-50% improvement in symptom scores, for ADHD the clinical trial response has usually been set at a 15-30% improvement in symptom scores (Kelsey et al., 2004; Spencer et al., 2001). In most cases, a patient who responds to this extent no longer meets the diagnostic criteria but since the initial level of symptoms is not accounted for there will be responders who still have significant amounts of symptoms and illness. In ADHD, the term response may involve a wide range of improvements and is rarely predefined and moreover- it does not necessarily indicate that the person has achieved a sufficient level of ADHD symptoms relief so that the disorder has a minimal impact on the daily life. In this regard, remission means “sufficient improvement” and has recently been introduced for ADHD (Ramos-Quiroga & Casas, 2011) even though there is yet no universal agreement upon the criteria for remission of ADHD. The need for better long-term follow-up and evaluation of treatment effectiveness with regard to predefined goals is warranted for ADHD and it may be recognized as the prolonged duration of remission commonly termed recovery or full remission in the application of other psychiatric disorders. The goal for treatment in ADHD thus ought to be full remission but the exact definition and measurement of such improvement has just recently begun evolving, and perhaps it has been delayed somewhat because of the lack of objective and reliable measures of the disorder as well as of the search for an optimal definition of the diagnostic criteria and especially for ADHD in adulthood. It is nevertheless important for clinicians to have a robust and well-defined outcome-criterion so that treatment efficacy may be rigorously evaluated and the quality of treatment may be stressed further, tailored to individual management as well as used to drop the escalation of suffering, risks and costs associated with prolonged undertreatment of ADHD.

Remission is not only regarded as the amount of symptomatic improvement but should also be accompanied with sufficient amounts of functional development to be considered successful (Steele, Jensen, & Quinn, 2006). There is much empirical support for the correlation between symptomatic and functional development and especially in ADHD since it occurs during early life and interferes seriously with academic, employment, cognitive, social and medical domains (Biederman et al., 2006a). However, there is also much support for the reverse effect- achieving a state of remission with regard to ADHD symptoms is strongly associated with improvements in these domains and the earlier the onset and duration of remission the greater functional recovery will be achieved (Barkley et al., 2006a;
Biederman et al., 2006a; Murphy et al., 2002; Ramos-Quiroga & Casas, 2011). These and many other long-term follow-up studies of ADHD patients neuropsychological functioning and symptomatic burden suggest that a proportion of patients do very well both symptomatically and functionally, i.e., spontaneous remission, and that a lower symptom load correlates positively with functional improvement. But a majority of children without efficient rate and duration of remission will continue to experience substantial suffering and diagnostic burden into their adult life.

Studies of goal-directed management with first-line ADHD treatment demonstrate satisfactory results and patients may respond to the point that they become essentially asymptomatic and clinical criteria are no longer fulfilled (Retz et al., 2012; Rösler, Fischer, Ammer, Ose, & Retz, 2009; Spencer et al., 2005). In their review on the subject, Steele and colleagues (2006) suggest that remission in ADHD be defined as “a loss of diagnostic status, minimal or no symptoms, and optimal functioning when individuals are being treated with or without medication” and further that “symptomatic remission can be operationalized as a mean total score of $\leq 1$ on most standardized questionnaires”. There have been similar proposals of working definitions for remission in especially childhood ADHD based on cut-offs from behavior rating scales such as the Swanson Nolan And Pelham-version IV (SNAP-IV; Swanson, 1995), the ADHD rating scale-version IV (DuPaul, Reid, Power, & Anastopoulos, 1998) and the Clinical Global Impression, CGI, scale (Guy, 1976). Even though this methodological approach allows psychometric and clinical evaluation to some extent it is nevertheless based on personal ratings and therefore primarily accentuates subjective experience of behavior with the risk of biasing outcome and not gaining fully from therapeutic interventions (Culpepper & Mattingly, 2010). The use of quantifiable metrics with objective outcomes and standardized interpretation permit reliable estimation of treatment effectiveness and comparisons which may be of great help for the goal of remission (Ramos-Quiroga & Casas, 2011).

For the study of ADHD symptoms, it may be noted that preliminary reports from the DSM-V work-group (DSM Taskforce, 2012) suggest forthcoming diagnostic updates for ADHD using more adapted diagnostic standards for adulthood. Revisions seem focused on developmental and dimensional aspects of the disorder which further strengthen quantification of symptom domains using well-founded criterias. Current working proposals for the diagnostic criterias reflect the notion that impairments resulting from ADHD symptoms may develop later in life.
and symptoms may not always be clearly identified until adolescence. Therefore, the age-dependent decline and natural course of the disorder will be better reflected as previously subthreshold scoring adults may achieve a full diagnosis of ADHD (Kooij et al., 2010). This is likely to affect also the number of adults considered to be in partial and full remission. Whether using behavior rating scales or other measures of assessment, a reasonable cut-off should be found in matched control populations without ADHD for calibration of efficient standards (Steele et al., 2006). Finally, remission of ADHD is likely to occur as a result of high-quality and enduring symptom relief but except from targeting core symptoms with first-line treatment, several authors have noted (Kooij et al., 2010; Nutt et al., 2007) that complementary techniques for improvement and enhancement of cognitive and coping strategies may be of great help to achieve this goal, and particularly when ADHD has triggered secondary psychiatric problems, addictive behavior, self-injury, conduct and personality problems.

**Treatment for ADHD**

A WHO rapport (Murray & Lopez, 1996) on mental disorders concluded that 30% of the total disability and premature death globally is attributable to the effects of neuropsychiatric disorders. A majority of persons with mental health disorders are not correctly diagnosed or receiving evidence-based, guideline-concordant care and improvement (Kooij et al., 2010). For ADHD specifically, there are support for underdiagnosis and undertreatment of adults despite of good empirical support for available diagnostic techniques and treatments (Nutt et al., 2007). The National Institute for Health and Clinical Excellence (NICE) provided an expert judgment optimal treatment algorithm for adult ADHD in 2009 (Kooij et al., 2010) which basically states that a multimodal treatment approach should be taken for ADHD and its associated comorbid psychiatric disorders, and preferably the treatment plan would involve the adults partner, family and/or close friends. Psycho-education is a primary component for the treatment plan and aims to educate and inform the patient and relatives of ADHD symptoms, brain mechanisms, comorbidity, heritability and treatment options. First-line treatment for core symptoms of ADHD in adults includes stimulant medication (methylphenidate, dexamphetamine) whose effects have been documented in several randomized controlled trials (Biederman et al., 2011; Retz et al., 2012; Rösler et al., 2009; Spencer et al., 2005). There have been some long-term follow-up studies (Biederman et al., 2010; Buitelaar et al., 2012; Wender et al., 2011) of stimulant treatment in adults, the longest
was for thirteen months (Buitelaar et al., 2012), and the mechanisms has been thoroughly monitored in long-term studies with children and adolescents (Hechtman & Greenfield, 2003) as well and there are good support for the appropriateness and workings of these medical agents. Pharmacotherapies especially address the core symptoms of ADHD but they also improve secondary problems like mood instability, low self-esteem, anger outbursts and social functioning (Hechtman & Greenfield, 2003). Long-term prospective studies in adulthood show that stimulant treatment in childhood significantly reduces risks of developing comorbid disorders such as anxiety, depressive and disruptive disorders and treated children were less likely to have repeated a grade (Biederman, Monuteaux, Spencer, Wilens, & Faraone, 2009). In adults, treatment considerations depend much upon the existence of comorbid disorders and a key factor for good results is skillful and qualified diagnostic approaches (Nutt et al., 2007).

Oral intake stimulants like oros-methylphenidate, mixed amphetamine salts, dexamphetamine and lis-dexamphetamine is well-known to decrease symptoms associated with ADHD due to eliciting slow steady-state dopamine increase in the brain by inhibiting reuptake and releasing dopamine. A meta-analysis of six trials (Faraone, Spencer, Aleardi, Pagano, & Biederman, 2004) including in total 140 MPH-treated adults and 113-placebo treated adults found a mean effect size of 0.9 for stimulant treatment but the effects also depended upon identifying the correct dosage and when treatment was optimized to higher doses, the effect size was 1.3. Extended release preparations have an effect between 6 to 14 hours which facilitates once-daily dosing but many adults need twice-a-day dosing in order to gain full effect from treatment (Kooij et al., 2010). Combinations of immediate and extended release preparations are often used to tailor treatment which according to experts in the field (Kooij et al., 2010) should be individualized to each person based on response and tolerability during careful titration starting with a minimum dose and increasing to effective dose with minimal side-effects rather than standardizing dose-level on a mg per kilo basis. There are currently no specialized objective tools aiming to optimize the titration process despite its crucial role for effective treatment. Second-line psychopharmacology treatment include for instance atomoxetine which is a non-stimulant that works by inhibiting norepinephrine reuptake, and even though it has good effects (Faraone et al., 2005a) it is generally not as good as stimulants.
Except from pharmacotherapy, many adults with ADHD may need additional therapeutic support to stabilize associated secondary problems and comorbidities to ADHD (Kooij et al., 2010). Various forms of psychotherapies that may be helpful are Cognitive Behavior Therapy- CBT (Safren et al., 2005) and psychosocial and family therapy that is targeted towards relationship problems (Aim, 2006). Reports indicate that psychotherapy may play an especially important role in managing ADHD for adults who are motivated and developmentally ready to acquire new skills (Weiss et al., 2008). When comparing groups with medication or medication plus CBT, the combined group demonstrated extra benefits from treatment (Safren, 2006), and other studies have found similar results (Rostain, 2008). Dialectic Behavior Therapy (Hirvikoski et al., 2011) and Mindfulness (Zylowska et al., 2008) have documented positive effects for ADHD symptoms and emotional skills in on-treatment individuals who remained stable regarding medication status. Other effective cognitive strategies involve for instance neurofeedback (Arns, Ridder, Strehl, Breteler, & Coenen, 2009), working memory training for children and adolescents (Beck, Hanson, Puffenberger, Benninger, & Benninger, 2010), and metacognitive approaches (Solanto et al., 2010).

**Gender issues**

The presentation of ADHD with regard to gender is not well understood. Gender has been considered a moderating factor in ADHD for a long time despite the fact that many studies have been conducted solely with male participants or a limited number of females and studies have often failed to control for possible gender effects among children and adults. A well-known gender difference is the prevalence since boys are three times more prone to have the disorder than girls and the ratio is even higher for childhood clinical samples, e.g., 9:1 (Hasson & Goldenring Fine, 2012). For adults, the difference in prevalence and diagnostic rates become less skewed with age since more females are identified in adulthood, and the ratio are more balanced among adult clinical samples (Biederman et al., 2004a). Two other frequently cited gender differences concern the pattern of co-morbid psychiatric disorders and the level of impulsivity and hyperactivity. Here, boys tend to present higher levels of especially hyperactive and impulsive behavior than girls (Hasson & Goldenring Fine, 2012). The moderating effects of age upon gender-differences in ADHD create a more complex and uncertain picture with regard to symptoms presentation. Even though potential gender differences with regard to hyperactive and impulsive behavior tend to persist with growing age, the impact of these behaviors upon ADHD presentation seem to decrease with regard to
gender since overt hyperactivity and impulsivity become less manifest and prevalent in older subjects (Kooij et al., 2010). Nevertheless, hyperactive and impulsive behaviors are frequently reported by adults with ADHD but their manifestations become more peripheral such as in fingers and toes for example (Barkley, Knouse, & Murphy, 2011). Adults with ADHD may become easily bored, restless, distracted and may seek stimulating, fast-paced and rewarding tasks which may be manifestations of hyperactivity and impulsivity too (Kooij et al., 2010). Another well-documented gender difference involves the pattern of comorbidity. Here, boys tend to have more externalizing disorders such as conduct disorder and oppositional disorder than girls and men are more prone to suffer from anti-social disorders and to be found within the forensic psychiatry as compared to their ADHD female counterparts (Ginsberg et al., 2010; Kooij et al., 2010; Nutt et al., 2007). Females with ADHD tend to suffer from more additional internalizing disorders such as anxiety and depression compared to males with ADHD and some research also suggest they are more prone to have the inattentive subtype and later onset of impairments (Kooij et al., 2010) while other studies of adult ADHD report no gender difference in the frequency of subtypes (Grevet et al., 2006).

Because ADHD in females are associated with less externalizing disorders, research (Biederman et al., 2004a) suggests that females tend to be diagnosed less often than males and their higher levels of internalizing disorders may mask ADHD with effects on diagnosis and treatment. Therefore, women with the most severe and manifest, i.e., male-like, forms of symptom presentation are more likely to be diagnosed (Biederman et al., 2004a). Moreover, women are more prone to seek psychiatric help than men which may influence gender ratios in clinical samples. This in turn may create a bias when studying clinical samples of ADHD since the participants’ may not be representative for adults with the disorder in general. In addition, the variability of clinical assessment and methodology hinder understanding of how gender may moderate and influence ADHD symptoms and daily functioning. Rating scales of ADHD performed by second part may for example be biased with regard gender or affected by the indirect gender-based impact of psychiatric comorbid disorders upon functioning. Subjective ratings may also be influenced by the level of awareness and may not be sufficient to address dysfunctional levels of symptom manifestations in both genders across situations (Bussing et al., 2008). Therefore, more direct observations of behavior manifestations performed on equal terms, like the CPT, are often preferred for a more objective evaluation of symptom severity and to compare with age- and gender matched norms. A meta-analytic review (Hasson & Goldenring Fine, 2012) of the influence of gender upon CPT performance
in children with ADHD examined the pattern of error response with regard to gender. Here, tests that triggered behaviors of both impulsivity and inattention were examined. Between-gender analyses yielded small but significant \( (d = 0.31) \) gender differences regarding commission errors, and boys turned out to be more impulsive than girls. With regard to inattention as in omission errors, no significant \( (d = -0.09) \) gender interactions emerged. This finding is consisted with the notion of more hyperactive/impulsive behavior among boys than girls with ADHD. Meta-regression analysis of general neurocognition with regard to gender in adult clinical samples with ADHD (Simon, Czobor, Balint, Mészáros, & Bitter, 2009) found higher levels of dysfunction among males but all subjects with ADHD were severely impaired on the neurocognitive battery as compared to non-affected controls. This supports the validity of ADHD in adulthood but gender differences among adults with ADHD in clinical samples may be related to referral-and diagnosis biases, results vary across studies, and more studies are needed to draw firmer conclusions about possible gender related differences in symptom presentation and subtype frequencies.

**Subtypes issues**

Following childhood samples with ADHD into adulthood (Biederman et al., 2000; Faraone et al., 2006) we find that symptoms decline in absolute terms but remain abnormal relative to age-matched peers. From this perspective, the most common subtype in both children and adults is the combined subtype, including abnormal levels of hyperactivity, impulsivity and inattention. Symptoms of hyperactivity and impulsivity tend to decrease or change in presentation with age, e.g., become more covert and peripheral, while symptoms of inattention are likely to persist at higher levels and be associated with obvious impact and limitations to adult life (Nutt et al., 2007). Also, the overall impact of having continuous symptoms in adulthood may heighten since functional demands increase in adulthood. Therefore, measuring ADHD in adulthood requires careful consideration of all core symptoms and accounting for the likelihood of decreased level and/or changed presentation of some symptoms. Since ADHD is a neurodevelopmental disorder, the symptoms are likely to decrease with age but this is not the same as growing out of ADHD. About a third of children with ADHD will undergo such a development that they no longer qualify for a diagnosis as adults but a majority will still have abnormal levels of ADHD behaviors and related impairments. The difference between having ADHD combined subtype and having ADHD predominantly inattentive subtype may vary from presenting none to up to five symptoms of
hyperactivity/impulsivity in addition to the minimal of six out of nine symptoms of inattention. Therefore, the inattentive subtype in its current definition is not the same as having no symptoms of hyperactivity/impulsivity and the subtype include a lot of variation regarding these symptoms. Working proposals for the next diagnostic system (DSM-V) include greater adherence to a more pure form of inattentive symptoms presentation and subdivisions of the current predominantly inattentive subtype into two constructs depending on the occurrence of additional hyperactive/impulsive symptoms. Research and clinical practice to date that builds upon the current DSM-IV system have been likely to find great similarities between the two common subtypes of ADHD with regard to symptom scores on ratings scales and behavior measures (Epstein et al., 2003; Nigg, Blaskey, Huang-Pollock, & Rappley, 2002). Objective measures of ADHD core symptoms generally report more similarities than differences between symptoms presentation across diagnostic subtypes in adulthood (Polcari, Fourligas, Navalta, & Teicher, 2010; Nigg et al., 2002). And so for example, objective levels of hyperactivity are abnormal in both ADHD combined and predominantly inattentive subtypes (Dane, Russel, Schachar, & Tannock, 2000; Polcari et al., 2010; Wood et al., 2008).

Subjective ratings, behavior observations and laboratory measures of hyperactivity and impulsivity frequently report high and abnormal symptom levels in adults with ADHD and regardless of their subtype. Future research and especially if the diagnostic subtypes are being re-defined may be more prone to find differences between the more extreme forms of ADHD such as between combined and predominantly hyperactive/impulsive subtypes and more pure inattentive subtype. It is also crucial to rule out hyperactive and impulsive behaviors based on gender- and age-matching and with regard to comorbid disorders since diagnostic subtypes so far have been indicative of variations in secondary problems and dysfunctions in various areas of life (Nutt et al., 2007). From a clinical perspective, the diagnostic subtypes have a great value for the prognosis of diagnosis and treatment but for the understanding of ADHD from life-course, phenomenological and endophenotype perspectives, all core symptoms are of great relevance for ADHD regardless of the current diagnostic subtypes. The levels of core symptom presence/absence with regard to age-matched peers may eventually be used to elucidate appropriate diagnostic subtypes.
1.1.4 The Continuous Performance Test Paradigm

The Continuous Performance Test (CPT) was originally used for testing signal detectability of radar operators, but in the 50s, development intended for psychiatric care and research begun in human subjects with brain damages (Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956). From early on, neuropsychological performance deficits were targets of much research because of the association with poor attention and impulse control. CPT-measures were found to correspond with cardinal symptoms of Attention Deficit Hyperactivity Disorder (ADHD), that is, hyperactivity, impulsivity and inattention (American Psychiatric Association, 2000) but were merely considered for child- and adolescent populations. Since then, the CPT-paradigm has expanded both by means of apparatus and techniques of testing, from merely being revolving drums on which letters are mounted side by side (Rosvold et al., 1956), it nowadays typically include computerized presentation of visual or auditory stimuli in rapid pace for a fixed time. The participant is instructed to respond to some stimuli, i.e. targets, and withholding response to other stimuli, i.e. non-targets. What the CPT paradigm actually measures is based on clinical assumptions, expert judgments (Riccio, Reynolds, & Lowe, 2001a), and face validity (Brocki et al., 2010) so that omission errors are related to inattention and commission errors to impulsivity. Inattention may be defined as the incapacity to persist during task, while impulsivity is the incapacity to inhibit inappropriate response (Kaplan & Stevens, 2002). The CPT has been described as a measure of attention and impulsivity, including measures of selective attention, inhibition or filtering of attention, focusing of attention, sustained attention (i.e., vigilance), response selection and response control (Cohen, Malloy, & Jenkins, 1999). But the CPT paradigm is primarily used to obtain quantitative information on the ability to sustain attention and to a somewhat lesser extent the ability to inhibit responses. Recent meta-analytic findings support these appraisals since omission errors more so than commission errors are sensitive to adult ADHD (Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Frazier et al., 2004). For the laboratory assessment of impulsivity, tests within the Go/No-Go paradigm are often used. Even though they are sometimes referred to as CPT tests they are different since they have a larger than 50 % target probability. The target probability affects the expectations of the participant and higher probabilities stimulate an active response style, making the Go-condition into default. Therefore, Go/No-Go tests primarily tap the ability to inhibit responses although the ability to sustain attention will also be engaged to some extent depending on the duration and other specific qualities of the test,
as well as the characteristics of the participant. Except from symptoms severeness, the participants age may affect performance on some Go/No-Go tests so that older kids, adolescents (Kuntsi, Wood, van der Meere, & Asherson, 2009) and adults (Dillo et al., 2010) with for instance ADHD manage to sustain attention and respond correctly, making the test too easy, which is referred to as a ceiling effect.

Types of CPTs
There are numerous of CPTs available, a hundred it has been suggested (Greenberg & Waldman, 1993), and the extent to which any certain CPT covers the specific areas of attention and response inhibition varies depending on the modality, type of target, measure, score and other technicalities of the CPT employed for testing. Because of the associations between memory and attention, tests of attention ought to rule out other confounding factors, such as cognitive processing and memory load so that true aspects of attention are measured.

The CPT developed by Rosvold and colleagues is called an X-type CPT and it was constructed to measure vigilance by means of letters presented at a fixed Inter-Stimulus Interval (ISI). Subjects were instructed to respond to the target letter X and to withhold responses to any other letter. The original CPT paradigm also includes the AX-type which defines X as target if preceded by another letter (A). These types of CPTs were used for patients with brain damage and successfully identified a majority of the subjects. However, modifications of the first CPT paradigm have been developed for broader psychiatric applications and include variations in targets, modalities, duration, ISI and adaptive ISI (presentation speed is interactively affected by response pattern). Type of targets include the XX-type (target must precede itself), IP-type (Identical Pair, respond if identical pairs of two digits appear in a series of successive stimulus sets), not-X type (respond to all targets except X), DTM type (respond if three targets appear in any order), and ABCD type (respond to four-target patterns). The modality may be visual, auditory or both, and in some tests for adult subjects the target may appear blurred on the screen (Riccio et al., 2001a). Effects of these modifications on performance have been studied with consistent findings suggesting that the X-type is easier than the AX- and the XX-type (Friedman, Vaughan, & Erlenmeyer-Kimling, 1978, 1981), and concerns have been raised about ceiling effects on the X-type in adult populations (Riccio & Reynoldds, 2001). In two studies comparing X, XX, and AX- types with the same ISI and target display time, Schachar and colleagues (1988a, 1988b) found increased performance deterioration and more incorrect responses in the two latter CPT types.
and more frequent commission errors in the XX-paradigm. The authors proposed that increased impulsivity and decreased reaction time demonstrate “response preparedness” resulting in a speed/accuracy trade-off effect for the AX- and XX-types.

Except for the many methods of measuring sustained attention, recent CPT paradigms also apply two broad categories of response errors into the measurement of impulsivity and these are target-related and random errors. Target-related errors refers to responses to parts of stimuli relevant for target occurrence, so for example in AX- and XX-type CPTs, the subject may respond to the occurrence of A or X when it is not followed by an X, or the subject may respond to the occurrence of X when it is not preceded by an A or X. Except for false responses, target-related errors may also be associated with delayed responses (Halperin et al., 1988), which is calculated on basis of the reaction time for fast responses. Moreover, random errors are related to responses to irrelevant stimuli for target occurrence, so for example, this would be the subject who respond to other letters than A or X in the AX-and XX-type CPTs. It is not clear however whether random errors are directly associated with any core symptom of ADHD but rather, the random-error type of commission errors have been associated with cognitive dyscontrol in general (Halperin, Sharma, Greenblatt, & Schwartz, 1991). There are other error types too such as anticipatory and multiple response styles, and they have been related to hyperresponsivity (Sandford & Turner, 1994-1999).

**Outcome of CPTs**

What the CPT variables actually measure and how various aspects of attention and impulsivity are scored, summed and reported have been the target of much attention throughout the years. Early on (Rosvold et al., 1956), the number of correct responses was reported as a measure of selective attention. Modified paradigms are built upon this principle but additional measures of attention and inhibitory dysfunctions have been applied as well. Selective and focused attention may for example be related to omission errors, correct hits, relative accuracy, total error and perceptual sensitivity, i.e., d’ or d-prime (the likelihood of responding to target or sensitivity for target versus non-target). Furthermore, sustained attention may be related to reaction time block changes, consistency and inconsistency in response pattern, vigilance decrement, block-based comparisons of accuracy and response errors. Response inhibition or impulsivity may be related to commission errors, anticipatory errors, random errors, and multiple responses, while reaction time and reaction time variation
are two measures thought to indicate cognitive processing and/or motor response speed (Riccio et al., 2001a). The standard variation of the reaction time are sometimes reported as a measure of sustained attention, but researchers (Cohan, 1995) has argued that the standard error of the reaction time is a better measure while still others (Mahan, 1996) prefer the standard deviation of the standard error of the reaction time variation as a measure of sustained attention. Other methods to make sense and utilize CPT measures include Quotients. The Visual and Auditory Continuous Performance Test (IVA) for example (Sandford & Turner, 1995), report Consistency Quotients by looking at block-based changes in reaction time, Focus Quotients by taking notice of responses with significantly different reaction times (outliers) as compared to the majority of responses, and Stamina Quotients by means of analyzing response decrement in the beginning and at the end of the task.

The most common way to interpret measures obtained from a CPT is to use direct raw scores from performance parameters like omission and commission errors into dependent variables since they have high face validity and correlate with other behavioral (Epstein et al., 2003), neuroimaging (Tamm et al., 2004), and genetic (Kollins et al., 2008) measures of ADHD. Another common way has been by means of applying Signal Detection Theory (SDT) to CPT measures (Keilp, Herrera, Stritzke, & Comblatt, 1997; Liu, Hwu, & Chen, 1997). SDT is a theory within psychophysics and a method to quantify the ability to discern between information-bearing energy patterns (called stimulus in humans and signals in machines) on the one hand and random energy patterns that are separate from the information (which are called noise and consist of random activity) on the other hand. Thus in conjunction to the CPT paradigm it refers to response styles and response criterions by means of the distribution of responses to both signal/stimulus (target) and noise (non-target). One example of an index derived from SDT is sensitivity or d’ which refers to the subjects’ response style or sensitivity towards detecting a target given the intensity of the target. Another example is response bias or Beta index (B) which is related to the subjects’ response style in terms of impulsive or conservative tendencies. However, authors (Huang-Pollock, Karalunas, Tam, & Moore, 2012; Parasuman & Davies, 1977) have questioned the use of SDT on the CPT performance paradigm since, they claim, CPTs do not fulfill criterions for SDT. For example, sensitivity towards successive discrimination requires that the target changes over time, so that the color or size of the target for instance would successively alter in order to assess potential sensitivity in target detection or d’. It is claimed that SDT theory is not suited for todays’ distinct target versus non-target distribution as the discrimination requires too little demand.
on the ability to discern between stimulus and noise and indexes like $d'$ and Beta becomes less reliable (Huang-Pollock et al., 2012). Also, authors (Parasuman & Davies, 1977) have argued that $d'$ is dependent upon duration of task and that most CPT tests do not meet duration criteria of 30-45 minutes. Moreover, it has been argued (Buchsbaum & Sostek, 1980) that $d'$ varies as a function of $d'$ in the first block and so, low initial $d'$ potentially indicate lower decrement of $d'$ in block two. Another problem in applying SDT to CPT refers to Beta dependency upon $d'$ which is reflected when $d'$ is high in block one and lower in block two which causes increased Beta to suggest conservative behavior in block two (Buchsbaum et al., 1980).

More recently, the raw score and SDT analysis of data, i.e., error rate data, have been criticized for simply reflecting the overall level of performance and not the potential level of variation during testing (Huang-Pollock et al., 2012). For ADHD research, this has been linked to the heterogeneity and variability of neuropsychological performance that is symptomatic for groups with ADHD and thus the usability of more sophisticated CPT-parameters in order to better reflect the disorder. Parameters that reflect the Performance Over Time (POT) have been suggested for this reason as they potentially measure the solidity of sustained attention and fluctuations of attention during task (Huang-Pollock et al., 2012). Significant Diagnosis and Time/block interactions would be needed in for example omission and commission errors, Reaction Time (RT), reaction time variability which is the Standard Deviation of RT (SDRT) or other types of intra-individual response variabilities. RT and SDRT measures are however more composed than the raw score measures of for example omission and commission errors which make them less readily interpretable with regard to behavior. Within a diffusion model framework it is assumed that the reaction time for instance is the results of at least three interacting processes. The processes involves the time it takes for an individual to define a stimulus, i.e., drift rate ($v$), the time it takes to decide whether or not to act upon the indication of a stimulus, i.e., boundary separation ($a$), and the time for all of the other processes that are involved during stimulus discrimination and performance, i.e., motor preparation, memory access etc. (ter). Of course these processes are assumed to be relevant during all forms of response- and non-response trials but they are one means to make sense of ADHD-related performance differences for more composed measures. Studies examining variability in the activation of brain regions involved in attentional processes has been one way to provide clinical and neuroimaging evidence for the relevance of these measures as behavioral markers of cognitive deficits. Periodic measurement structures such as POT, RT and SDRT allow for
investigation of coinciding variations in brain activation such as subtle oscillations of the default brain mode network (Castellanos et al., 2005; Depue et al., 2010) and it may therefore provide new insights into the neuronal workings of ADHD, potential endophenotypes and indications for genetic studies. Interestingly, a recent meta-analytic review of CPT studies published between 1995 and 2010 for children with ADHD compared both error rate data and POT measures. The most reliable and robust associations with the disorder were found for omission and commission errors with effect sizes of 1.34 and .98 respectively versus RT and SDRT with effect sizes of .61 and .93 respectively (corrected for both sampling and measurement error) and the POT effects were small and moderate for all variables ranging from .22 to .54. When corrected for publication bias, the RT dropped to .29, omission dropped to .97, commission to .83 and SDRT to .81 and the POT variables dropped to .18 and .14. The authors also calculated a file drawer analysis, i.e., the amount of unidentified studies that would be needed in order to reduce effect sizes to negligible levels and they ranged from 1006 for omission errors and 281 for SDRT, for POT data they ranged from 14 (POT SDRT) to 68 (POT omission). This suggests that basic measures of especially omission but also commission errors are generally more representative than POT, RT and SDRT measures when it comes to discerning CPT performance of children with ADHD. One may also mention that the meta-analysis generally found larger effect sizes for omission errors in older children and samples with larger proportion of males generally generated larger effect sizes for SDRT which suggest that omission errors may be especially sensitive to older subjects with ADHD and that SDRT may be more sensitive to gender-effects. There were no between group differences at the aggregated level for Beta (b), boundary separation (a) or non-decision time (ter) but the drift rate (\( \nu \)) was faster and sensitivity (d) larger for non-ADHD controls. Corresponding meta-analytic work for adults with ADHD has yet not been conducted for comparisons.

The many methodological differences in CPT data and the almost infinite variation of measures derived from CPTs suggest that they are not a unitary measure but more of a family of measures with different parameters and scoring indexes (Conners, 1995). Comparative analyses regarding the utility of various scores used for interpretation by clinicians and researchers has yet not been investigated systematically and one reason for this may be the lack of golden standards for construction and interpretation of test statistics to begin with. It is however encouraging to find that contemporary studies are more prone to critically analyze and compare parameters between relevant groups and assess their correspondence with
symptoms domains of ADHD in order to investigate their clinical validity and psychometric construct. CPTs applied in clinical practice require satisfactory psychometric properties and interpretation standard guidelines with relevance for the area of application.

1.1.5 Clinical applications of continuous performance tests

Areas of psychiatric application
Throughout the years, the CPT paradigm has been investigated and applied onto a broad range of psychiatric disorders in both children and adults. The top most common psychiatric disorders are ADHD (Hasson & Goldenring Fine, 2012; Hervey, Epstein, & Curry, 2004; Huang-Pollock et al., 2012; Losier, McGrath, & Klein, 1996), Schizophrenia (Ventura, Thames, Wood, Guzik, & Hellemann, 2010) and bipolar disorders (Kurtz & Gerraty, 2009). When it comes to ADHD, the CPT-paradigm has been developed with prime reference to children but frequently also being administered to adults having the disorder. However, the paradigm has been criticized for lacking sensitivity for ADHD in adults and as with the diagnostic criterions, a ceiling effect has been suggested when applying child norms to adult populations and especially in those cases with less severe symptomatology (Riccio & Reynolds, 2001). A meta-analytic review (Losier et al., 1996) of error patterns in children with and without ADHD, revealed both errors of omission and commission being significantly more frequent in the group with ADHD. Robust findings throughout the years are that children with ADHD typically identifying fewer targets, respond to more non-targets and demonstrate decreased target detection with time (Teicher, Ito, Glod, & Barber, 1996). Studies demonstrate discriminative power in children with ADHD and normative groups (Epstein et al., 2003; Ogrim, Kropotov, & Hestad 2012) but other studies (McGee, Clarks, & Symonds, 2000) present a lack thereof and especially in relation to other psychiatric disorders. The impact of comorbid psychiatric disorders, small sample sizes, age effects and the specific qualities of the CPT employed for testing have been discussed, but the CPTs are popular features of neuropsychological batteries used for both assessment and treatment strategies for ADHD. The CPT have been used for studying effects of therapeutic dosages of methylphenidate (MPH), and so for example a meta-analysis (Losier et al., 1996) revealed on average a 39 % reduction of error patterns in children with MPH versus placebo conditions.
CPT findings and adult ADHD

When it comes to between groups comparisons of adults with ADHD versus adults with and without other psychiatric disorders, i.e., discriminant validity, there is an ample amount of research. Looking at the aggregated level, groups with adult ADHD have most often been identified as impaired on CPT measures in contrast to normal controls. And so for example a meta-analytic review (Boonstra et al., 2005) of 13 studies with the Multi Health System (MHS) Standard not-X-type CPT including adult ADHD (N = 215-245) and controls (N = 189-219) reported medium to high effect sizes (Cohen’s d) for commission errors (0.64, p = 0.001), d’ (0.55, p = 0.001), omission errors (0.50, p = 0.001) and the standard error of the reaction time (0.57, p = 0.001). Another meta-analytic review (Hervey et al., 2004) of 33 studies found higher effect sizes for omission errors (Cohens´ d = 0.76) on traditional AX- and X-type CPTs with lower signal probability (i.e., GDS and TOVA) than a not-X-type CPT with higher signal probability, i.e., Conners´ CPT (Cohens´ d = 0.51). Effect sizes for commission errors were 0.63 for the not-X-type CPT and 0.26 for the traditional X- and AX-CPTs. This finding is consistent with the previous notion about target probability as a means to manipulate the speed- and accuracy- trade-off with increased levels of impulsivity and decreased levels of inattention as a result of increased target probability. Children with ADHD tend to have increased errors of commission but adults seem to be consistently impaired on at least omission errors and sometimes also reaction time variables when compared to normal controls.

Schoechlin and Engel (2005) found a significant (p = < .001) pooled weighted effect size for sustained attention (-0.52) on various CPTs (MHS, X-type, AX-type, and auditory) in their review of 50 neuropsychological measures from a total of 24 empirical studies which placed CPTs among the top discriminating measures of ADHD versus controls. Overall good specificity and predictive power in distinguishing ADHD from non-psychiatric controls were also reported in Woods and colleagues review from 2002 in which 92 % of the CPT-studies found significant differences between ADHD and controls on at least one CPT variable, most commonly being omission errors, commission errors, and the total number of incorrect indices, which reflects good overall sensitivity and positive predictive power for ADHD. Few of the studies did however report significant differences between adult ADHD and clinical controls and this goes for the CPTs as well as for the other neuropsychological tests (i.e., Epstein et al., 2001; Katz, Wood, Goldstein, Auchenbach, & Geckle, 1998; Solanto, Etefia, &
Marks, 2004; Walker, Shores, Trollor, Lee, & Sachdev, 2000; Woods et al., 2002). Overall findings are also consistent with studies on young adults and children with ADHD (Murphy et al., 2001) and illustrate the generally somewhat limited specificity and discriminant validity for ADHD versus other clinical groups by means of various CPT measures. Another recent neuropsychological meta-analytic review (Frazier et al., 2004) examined 121 studies with neurocognitive, intellectual and sustained attention measures to find the highest weighted mean effect size for CPT correct hits (1.0) and the effect size for omission errors were 0.66. The collected meta-analytic literature reports effect sizes in the range of medium to high for omission and commission errors. When comparing effect sizes for the so called FISQ (Full Scale IQ) versus other common neurocognitive measures, the FISQ measures render larger effects than those of Block design, the Stop Signal Test (SST)-probability of inhibition, Wisconsin Card Sorting Test (WCST)-categories and set failure, Rey Complex figure Test (RCT)-copy and recall. The authors concluded that FISQ measures provided as large a difference between ADHD and healthy controls as many of the other commonly used neurocognitive measures. Despite their high sensitivity, the FISQ measures were however not more sensitive than CPT correct hits and omission errors when it came to identifying adult ADHD.

Additional studies of discriminant validity include for example those of Epstein et al. (Epstein, Conners, Sitarenios, & Erhardt, 1998; Epstein, Johnson, Varia, & Conners, 2001) in which ADHD participants (N = 25), participants having anxiety symptomatology (N = 15) and normal controls (N = 30) was compared by means of Conners’ CPT (2001). Analyses yielded significantly higher rates of commission errors for the ADHD versus both other groups, and non-significant commission error rates for anxiety versus the control group. When examining test results among healthy controls and ADHD (1998), the authors found elevated rates of both omission and commission errors in the latter group. Experimental studies with small sample sizes have been typical for the examination of CPT discriminant validity but a typical finding is group differences for at least some of the parameters. Barkley and colleagues (1996) found young adults with ADHD to perform poorer than normal controls as reflected in higher rates of omission and commission errors and other experimental studies have found similar impaired response patterns for various CPT tests (Epstein, Conners, Erhardt, March, & Swanson, 1997; Epstein et al., 1998; Gansler et al., 1998; Johnson et al., 2001; Murphy, Barkley, & Bush, 2001; Seidman, Biederman, Faraone, Weber, & Ouellette, 1997), while other studies found only significant effects for commission errors
(Cohen & Shapiro, 2007; Ossman & Mulligan, 2003; Shaw & Giambra, 1993), omission errors (Johnson et al., 2001; Weyandt, Mitzlaff, & Thomas, 2002), reaction time (Holdnack Moberg, Arnold, Gur, & Gur, 1995), or response speed (Himelstein & Halperin, 2000; Johnson et al., 2001). A larger study (Nigg et al., 2005a) with neuropsychological tests and CPT in ADHD \((N = 105)\) and normal controls \((N = 90)\) found two major factors called the executive factor and the speed factor that differentiated participative groups and were related to inattention and hyperactivity-impulsivity respectively, and interesting was the finding that factors was unrelated to participants age, IQ, gender, educational level and comorbid disorders. An attempt to estimate executive functioning abilities and controlling for non-executive task demands was made by Boonstra et al. (2010) who operationalized and compared executive functioning domains (inhibition, fluency, planning, working memory and set shifting) with control domains of non-executive functioning (i.e., vocabulary, response speed, perceptual-motor skills, finger tapping motor speed, verbal short term memory) in which the Conners CPT commission errors were classified as an index of inhibitory executive (dys-) functions. After controlling for non-executive functioning demands and IQ, adults with ADHD showed impairment in inhibition (CPT) and set shifting (operationalized as the mean reaction time of the change task which is an extension of the Stop Signal Test plus the shifting module from the WCST) but not in any other executive functioning domain. This led the authors to suggest that neuropsychological difficulties may not be restricted to executive dysfunctions in adult ADHD and that the field is in urgent need for better designed test with clinical specificity.

An interesting study (Ginsberg et al., 2010) was conducted with ADHD long-term prison-inmates \((N = 30)\), ADHD outpatients \((N = 20)\) and healthy controls \((N = 18)\). The prison inmates had high rates of comorbid disorders including for instance antisocial personality disorder (96%) and substance use disorders (100%) with 63 % having a preference for amphetamine. The ADHD prison group showed poorer results on several measures of cognitive control, including Conners’ CPT II omission and commission errors, compared with both other groups and also when controlling for estimated IQ. However, the ADHD psychiatry group (whose potential comorbidity was not reported) showed similar results as the control group. Notably, there were no group differences in reaction time but a measure considered to reflect flexibility (CPT perseveration) was highly marked in the ADHD-prison group only as they were less flexible. Even though interrelated causal pathways and effects of long-term substance use are complicated, laboratory findings that present high clinical
specificity for a subgroup of persons with ADHD may serve as a valuable marker for identification and prevention of subjects at high risk for developing substance use and antisocial character. Using a somewhat similar design, Roy-Byrne et al (1997) compared groups \((N = 46-51)\) with “Probable ADHD” (adults with diagnosed ADHD), “Possible ADHD” (current ADHD symptoms without credible childhood history) and “Not ADHD” (clinical controls) by means of Connors’ CPT and found the Possible ADHD- group to have most errors on the composite CPT score, while the Not-ADHD-group had the least errors and the Probable-ADHD-group was located between the other groups- a finding that may serve as an illustration of the dimensional nature of the disorder. Two other studies (Downey et al., 1997; Seidman et al., 1998b) used an X-type CPT and found more omission and commission errors by using normative data from TOVA (Test of Variables of Attention, please see the section on TOVA below), and by using normative and clinical controls (adults with schizophrenia). Here, the adults with ADHD made fewer errors than clinical controls but more errors than normative controls, but even though the Schizofrenic group was possible to identify, the ADHD group was not possible to differentiate from either normative or clinical controls using the X-type CPT. This type of test may be too easy for detection of adult ADHD (Dillo et al., 2010; Kuntsi et al., 2009) but the finding is also rather typical for experimental studies with clinical controls.

For the most part, CPT studies in adults with ADHD are constrained by the fact that small sample sizes and assorted CPT paradigms limits the statistical power to detect effect sizes and generalize specific findings. To date, there has not been any meta-analytic work conducted specifically for CPT findings and comparisons of different CPTs among adults with ADHD. Instead, meta-analytic reviews have focused on comparing neuropsychological tests and test domains for adult ADHD in general and here, the CPT is considered a common test of sustained attention and response inhibition. When the CPT is compared to commonly used neuropsychological tests in terms of discriminant validity among healthy controls, the paradigm have among the highest levels of predictive power and sensitivity for detection of ADHD. Relatively few studies with in-between group designs report the levels of sensitivity and specificity for CPT measures but instead the statistically significant group differences are reported. It deserves to be mentioned that even though statistically significant group differences are a typical finding for participants with ADHD and normal participants, these findings do not automatically support the ecological validity and diagnostic utility of CPT tests. Group statistics may for example not be applicable in individual cases and therefore, in
addition to group statistics, it is useful for clinicians to look for reports on the levels of sensitivity, specificity, as well as positive and negative predictive power. There is a lack of between group comparisons for adult ADHD and clinical controls when it comes to the CPT paradigm as well as other neuropsychological tests. The existing literature presents mixed results but there seems to be a general lack of specificity and negative predictive power when clinical controls are involved. But again, single studies with between group comparisons are difficult to generalize across the CPT paradigm and more studies that are ultimately accumulated on a meta-analytic level are needed in order to better understand the limitations and strengths of various CPT measures among ADHD and clinical controls.

Another aspect of the validity of CPT measures in adults with ADHD are convergent validity as in associations with other behavioral and cognitive measures such as behavioral ratings and observations, cognitive-electrophysiological activity measures during performance, and neuroimaging assessment of cerebral mechanisms involved in attention and inhibition. Some of the studies examining CPT measures as possible endophenotypes (section 1.1.3) include validity aspects since the connections between laboratory performance and ADHD genetic analysis are being investigated within that framework. Starting by looking at convergent validity in terms of associations with other behavioral measures in children and adults, Epstein and colleagues (2003) examined relations between CPT variables and phenotypic behaviors reported by parents of children in an epidemiological sample of children (N = 817). Parents were interviewed according to the Child and Adolescent Psychiatric Assessment (CAPA) diagnostic algorithm about the presence/absence of the 18 DSM-IV ADHD symptoms in their children who performed the Conners CPT. According to the CAPA interview, 2.6 % of the sample had ADHD and 81 % of these were male. The CPT measures predicted the presence of most ADHD symptoms but a majority of the measures did not present associations with specific symptoms or symptom domains but instead with multiple symptom domains. The mean reaction time was the only parameter that did not show this association with the ADHD symptom domains. Interestingly, overall omission errors and omission errors over time was related to several inattentive symptoms as well as impulsive symptoms. This pattern was found for the total rate of commission errors with regard to impulsive and inattentive symptoms as well which made the parameters less specific of ADHD symptom domains but instead indicative of global ADHD symptomatology. Another similar study (Avisar & Shalev, 2011) for adults with ADHD (N = 51) and non-ADHD participants (N = 91) with a good gender-blend included the conjunctive CPT which is a 10
minutes 30 % target probability test. The target is one out of 16 possible geometrical shapes with different colors and the ISI are randomly intermixed. Participants also completed the 25-item Wender Utah Ratings Scale (WURS) which measures retrospective ADHD symptoms. Since there were no gender differences, all within group data were pooled together. Between group differences included all CPT measures of omission, commission and SDRT as well as the WURS subscales of inattention, oppositional/defiant behavior, dysthymia and total. Pearson’s ($r$) intercorrelations between CPT proportions of omission, commission and SDRT was strong ($p < 0.001$) and of medium size ($r = 0.33 – 0.48$) in the overall sample and even higher ($r = 0.33 – 0.64, p < 0.05 – p < 0.001$) in the ADHD group. Pearson’s overall correlations between CPT and WURS domains were significant both for the SDRT and omission errors (which are both assumed to reflect sustained attention) vis-a-vis inattentive ratings and for SDRT strong also for the oppositional/deviant and total scores. The percentage of commission errors only had a positive non-significant trend to correlate with WURS domains. The authors suggested that the non-significant results of commission errors in relation to WURS factors may be due to greater variability in SDRT (of correct response) compared to the other CPT measures which was reflected in the overall low error rate (circa 1.1 %) for adults performing the conjunctive CPT.

It may also be noted that retrospective ratings of childhood symptoms may not be captivating enough of the present symptomatology in order to correspond with current behavioral measures. However, determining if an adult had significant ADHD symptoms as a child is required for a diagnosis in adulthood but adults have also been shown to be poor historians of their ADHD symptoms in terms of low correspondence with parent ratings (Wender, Reimherr, & Wood, 1981) which may also have been reflected in the above study and altogether indicative of the usability of collecting both current and previous symptoms. Comparisons of Conners CPT measures and behavioral ratings from an interview of DSM-IV symptoms in adulthood (Epstein, Conners, Sitarenios, & Erhardt, 1998) separated symptom domains of inattention and hyperactivity/impulsivity as well as the total ADHD score symptomatology but none of the investigated correlations for CPT measures were significant ($p > 0.05$) despite the significant between group differences for CPT measures. Sensitivity for ADHD was 55 % and specificity among normal controls was 76 %. Other studies (Asbjörnsen, Jones, Munkvold, Obrutz, & Manger, 2010; Rasmussen, Almvik, & Levander, 2001) with CPT measures and WURS generated significant correlations with for example Conners CPT omission errors ($r = 0.39$) when screening for above threshold levels of ADHD
symptoms among prison inmates while other studies in similar populations did not (Mackin & Horner, 2005) which makes the convergent validity with childhood symptoms somewhat conflicting and challenging to evaluate. CPT parameter correlations for ADHD symptom domains have yielded somewhat conflicting results with a tendency of the parameters to be indicative of the level of global symptomatology rather than specific symptoms or symptom domains but results also seem to be dependent upon what behavior ratings and CPTs are employed for the assessment.

Moving on to some of the cognitive-electrophysiological correlates for CPT measures we learn that the most regular finding of childhood ADHD is impairments in the covert attentional orienting, attentional resource allocation, as well as the expectation and preparation to cued stimulus during CPT-OX which typically results in omission errors (Banaschewski et al., 2003, 2004). Two studies for adults with ADHD conducted by McLoughlin et al. (2010, 2011) found similar patterns of altered cognitive-electrophysiological processing using the CPT-OX and a CPT with flankers. Significant group differences were found in the number of omission errors, mean reaction time, SDRT and SDRT/MRT with the ADHD group being slower and more variable than controls (2010). There were however not significant increases in the number of commission errors despite evidence of abnormal cognitive processing which illustrate the usability of electrophysiological evidence. The group with ADHD showed reduced attention towards cues in the flanker CPT which was also correlated with reduced expectancy and worse performance with regard to upcoming stimulus and also associated with reduced strength in inhibitory processing, two processes claimed to be measured with CPT parameters. There were also important findings regarding the causal mechanisms of these cognitive processes as the reduced level of attention contributed to the response inhibition deficits. This indicates that the underlying cognitive processes resulting in poorer CPT performance in adult ADHD is related to attentional and inhibitory deficits also presented in children with the disorder and therefore proposed to be developmentally stable by the authors. The same authors also completed a family designs study (McLoughlin et al., 2011) adding further evidence to the 2010 study findings of the attentional and inhibitory deficits underlying CPT performance of adults with ADHD as well as its familial associations.
Further confirmation of the developmental stability of these underlying cognitive deficits and their relevance for understanding CPT performance of people with ADHD have been reported in several other studies as well (Alexander et al., 2008; Fallgatter, Brandeis, & Strik, 1997; Valko et al., 2009). For example, Alexander and colleagues (2008) had a visual CPT and examined adults with ADHD ($N = 175$) including representative proportions of all three diagnostic subtypes and their age- and gender matched controls and 65 of the ADHD participants re-performed the test after stimulant medication. The authors found decreased wave activity on the mean of 1 Hz during CPT which was consistently related to several behavioral measures of the DSM-IV symptoms ratings. The abnormal wave activity was correlated with false positive responses (commission errors) in the ADHD group only and they were also consistent with measures of hyperactivity/impulsivity rating scores. The peak correlation between wave activity and behavior scores occurred at approximately the same time and frequency as the maximal group difference between the ADHD and their matched controls on the wave activity measures during CPT. Post-medication measures yielded significant increases in the mean wave activity and the wave activity profile became markedly similar to that of control subjects and medication therefore normalized the activity level of ADHD subjects. The subjects who had the biggest drop of false positive responses on the CPT also had the biggest increases in brain activity following medication. There were no significant correlations in time or frequency between wave activity and the inattentiveness scores on the CPT however.

Valko (et al., 2009) examined ADHD related deficits during CPT-OX performance in children and adults with ADHD as well as controls to find similar but not identical deficits across age including correlations between overt behavioral performance on the one hand, i.e., greater variability and slower reaction time and more omission errors, and covert measures of brain activity on the other hand, i.e., weaker activation of posterior sites for children and weaker frontal activation for adults. Their results suggest a developmental change of ADHD-related impairments during CPT, from weak posterior activation among children to weaker anterior activation among adults with ADHD. Children also had a pattern of more anterior deficits during a flanker CPT compared to an easier standard CPT which resembled a shift toward the more ADHD-adult-like patterns. Other studies have showed that the anterior sites, involved in response preparation, are involved after age 11 which reflects the later development of these areas (Bender, Weisbrod, Bornfleth, Resch, & Oelkers-Ax, 2005). Bender et al. (2012) included three sources of measurement when they assessed 195 healthy
adolescents with regard to CPT-AX performance, genotyping and electrophysiological indices. There were significant interactions between two functional polymorphisms with regard to omission errors, namely DAT1 and COMT which has to do with dopamine transporter function and the control of duration of dopamine action respectively. Notable, neither mean reaction time, reaction time variability nor commission errors were associated with genetic influence. There were also significant correlations between COMT and DAT1 with the lateralized motor PINV amplitude which is related to motor and cognitive response evaluation. The PINV in turn was also related to the number of omission errors ($r = -0.19$, $t = 2.5$, $p = 0.01$) so that stronger processing of motor response on correct responses was associated with higher level of omission errors. There were no associations between the other CPT measures and the electrophysiological measures.

In order to assess neural circuitry related to ADHD impairments during CPT and other attentionally-demanding laboratory tasks, techniques like fMRI have been employed to determine the set of brain regions whose activity is correlated with objective measures of symptom severity. Studies have examined both intra- and inter-individual variability of activation of brain regions during attention-demanding tasks and found that CPT indices provide measures of brain function in areas hypothesized to be involved in ADHD such as the anterior cingulate cortex, ACC, and dorso-lateral prefrontal cortex, DLPC. These areas are involved in motivated behavior, response inhibition, working memory and related also with symptoms in ADHD (Rubia et al., 1999, Rubia, Smith, Brammer, & Taylor; Rubia et al., 2011). Findings with CPT-OX in samples of adult combined subtype ADHDpersisters, ADHD partial remitters and controls includes for example lower NoGo activation in several brain regions such as the left premotor and prefrontal cortex which is crucial for orienting and selective attention (Schneider et al., 2010). The patterns of decreased cerebral activation in many of the fronto-striatal and -parietal networks in ADHD during CPT were correlated with increased behavior ratings of higher inattention, impulsivity and hyperactivity scores as well. A wide range of laboratory tasks assessing inhibition and/or attention, such as the stop task, Go-/NoGo tests and tests of cognitive interference have been investigated and found to generate abnormal patterns of activation in subjects with ADHD (Durston, Mulder, Casey, Ziermans, & van Engeland, 2003; Rubia et al., 1999, 2007, 2009; Teicher et al., 2000; Vaidya et al., 2005). During Go-/No-Go tasks with male adolescents with ADHD and their controls, Tamm et al (2004) reported increased levels of omission and commission errors accompanied by between group brain activation differences directly related to behavioral inhibition such as
the right anterior/mid-cingulate cortex. Cubillo and colleagues (Cubillo et al., 2010; Cubillo, Halari, Giampietro, Taylor, & Rubia, 2011) have found similar patterns in grown up children with persistent ADHD using a response and inhibition task and the task response and brain activation pattern showed great similarities with those typically observed in childhood ADHD, i.e., fronto-striatal dysfunctions as well as negative correlation between brain activation and behavioral measures of symptom severity. This type of research suggests brain functional abnormalities during CPT and other laboratory task of attention and impulsivity that are correlated with behavioral measures and remains persistent in adult ADHD. The outcomes have been suggested to be more fully investigated with regard to diagnostic subtypes, comorbidities and possible gender differences as well as controlled for a history of medication since these agents may produce permanent changes of brain functioning and possibly produce compensating strategies (Cubillo et al., 2011; Solanto, Schulz, Fan, Tang, & Newcorn, 2009).

Another interesting approach for validation of CPT measures as involving ADHD-specific biological impairments is exemplified by Gizer and Waldman (2012) who found associations between inattentive CPT-AX scores and dopamine genes like DRD4 and with impulsive scores and DAT1 in a sample of 165 children with ADHD and their siblings between 6 and 18 years of age. The CPT inattention index also moderated the relationship between inattentive symptoms and the DRD4 so that the higher levels of CPT inattention co-occurred with the higher levels of inattentive symptoms and their genetic expression. Barkley et al (2006b) investigated relations between CPT performance correlates with gene polymorphisms in young adults with ADHD and found that those participants with a variation of the DAT1 made more errors of omission than participants without it. However, there have also been conflicting results among studies assessing response inhibition, variability and sustained attention with regard to gene polymorphisms and while some of these studies find associations between especially DAT1 and DRD4 with laboratory and CPT measures (Kuntsi et al., 2006; Rommelse et al., 2008a, 2008b, 2008c, 2008d), other studies have not been able to replicate these findings (Barkley et al., 2006b; Johnson et al., 2001). This research area is promising but it also seems like there is a great variation in both the results and in the study protocols and measurements used for assessment which makes direct comparisons and conclusions with regard to CPT measures complicated.
Yet another aspect of the validity of the CPT measures in adult ADHD is the ability to measure behavior changes by means of well-documented treatment such as stimulants, i.e., predictive validity. Here, there has been a great deal of research that generally supports the utility of CPT parameters to direct significant pre-post/treatment differences among children and adults. Across studies it also seems like performance indications may be a function of both the medication as well as the task difficulties and there is no consensus as to which parameters that has the best predictive ability. Common findings (Riccio & Reynolds, 2001; Riccio, Waldrop, Reynolds, & Lowe, 2001b) are that a mean effect size for the CPT paradigm is around 0.56 with an average error rate decrease of 75 % including reductions in both omission and commission errors as well as increased reaction time and SDT measures like d’.

A review of the effects of stimulants on objective measures (Swanson, Baler & Volkow, 2011) reported that medication produced significant reductions in response errors as well as faster and more accurate responses for lower and higher doses in children. Biederman et al (2008) assessed a large cohort of adolescents and adults (N =120) that had been followed from childhood and a majority (n = 94) were not taking stimulants while the rest (n = 26) did. When they were compared on a large set of neuropsychological tests including a CPT and also with regard to controls, the subgroup without medication performed worse than both other groups while the ADHD subgroup on medication performed better than the non-medicating ADHD group. A meta-analysis by (Pietrzak, Mollica, Maruff, & Snyder, 2006) compared the nature, magnitude and types of cognitive effects of clinical doses of stimulants and found better performance following treatment for some tasks including the CPT and other tasks of attention and vigilance but not for tasks of for example planning and cognitive flexibility. The analysis included 17 studies with CPT tests, and 12 of them, i.e. 70.6 %, reported positive medication effects, 33 % reported effects to low doses and 100 % reported effects for high doses. Even though CPT performance generally improved with higher doses, the authors found that there exists both intra- and inter-individual variation with regard to medication effects that should be taken into consideration for evaluation of medication as well as of test performance. Four CPTs that are available for the clinical practice and perhaps associated with the greatest amount of research for ADHD will be mentioned briefly.
The Gordon Diagnostic System

The Gordon Diagnostic System, GDS (Gordon, 1983) was one of the first commercial tests to be widely used in clinical practice and it has been extensively researched as well. The GDS is a separate microprocessor generating 11 computerized tasks and two of them are continuous performance tasks, i.e., the vigilance and the distractibility task, which are available in editions for preschool children (4 to 5 years old), children (6 to 16 years old) and adults (Gordon, 1983). The adult vigilance task is a fifteen minutes AX-type consisting of two-target number combinations of 1 followed by 9 during an ISI of 1000 ms and a target display of 200 ms for three blocks with real-time performance monitoring. In addition to vigilance, the task is assumed to include cognitive skills, behavioral regulation and motivational aspects (Gordon Systems Inc., 1986). The distractibility task is the exact same AX-type CPT described above combined with distracting digits presented onto the screen simultaneous as the standard stimuli in order to investigate levels of sustained attention. No scoring lists are provided for GDS and the results therefore are based on subjective interpretation and qualitative information. Normative data are available for preschoolers, children and to a somewhat lesser extent adults (Gordon Systems Inc., 1991; Gordon & Mettelman, 1998). However, normative data are not related to either CPT performance or observational scales in the GDS manual. Bauermeister and colleagues (1990) collected 433 children and adolescents (6 to 16 years of age) from Puerto Rico and randomly matched them with childrens GDS normative data on basis of age and gender which yielded statistically significant cultural differences as reflected in the American children having higher levels of correct hits, efficacy ratios and fewer commission errors than children from Puerto Rico. A small study by Mackin and Horner (2005) investigated relationships between the GDS and WURS among adult males with ADHD plus controls and found no associations ($p > 0.05$). Barkley et al (2006a) followed controls and children with ADHD into adolescence and adulthood with the GDS and other neuropsychological measures and found no between clinical group differences on the CPT but major life quality and psychiatric status differences. At follow-up, more omission errors were displayed in the subjects with a genetic polymorphism regardless of them having ADHD or not.

Test-retest reliability have been studied with non-referred and referred children on the vigilance and distractibility task (Gordon Systems Inc., 1987), and reliability estimates for the non-referred group of children was 0.72 for total correct hits and 0.84 for commission errors.
on the vigilance task, and for the referred group it was 0.68 and 0.94 on the same tasks respectively. Internal consistency reliability has been investigated for the vigilance and distractibility tasks even though the task demands are somewhat inconsistent and the correlation coefficients range from small ($r = -.22$) to moderate ($r = .57$) associations for different measures of the tasks. In one study by Johnson and colleagues (2001), the Gordon Diagnostic System demonstrated significant differences between adults with ADHD and controls for omission errors on the vigilance task only.

**Conners’ CPT**

The Conners CPT tests (Conners, 1992, 1995) is probably the most researched and utilized CPT, available in two standard editions and nowadays the second edition, i.e., CCPT II, is more commonly applied in clinical practice. The standard version is a not-X-type CPT and the second version is an AX-type CPT, both prolonging for 14 minutes, consisting of six blocks divided into three sub-blocks respectively, each sub-block entails 20 trials with a majority of non-targets and some targets, i.e., X, presented for 250 ms on the screen with both inter- and intra-block ISI variation so that each sub-block includes ISIs of 1000, 2000, and 4000 ms respectively, presented in distinct orders for the three blocks. Both of Conners’ tests belong to a customized CPT paradigm which provides almost endless variations of testing conditions and results. Clinicians and researchers may for example manipulate the number of blocks, number of targets per block, target frequency, length of letter-target combinations, number of trials, stimulus display time and ISI. This creates a plethora of research opportunities but the clinical interpretation and standardization are set aside within such a paradigm posing major reliability and validity challenges onto the analysis of data. The test produces the following measures; omission errors, commission errors, correct hits, mean reaction time, SDRT, standard deviation of the standard error for each sub-block, $d’$, Beta, changes in response time measured in slope, reaction time for sub-block ISI changes measured in slope, as well as standard errors of sub-block ISI changes measured in slope. The report is generated by means of the software program together with an interpretative guide that includes two brief case samples of children that highlight the importance of integrating results with other pieces of information (Riccio et al., 2001a). The manual (Conners 1992, 1995) reports no temporal, internal consistency or test-retest reliability measures but clinical validity studies on children with ADHD and a normative sample is reported that indicate for
example false negatives and false positives rates of 13 % respectively. When it comes to correlations between CPT II and other test for both children and adults, non-significant associations have been revealed (Epstein et al., 1998; McGee et al., 2000). There have been negative correlations between IQ scores and omission errors on this test, which raises questions of the validity of the measure (Weiss & Totten, 2004). When comparing the Conners not-X test, i.e., more of a response inhibition task, with the AX-CPT, i.e., more of a sustained attention task, among normal adults, Ballard (2001) found that the AX-test produced performance decrement across blocks while the not-X test produced improvements in performance over time. The authors suggested that the two versions of the Conners CPT may therefore represent tasks of different cognitive functions.

The Test of Variables of Attention (TOVA)

TOVA (Greenberg 1988-1999; Greenberg & Kindschi, 1996) and the TOVA auditory, TOVA-A (Cenedela, 1996; Greenberg, 1996-1999; Greenberg, Kindschi, & Corman, 1999; Leark, Dupuy, Greenberg, Corman, & Kindschi, 1996), is an X-type CPT available in clinical standard versions for children and adults and a screening version for pre-schoolers. The TOVA target is a colored square with a smaller square at the top edge while the non-target has the smaller square at the bottom of the larger square, and TOVA-A target and non-targets are two tones. Both clinical tests prolong for 22.5 minutes while the preschool version lasts for 11 minutes. The clinical versions have random target presentations for 100 ms with an ISI of 2000 ms during four intervals where the two first intervals are defined as target-infrequent and designed to assess attention by means of target-presentation rates of 22.5 % while the latter intervals are defined as target-frequent and designed to measure impulsivity using target presentation rates of 77.5 %.

The TOVA tests provide the following measures; omission errors, commission errors, mean correct response time, standard deviation of response time, and d’. Omission errors are reported as the difference between number of possible responses and number of correct responses minus the anticipatory responses (responses made within 200 ms after presentation of target/non-target). Similarly, commission errors are reported as the difference between the number of incorrect responses and the number of possible non-targets minus the anticipatory responses. The report also include multiple responses, anticipatory responses and the reaction time of post-commission responses, i.e., the average response time for the correct responses.
after committing a commission error. Measures are presented also in a total index called the ADHD scale, in which the results are automatically compared to age and gender matched controls with ADHD by means of the software program database.

Internal consistency reliability has been investigated (Leark, Dupuy, Greenberg, Corman, & Kindschi, 1996) for childrens TOVA and TOVA-A on separate high and low target frequent conditions with estimates ranging from a low .52 (d’ in target infrequent condition) and a high .99 (reaction time for target frequent condition), and similar results were reported for TOVA-A, ranging from low .63 (d’ in target infrequent conditions) and high .99 (reaction time, reaction time variability and omission errors in both target frequent and infrequent conditions). Other studies (Llorente et al., 2001) have found strong internal consistency and test-retest reliability for childrens TOVA, ranging from .51 to .82 when compared at a four month follow-up in which omission and commission errors were found have the lowest reliability estimates and measures of reaction time and reaction time variability had the highest. Clinical validity has been investigated for children on the TOVA as well (Leark et al., 1996) and sensitivity was found to range from 60 to 76 % while the false positive rates ranged from 80 % to 90 %. The test has been utilized in children and adults both as an assessment and medication tool and results are generally satisfactorily (Leark, Wallace, & Fitzgerald, 2004; Weyandt, Rice, Linterman, Mitzlaff, & Emert, 1998) but differences between a small number of young adults with ADHD and controls only involved those of omission errors. In one study, Forbes (1998) found significant differences between groups of children with ADHD and controls in that 80 % of the ADHD group and 72 % of controls were correctly classified.

The Integrated Visual and Auditory CPT (IVA)
The IVA is an X-type CPT (Sandford & Turner, 1994-1999; Sandford & Turner, 1995) presenting both visual and auditory stimuli during 13 minutes with modalities being altered within the same task. The target is the letter 1 and non-target is 2, both presented pseudo-randomly in a fixed order on the screen and via speakers during 500 trials with an ISI of 1500 ms. Target to non-target frequency and modality are altered during blocks in attempts to reduce learning effects and weariness and to stimulate potential latencies of committing omission and commission errors. IVA generates 11 raw score measures, 6 quotient scales and 2 composite measures that are provided for the audio and the visual tests separately. The
composite scores are the Response Control Quotient (RCQ) and the Attention Quotient (AQ) that are provided in total and for the separate modalities and each composite measure incorporate three of the quotient scales. RCQ consists of the quotients called prudence (lack of commission errors), consistency (presence of minimal variability in response time), and stamina (maintenance of response time across testing). AQ consists of the quotients called vigilance (lack of omission errors), focus (response time outliers across testing), and speed quotients (Sandford, Fine, & Goldman, 1995a, 1995b; Turner & Sandford, 1995a, 1995b). The IVA also generates parameters called comprehension (including random errors), persistence (decrement in performance), sensory/motor (slow reaction time that may impair performance), readiness (performance differences along with target frequency), and balance (differences of performance on the modalities).

There is a 21-step procedure for diagnostic decision making and a section on how to rule out ADHD in adults (Riccio et al., 2001a). A measure called Performance IQ (PIQ) is assumed to adjust normative standards for nonstandard performance and is used to identify scores with high PIQ (above 120) and low PIQ (below 80), i.e., clinicians are recommended to use older age ranges for persons with high PIQ. However, as Riccio and colleagues (2001a) points out, there is no evidence that the assumptions underlying this interpretation of CPT data is valid or that the PIQ scale is pertinent for this purpose. Seckler and colleagues (1995) performed studies on temporal reliability for both modalities using test-retest designs with 70 subjects ranging from 5 to 70 years of age and post-test intervals varied from one to four weeks. Correlations for composite measures ranged from 0.37 (Visual RCQ) and 0.75 (Visual AQ), and correlations for the quotients sub-measures ranged from 0.18 (Stamina Visual Reaction Time) to 0.88 (Mean Visual Reaction Time). Clinical validity for children has been investigated (Sandford et al., 1995a) using groups with ADHD (N = 26) and normative controls (N = 31) and 92 % accuracy was found. In one study by Tinius (2003), The IVA test was compared between groups of adult ADHD, controls and brain damaged patients. The brain damaged group and the ADHD group demonstrated similar response patterns of lower performance on measures of reaction time, SDRT, sustained attention and response inhibition with regard to the control group.
1.1.6 Psychometric properties of continuous performance tests

Validity measures and CPT

Validity is a means of evaluating the quality of a measure and it relates to the meaningfulness of a test or the interpretation given to scores and performances rather than the test itself (Anastasi, 1988; Riccio et al., 2001a). Validity may be explored by means of various psychometric properties such as content validity, i.e., level of adequacy in item content relative to the area of interest for measurement, concurrent validity, i.e., degree of association between the measure construct and constructs of other measures, and criterion-related validity, i.e., level of test score inference on criterion variables and other tasks (Anastasi, 1988). The CPT paradigm started off as a research approach for various psychiatric disorders and is intended to measure components of sustained attention and response inhibition. It has been widely accepted within clinical practice on both formal and informal grounds. A CPT involves high levels of face validity related to its presumed ability to measure sustained attention which is based on the common sense view that missed targets are associated with lapses of attention. Theoretically however, poor performance can be the results of deficits in many stages of information processing and the precise nature of the cognitive and behavioral processes that is assessed within the paradigm has not been systematically investigated and defined. Instead, the validity has been increasingly depended upon the areas of clinical application and the ability to measure the presence of symptoms, e.g., significant between group differences with regard to normal controls, associated with ADHD. Statistical and clinical significance has been taken as support for the measurement of ADHD cognitive symptoms of attention and impulsivity. Although research has been illuminating between group differences for ADHD versus normal and sometimes clinical groups, the CPT is not defined as a test only for ADHD. This makes sense from a clinical point of view since psychiatric disorders presenting clinical symptoms different from, additional to and identical with those of ADHD, and therefore likely to involve at least partially different theoretical constructs than those of ADHD, are still expected to generate poor performance. Furthermore, the theoretical foundation of the neurological and associated causal mechanisms resulting in ADHD is not agreed upon or consistently made testable with experimental designs which have made the theoretical considerations of measurement constructs less well attended to. Nevertheless, from a clinical point of view it is likely to think that many of the mental disorders that involve inattention and impulsivity would generate poor CPT performance.
without this affecting but instead strengthening the ability of the CPT to measure clinical symptoms that are reflecting valid forms of ADHD. It may also be that the CPT generates measures that are contributory enough but not identical to clinical symptoms of ADHD and that provide a piece of information that is helpful during clinical assessments, i.e., ecological validity, and especially when it comes to examining symptoms severeness. Nevertheless, the clinical specificity of CPTs during diagnostic assessments has been a major concern and practical recommendations for the clinicians’ empirical approach of \( n = 1 \) commonly involve making a validity check by using not only methods of discriminant validity, i.e., normative comparisons, but also convergent and other criterion-related forms of validity, i.e., multiple sources and instruments to complement the CPT. It is well known that even though the sensitivity for ADHD is fairly high and the CPT paradigm contains some of the most predictive neuropsychological tools for ADHD, the level of specificity and especially clinical specificity is generally lower and no CPT is sufficient for either confirming or disconfirming a diagnosis. A closely related concern for many of the CPTs has been the frequent application of these research tools in adult psychiatry without standardized interpretation based on robust and age-relevant normative data which poses challenges onto the analysis of these objectively attained measures with regard to ADHD as a clinical and valid construct in adulthood. In sum, the CPT is a meaningful measure with regard to ADHD in both children and adults but the exact interpretation of test performance and scores has not been established once and for all.

The content validity of CPTs may be evaluated relative to the intended area of measurement both by means of statistical analysis and expert judgments made by clinicians and researchers within the discipline (Riccio et al., 2001a). In order to better understand what the CPT measures actually do measure, there have been studies investigating aspects of construct validity by using scientific methods such as factor and correlation analysis (Adams et al., 2011; Aylward, Gordon, & Verhulst, 1997; Das, Snyder, & Mishra, 1992; Epstein et al., 2003; Kardell, 1994; Lovejoy & Rasmussen, 1990). Studies report that CPT measures correlate with other laboratory measures of attention and executive functioning, including for example focused attention and selective attention (Burg, Burright, & Donovick, 1995; Das et al, 1992; Rasile, Burg, Burright, & Donovick, 1995), flexible attention (Boonstra et al., 2010; Ginsberg et al., 2010) as well as impulsive behavior (Adams et al., 2011). As with most of the CPT clinical studies, methodological studies too have been conducted with primary reference to child as opposed to adult populations and especially with regard to normal groups. In addition, and since attention is such a multifaceted construct that may be addressed using
various labels of distinct and inter-related sub-traits, other measures flanking the CPT may aid in the interpretation of its meaning-construct and still, a perfect one-to-one correspondence would not be expected (Riccio et al., 2001a). Much research has observed that the CPT paradigm measures some age-related processes even though the exact nature of these processes is less known (Brocki, 2007; Brocki et al, 2010; Halperin et al, 1991; Halperin, Trampush, Miller, Marks, & Newcorn, 2008; Rommelse et al., 2008b). Many researchers would also agree that the CPT errors may be divided into those that measure inattention and those that measure impulsivity and perhaps also some that measures less apparent qualities like dyscontrol (Halperin et al., 1991). Halperin and colleagues presents some empirical support for the association between omission errors and inattentive behavior on the one hand and commission errors and impulsive/hyperactive behavior on the other hand and the link has been examined especially for childhood ADHD. Yet it also seems like the CPT and other neuropsychological measures of ADHD symptoms holds sensitivity for the general ADHD symptomatology rather than for distinct symptom domains and diagnostic subtypes (Epstein et al., 2003; Frazier, Youngstorm, & Naugle 2007; Gualtieri & Johnson, 2006). The above question has also been extensively debated in relation to the dimensional versus categorical nature of the disorder (Nigg, 2001; Sonuga-Barke, 2003, 2005).

Kardell (1994) made a factor analysis with an AX-CPT, and two other neuropsychological tests interpreted as measures of attention and/or cognitive shifting, e.g., the Wisconsin Card Sorting Test (WCST) and the Trail making Test, parts A and B (TMT-A, TMT-B). Analysis suggested that number of correct CPT responses, time to complete TMT A plus B, and total number of errors on WCST loaded primarily on the same factor. Moderate associations were found for omission and commission errors with regard to the time scores for TMT A ($r = .41$, $r = .26$) and the total time on TMT tasks ($r = .46, r = .32$). The Stroop task (Golden, 1975) is another test interpreted as a measure of attention and executive control whose relations with CPT measures have been examined in several studies with medium correlations for CPT vigilance (Burg et al., 1995; Rasile et al., 1995). Another approach for examination of the latent construct of CPT measures is by comparing its relations to measures assumed to capture different constructs. Aylward and colleagues (1997) compared GDS measures for children ($N = 1280$) with tests believed to measure separate cognitive constructs, including for example the Wechsler Intelligence Scale for Children- Third edition (WISC-III) and tests of memory (Wide Range assessment of memory and learning, WRML) and academic achievement. Results suggested separate factors for CPT measures and a factor called Cognitive/IQ with
loadings of memory, VIQ and PIQ scores from WISC and math performance scores. Additional studies (Boivin et al., 1996; Lovejoy & Rasmussen, 1990) are consistent with the belief that CPT performance loads separate from intelligence factors and general cognitive ability ($g$). However, there are controversies as to if and to what extent the CPT may be influenced by IQ and recent studies (Park et al., 2011) with children and adolescents diagnosed with ADHD reported better performance among participants with high IQ (> 120) as compared to those within the normal range (70-120) even when controlling for age and gender, but the result may be regarded as a special phenomenon found only in the above normal IQ range. Further, it has also been suggested (Garretson, Fein, & Waterhouse, 1990) that age contributes to higher validity coefficients in younger samples. From a developmental perspective (Riccio et al., 2001a) this has been referred to as expected since that younger children’s attentional capacities tend to be more closely related to their general cognitive ability as opposed to older subjects in which explicit cognitive abilities become more distinct. Therefore, a tentative suggestion is that IQ may not have the same moderating impact on measures of attention and executive functions among adults. Because of attention is believed to forerun memory (Cohen, 1993), CPT measures are designed to decrease memory confounds and generally loads separate from memory measures (Boivin et al., 1996; Lovejoy & Rasmussen, 1990). The overall conclusion is that CPTs appear to be inclined to measure something unique from other cognitive abilities and that the concept of attention is a multifaceted one that may be served by adhering also to developmental routes related to chronological and mental age.

In terms of ecological validity, CPT measures generally have moderate to high levels since the overall strongest associations have been found for behavioral observations (Downey et al., 1997), measures of attention and related executive functions (Nigg et al., 2005a) and behavioral ratings of ADHD symptoms (Avisar & Shalev, 2011; Epstein et al., 2003). Factor-analytic work suggest that the CPT constructs of attention and impulsivity are related to ADHD (Epstein et al., 2003), are different from each other (Nigg et al., 2005a) and separate from intelligence, memory, general cognitive ability and executive functioning such as planning, organization and working memory. However, the relationship between CPT parameters and symptom domains/diagnostic subtypes in ADHD is not as straightforward as one would think. Associations between CPT measures and the exact neuropsychological constructs of inattention and impulsivity are multifaceted and seem to be dependent upon the qualities of the CPT. The paradigm in general seems to be inclined to measure global ADHD
symptomatology (Epstein et al., 2003) while the more Go-/No-Go focused tests taps behaviors of impulsivity to a larger extent than the pure sustained attention tests which are more inclined to measure inattentive behavior among ADHD (Aylward et al., 1997; Boivin et al., 1996; Lovejoy & Rasmussen, 1990). Finally, developmental aspects are much likely to affect performance since behaviors become both less apparent with age and less disabling during laboratory testing even though its impact in everyday life may still be huge (Riccio & Reynolds, 2001). Therefore, laboratory tests that are effectively triggering symptoms relative to the participants’ age are more likely to correlate to a higher extent with behavior ratings and observations collected during real-life settings as compared to the easier tests.

**Reliability and CPT**

The reliability of a measure refers to test score consistency and could be described as the proportion of total variance attributed to true score variance as opposed to error variance (Anastasi, 1988). A CPT measure is performed during experimental conditions, and as such it may be affected by a relatively large proportion of error variance including for example irrelevant environmental stimuli, instruction and conditional preparation. One way to investigate the level of reliability for a measure is by means of reliability estimates and coefficients and there are basically three techniques used for this purpose, test-retest reliability, internal consistency reliability and interscore/interrater reliability (Anastasi, 1988). There are relative few numbers of studies examining reliability for CPT measures and some of them will be reviewed for a few words here.

CPTs are often described as being “objective” measures and one reason for this may be the automatically derived test scores by means of computers and microprocessors instead of raters which make the inter-rater reliability seemingly not a big issue. Ideally however, the question would also be related to the significance and relative importance given to scoring parameters and indexes as well as the quality of interpretive guidelines. The effect of inter-rater reliability has not been extensively researched and the various CPTs provide different solutions for obtaining high levels of objectivity and reliability with regard to the choice of parameters, scoring indexes and interpretation of test scores. Some tests provide rather detailed guides for interpretation with an almost diagnostic ambition while others mainly provide pedagogical case samples. In either case, this is likely to affect the level of inter-rater reliability.
An obvious interest concerns the CPT temporal or test-retest reliability since it refers to the stability of measurement over time and the extent to which a test consistently measures the construct of interest over time (Anastasi, 1988) which is particularly important for measures of trait conditions, i.e., ADHD. Two main psychometric properties may be noted here. First the group indications of temporal stability or test-retest reliability and second, the intra-individual test-retest score agreement. For the second property, statistical methods that differentiate intra-individual chance test score variation from statistically rare changes in performance have been applied using for instance the Reliable Change Index (RCI). Both forms of reliability are meaningful when examining performance in clinical populations and the intra-individual variability is for example important when assessing cognitive improvement or decline in response to treatment as well as highly dependent upon the test-retest reliability (Zabel, von Thomsen, Cole, Martin, & Mahone, 2009). The original CPT (Rosvold et al., 1956) was found to have test-retest reliability estimates ranging from .74 to .90 with regard to brain damaged patients. Since then, studies (Halperin et al., 1991; Cornblatt, Risch, Faris, Friedman, & Erlenmeyer-Kimling, 1988) of non-referred boys and adults with normal attentional capacities found moderate test-retest reliability estimates for AX-type CPT and identical pairs-CPT. In Halperin et al’s study (1991), split-half reliability estimates for correct hits, commission errors, omission errors, reaction time, and RTSD was ranging between .67 and .92, which is modest to acceptable. Previously noted, test-retest reliability has been investigated specifically for GDS (Gordon, DiNiro, & Mettelman, 1988), TOVA (Leark et al., 1996; Llorente et al., 2001), IVA (Seckler et al., 1995), and Conners CPT-II (Zabel et al., 2009).

Regarding Conners CPT-II, Zabel and partners investigated test-retest reliability for several neuropsychological tests over a mean interval of 6 months in a typically developing pediatric cohort (6 to 18 years of age). The test-retest reliability of neuropsychological comparison tests like the WISC-IV block design was acceptable (ICC = 0.82 to 0.92) and modest for CPT raw scores (ICC = 0.62 to 0.82) and T-scores of omission error, commission error, hit reaction time, reaction time variability and d’ (ICC = 0.33 to 0.65). The mean average raw and T-scores for both time occasions were comparable according to the authors and suggest no significant learning/practice effects. The authors also suggest that the relatively lower level of test-retest reliability for the CPT versus other neuropsychological tools was expected and reasonable given the higher variability of the intended area of measurement, i.e., normal day-to-day variation associated with attention as compared to tests with longer time intervals for
completion of task. They also investigated the intra-individual change variation using 90% confidence intervals based upon the RCI methodology to assess the significance of test-retest differences. This set-up assumes that 10% of the sample would display statistically rare changes in raw test scores for each of five selected CPT variables. What they found was that three of the five variables, e.g., omission errors, reaction time variability and d’, exceeded the 90% confidence interval in 30% of the cases and thus displayed significant statistically rare rather than normal variations in raw scores which imply less temporal stability for these variables in many cases. This was not the case for commission errors and hit reaction time however. Regarding T-scores for the same parameters, they found that 32% of their sample (N = 37) presented at least one statistically rare change in test scores from time 1 to 2 and chi-square analyses indicated higher than expected changes in T-scores for omission errors and d’ but not for the other parameters. Altogether and since the sample came from the general population, these investigations raised questions about the hypothetical level of variation in test scores for persons with unstable neurological conditions, population norms and the reliability of Conners CPT.

A study with TOVA (Llorente et al., 2001) in a sample of children with ADHD presented similar results but used correlational analysis (pearson’s r) to assess the temporal stability of group scores which was satisfactory, i.e., ranged from 0.51 to 0.82, between three occasions during four months. The coefficients were highest for response time (0.82), followed by response time variability (0.75), commission errors (0.71) and omission errors (0.61). Here, internal consistency correlations were examined between the two independent halves of TOVA, i.e., fast and slow response rate conditions, for the total number of correct responses (commission and omission errors) and results ranged from 0.93 to 0.99 for the two halves and their correlation with total test. Two shorter time intervals, i.e., 90 minutes and one week, was examined (Leark et al., 2004) for assessment of test-retest reliability with TOVA in normal children. Coefficients were satisfactory for both time intervals across omission errors (0.70 and 0.86), commission errors (0.74 and 0.78), response time (0.79 and 0.84) and response time variability (0.87). Except from measurement errors that may influence a tests reliability, there are also environmental and situational factors with documented potential influence on test performance, including for example lighting (Campanelli, 1970), time of day (Davies & Davies, 1975), room temperature (Hancock, & Warm, 1989), noise (Davies & Davies, 1975), examiner presence or absence (Power, 1992), and feed-back such as focus on accuracy or speed (Corkum & Siegel, 1993) which altogether suggest standardization and adherence to
test procedures for optimal reliability of CPT measures. It may also be worth mentioning that there are subject-related factors that may influence performance including for example nicotine and caffeine consumption (Hunt, Momjian, & Wong, 2011), some slight but relatively low effects of malingering (Quinn, 2003) but not circadian rythm (Hunt, Bienstock, & Qiang, 2012) which suggest consideration also of individual variance at the set-up.

1.1.7 Objective measures of hyperactivity in adult ADHD

Even though the CPTs have advanced in the past 60 years, demonstrating the ability to measure levels of attention and to some extent also impulsivity, the CPT do not facilitate measures of hyperactivity. Instead, for the activity domain of ADHD, lab measures like activity tracking systems (ATS) including single- and multiple channel actometry at various locations of the body, stabilimetric cushions or activity chairs as well as the more refined Motion Tracking Systems (MTS) have been used for recording motor activity in children (Brocki et al., 2010; Oades, Myint, Dauvermann, Schimmelmann, Schwarts, 2010; Sharma & Singh, 2009; Teicher et al., 1996; Wehmeier et al., 2010) adolescents (Jucaite, Fernell, Halldin, Forssberg, & Farde, 2005; Vogt & Williams, 2011) and adults with ADHD (Lis et al., 2010; Polcari et al., 2010). As reflected in the development of diagnostic criterions for the disorder during late 20th century in which proportion-based contributions of cognitive and motor domain-specific symptoms have been heightened, symptoms of hyperactivity as reflected in motor activity has been emphasized to variable degrees in the diagnostic assessment and theoretical consideration of the disorder. Two classical studies on the naturalistic assessment of motor activity in hyperactive boys and their matched controls (Porrino et al., 1983a; Porrino, Rapoport, Behar, Ismond, & Bunney, 1983b) used portable solid-state monitors for one-week and found out that motor activity was higher in hyperactive boys regardless of time of day/night and type of setting/activity which led the authors to suggest that hyperactive behavior was not simply an output of the attentional demands in a given setting but that excessive motor behavior was a clear attribute of ADHD that differentiated hyperactive boys from their age-gender- and classroom matched counterparts equally effective as the CPT standardized measures of attention as well as provided support for the ecological validity to the laboratory measures. Also, they assessed the effect of dextroamphetamine (Porrino et al., 1983b) which normalized activity levels during eight
hours with a 28% decrease in activity and the effect was most pronounced during class-room situations compared to placebo administration.

Actigraphy measures are consistent in reporting significant group differences between children with ADHD and controls (Halperin, Matier, Bedi, Sharma, & Newcorn, 1992; Halperin et al., 1993; Reichenbach, Halperin, Sharma, & Newcorn, 1992) and provide objective data on motor activity (Teicher, 1995; Tryon, 1993). For example, the discriminative validity of combined CPT and actometry was examined in a study of children (Halperin et al., 1992) using ADHD-patients, non-ADHD patients and normal controls, and both groups of patients were more inattentive than controls but not possible to differentiate from each other using the CPT, but the ADHD group was distinguished from both other groups on basis of their higher activity levels. These finding suggest that combined measures of activity and attention domains produce better accuracy and discriminative power of ADHD versus clinical and normative groups of children. They also found that the activity measures had god test-retest reliability and correlated with both parent and teacher ratings of ADHD symptoms (Reichenbach et al., 1992).

From a longitudinal perspective, CPT and actigraphy measures were examined in a pediatric cohort of 98 children (7 to 11 years) with ADHD who were re-evaluated ten years later and contrasted with never-had-ADHD controls (Halperin et al., 2009). At baseline, the clinical group performed worse than the comparison group on five out of six CPT measures, these being percentage of correct hits, false alarms, d’, beta, and hit reaction time SD but not hit reaction time. Also, both of the solid-state actigraphy measures of ankle and waist activity contrasted the groups since the ADHD group was way more fidgety. Interestingly, at follow-up the clinical group was subdivided based on current ADHD status into remitters (n = 29) or persisters (n = 44) and the outcome pattern differed across the two groups.Persisters differed from the controls on four CPT measures while only RTSD and d’ differed both ADHD groups from the controls. Thus a childhood diagnosis of ADHD was associated with more variable response time and less perceptive sensitivity towards target detection in both groups as compared to those who never had ADHD. But the persisters performed worse than both other groups also on correct hits, false alarms, reaction time and beta. Perhaps even more interesting was the follow-up-finding that the persisters differed from controls on both actigraphy measures while the remitters only differed with regard to their higher level of ankle movements. These findings challenge those common beliefs that activity levels decline in
adults with ADHD but suggest instead that higher level of motor activity is typical for childhood ADHD regardless of the current ADHD status even though persistent ADHD is associated with highest level of activity. Thus, the CPT and actigraphy measures were consistent with each other, indicative of the ADHD developmental course, and provided support for the persistence of both cognitive and motor activity deficiencies in adolescents and adults with a history of ADHD and especially in those with persistent forms of the disorder. The current ADHD status was possible to discern with both measures and as such may help in identifying true core deficits from those that are epiphenomenal or those who contributes to remission of ADHD. The study illustrated that objective measures are valid of ADHD from a life-course perspective and give valid credit for the longitudinal course of the disorder with practical implications of differential performance patterns in both psychometric and clinical domains.

Brocki and colleagues (2010) examined age-effects upon ADHD symptom domains using simultaneous MTS and CPT measures using the QbTest (QbTech AB, 2010d) in a population-based sample consisting of children ($N = 401$) between 6 to 12 years old. Younger children made more errors of omission and commission, had longer and more variable reaction times, moved longer distances, covered greater areas and had less complex movement patterns than older children. Boys had higher motor activity and showed poorer CPT performance on all variables compared to girls at the same age which is interesting given the generally slower neural development and more frequent rate of ADHD among boys. In boys with ADHD, recordings of the movement pattern of the head, shoulder, back, and elbow with motion tracking during CPT performance reported 2.3 times more frequent head shifts, covering longer distances, greater areas and having a more linear but 44.5 % less complex movement pattern as compared to normative controls (Teicher et al., 1996). This study also documented how younger boys responded more slowly and more inconsistently on the CPT while no significant age effects was found for the number of movements, displacements, complexity, or temporal scaling of any motor activity marker. However, the area covered by each marker tended to be affected by age (i.e., head, $p = .07$; shoulder, $p = .07$, and elbow, $p = .10$), and the complexity of head movements and variability in response correlated with teacher ratings of ADHD symptoms.
Based on actigraphy and CPT measures, Reichenbach and colleagues (1992) suggested that age accounted for almost a third of children's variance in motor activity and for almost 25% of their CPT performance. However, combined measures of cognitive and motor domains showed good discriminative validity, test-retest reliability and construct validity by means of parent- and teacher ratings of children with ADHD. And there is support for strong relations between CPT-derived measures and ADHD symptoms in experimental groups (Losier et al., 1996) and epidemiological samples (Epstein et al., 2003). Attempts to address the effect of comorbid psychiatric disorders upon combined CPT and MTS has been made by for example Glickman (2003) who studied clinical samples of children with ADHD alone or ADHD plus major depressive disorder (MDD) to find out that groups was possible to differentiate on basis of five out of six motion and attention measures respectively and that these combined measures correctly classified ADHD in 84% of the cases but that sensitivity for detection of ADHD in comorbid cases was significantly reduces using tests of executive function performance (card-sorting task). The clinical utility of CPT and actigraphy measures was evaluated (Matier-Sharma, Perachio, Newcorn, Sharma, & Halperin, 1995) among pediatrical groups with ADHD, non-psychiatric controls and a mixed non-ADHD patient group with for example anxiety, disruptive, or affective disorders. Here, the omnibus analysis yielded significant group differences for inattentive, impulsive and activity measures but no gender differences. Post-hoc analyses reported that the ADHD group was more inattentive, impulsive and hyperactive than both other groups. Examining correlations among measures reported no significant relations in the ADHD or normal control group. Discriminant functional analyses reported 63% correct ADHD classification and 94% correct classification of normal controls. Similar analysis in ADHD versus non-ADHD patients yielded 68 and 66% correct classifications respectively. The order of entry of significantly contributing factors was activity level, CPT inattention and CPT-impulsivity. Especially hyperactivity and impulsivity yielded high levels of specificity among clinical controls, 95 and 88% respectively and the authors suggested that these measures are helpful in diagnostic assessment and that impaired performance are likely to indicate presence of ADHD.

Further, actigraphy has been employed to assess potential differences between ADHD subtypes in childhood (Dane et al., 2000) and there were no differences between the combined and predominantly inattentive subtypes while both subtypes were more active than the non-ADHD controls. This finding contradicts the assumption that inattentive children with ADHD are less hyperactive than those with combined subtype and teacher ratings also
correlated with abnormal fidgeting across the subtypes. Moreover, the authors discussed situational and temporal variation in hyperactivity as children with ADHD are found to be naturally more active across most settings compared to normal but the difference may be more extreme under certain conditions such as in school, during afternoon and in familiar settings but it decreases during more novel settings. Also, the task at hand may influence the level of difference between ADHD and controls since tasks that demands higher levels of self-regulation and involves less frequent instruction and/or task input as well as situations that are less reinforcing and involve less one-to-one communication create higher levels of hyperactivity among children with ADHD (Dane et al., 2000). A study of 50 children and adolescents with ADHD (Sharma & Singh, 2009) examined the diagnostic ability of combined MTS and CPT (QbTest) and found the test to correlate with clinical diagnosis in 90 % of the cases, the sensitivity was 96 % and specificity was 81%. The results were based on Qb-test output as well as careful consideration of comorbidities which made interpretation subjective and dependent upon the raters of the study, but the test was nevertheless helpful as a clinical tool.

Two studies (Boonstra et al., 2007; Tuisku, Virkkunen, Holi, & Et, 2003) using actometry in adults with ADHD or ADHD and antisocial personality disorder (ASP) both reported higher frequencies of movements compared to controls. Patients with ADHD did however present similar features of restlessness as patients with neuroleptic-induced akathisia which is interesting from a dopaminergic point of view (Tuisku et al., 2003). A one-week non-standardized day and night observation similar to those performed in childhood ADHD (Boonstra et al, 2007) demonstrated higher levels of motor activity also in adults with ADHD as compared to their controls. Participants with ADHD also took longer to fall asleep, had poorer sleep quality and periods of uninterrupted sleep which were consisted with subjective ratings. The continuously heightened activity level was steadier and less variable during 24-hour intervals compared to controls. However, a methylphenidate assessment resulted in positive effects upon sleep quality and normalized activity levels and similar outcome have also been reported elsewhere (Kooij, Aeckerlin, & Buitelaar, 2001; van Veen, Kooij, Boonstra, Gordijn, & van Someren, 2010). The activity domain being objectively accessible and measurable in adult ADHD have been critically discussed referring to reduced levels of motor activity with increased age (Brocki et al., 2010) and the influence of diagnostic subtypes. On the other hand, year of cumulated research with objective measures strongly contradict such a view since elevated rates of motor activity has been consistently reported for
the group regardless of age and diagnostic subtype as well as supported by discriminant and convergent validity measures. Further, the clinical definition of ADHD (DSM-IV; American Psychiatric Association, 2000) stipulates age-relevant symptoms of hyperactivity for diagnosis and many adult subjects (74 %) with ADHD report fidgeting their feet and fingers and having problems remaining seated (66 %) several times a day (Barkley et al., 1996; Barkley et al., 2011). Symptoms of inattention holds low specificity for ADHD and most studies of clinical samples report low discriminative power for conventional CPT measures. Empirical findings suggest that objective measures of hyperactivity provides a valid measure of ADHD in adults with higher separation than the solitary CPT when it comes to other psychiatric disorders with elevated susceptibility for symptom overlap commonly found in the adult clinical population. Lis and colleagues (2010) were among the first to investigate motor activity in adult persons with ADHD (\( N = 20 \)) by means of MTS and simultaneous CPT (QbTest-Plus) in comparison to healthy and matched controls (\( N = 20 \)). The highest separation of groups was reported for MTS measures including microevents, time active, distance, and area. For CPT measures, significant group differences were found for omission errors only. Adult subjects with ADHD showed no impairment with regard to commission errors which is viewed as a measure of impulsivity based on childhood studies. Motor activity was found to be associated with increased levels of cognitive impairment on the CPT parameters for the ADHD group only. Motor activity of adults with ADHD was up to 3.5 times higher than controls during 20 minutes standardized testing and differences between groups became more accentuated during the testing period. The authors suggest that although observable motor behaviors might decrease with age, higher motor activity persist and may be recorded in adult subjects with ADHD.

Consistent with these findings are studies with the ADHD Quotient system in adults (Polcari et al., 2010) which is similar to the QbTest-Plus with a combined CPT and MTS measurement technique except from some variation in the CPT stimuli and index and the MTS recordings includes both head and leg movements. Forty men and women with either combined or inattentive ADHD subtype plus additional normal controls generated robust findings for many of the CPT parameters such as accuracy, percent of time spent fully on task and variation in response latency and even more robust findings for motor measures including for example a 2-fold increase in head movements and 5.4-fold increase in leg movement as well as temporal and spatial diversity for the ADHD versus contrast group. There were no differences between men and women with regard to movement measures but male controls were more active than
female controls so that the difference between groups were more marked among females. Accordingly, elevated activity levels were found to persist in men and women with various subtypes of ADHD (there were no significant gender x diagnosis interactions) and distinguished them from normal controls which are frequently reported for affected children performing the ADHD Quotient system as well (Ohashi, Vitaliano, Polcari, & Teicher, 2010; Teicher et al., 1996; 2006). One advantage with MTS over actigraphy is the amount of ecologically valid information that you will get regarding movement pattern by detailed parameters that correlate together and reflects valid aspects of hyperactive behavior typical for ADHD. Teicher (1996, p. 336) writes that “actigraphs simplify and reduce the complexity of activity”. Another advantage is the minimizing of variability in measurement units which facilitates the ability to compare and reproduce information across studies and samples. The actigraphs needs to be programmed with regard to epoch length of data-sampling and the amount of vibration that is to count as one unit of measurement. The MTS on the other hand is a more valid reflection of the actual movement pattern and degree of movement that actually occurs and the outcome does not vary as a function of the programming of measurement.

A great deal of research with combined measurement (CPT and MTS) has been conducted with pre-post treatment designs for especially children and adolescents with ADHD. For example, all cognitive and motor parameters under investigation, i.e., microevents, spatial scaling, commission errors, accuracy and reaction time variability reported significant improvement in performance after therapeutic doses of Methylphenidate, MPH (Heiser et al., 2004). Another study with combined MTS and CPT, i.e., OPTAX (Tabori-Kraft, Sorensen, Kaergaard, Dalsgaard, & Thomsen, 2007) in children with ADHD and ADD during stimulant treatment found significant improvements on all parameters as well as much improvement with the Clinical Global Impression Scale. Temporal scaling, i.e., a measure of the extent of activity, was significantly reduced with 39 %, reponse accuracy improved with 24 %, incorrect responses decreased with 42 % and responses became faster and less variable as a result of treatment and compared with placebo. The external validity and effectiveness was further strengthened here because of inclusion of children who had comorbid disorders and by correlations with ratings made by physicians based on parents and teachers. A triple-blind (parent, child, rater) within-subject efficacy study of response to stimulants with combined CPT and MTS called McLean Motion Attention Test, M-MAT (Teicher, Polcari, & McGreenery, 2008) reported that the dose that produced the best improvement on objective
measures of attention and activity was also producing highest amounts of clinical improvements as measured with parent ratings which were also significant compared to ratings of the effectiveness of other doses. Objective measures of especially activity but also attention were strongly associated with the clinical ratings of effectiveness which support the ecological validity during titration. Sumner et al (2009) conducted a three week double-blind trial in which children aged 6 to 14 \( N = 30 \) were randomized to atomoxetine or extended-release MPH with three conditions each: placebo, low dose, medium dose or the reverse order of conditions. The reponse rate was classified using thresholds based on the subjective rating of ADHD-RS total score or the objective ADHD Quotient Total score into any improvement, greater than 25 % improvement or greater than 40 % improvement. The concordance correlations for baseline and placebo conditions were 0.78 for the objective quotient and 0.38 for the rating scale. Concordance between baseline and week-3-placebo was 0.84 for the quotient and 0.45 for ratings, 0.75 and 0.27 for baseline and week-1-placebo. Altogether, the study suggested that placebo response rates were minimized when the objective system was used along with the most stringent threshold for response rate, i.e, 40 % improvement, but the subjective ratings poorly discriminated placebo responses. A study with QbTest was recently conducted to examine the effects of exended- versus immediate-release MPH in older children with ADHD during the course of a day (Gunther, Kahraman-Lanzerath, Knospe, Herpertz-Dahlmann, & Konrad, 2012). Three parameters were chosen to represent core symptoms of ADHD, inattention was SDRT, impulsivity was commission errors and hyperactivity was “distance” which is the length of the head-band path (motor activity). In controls, they observed a post-lunch dip in attention and a trend of increased hyperactivity throughout the day while impulsivity remained stable. The groups with MPH had similar benefits from treatment and their performance was normalized to equal the controls approximately two hours after medication. A difference in treatment conditions were the better effect of immediate-release MPH on levels of impulsivity and the authors suggested that core symptoms should be monitored during the course of a day to decide optimal stimulant formulation and titration among children.

A series of studies with the QbTest performed by Wehmeier and colleagues (Wehmeier et al., 2011a; Wehmeier, Dittmann, Banaschewski, & Schacht, 2012) also examined ways to optimize treatment response for children with ADHD. The first study from 2011 was double-blind and examined objective outcomes during the course of a day in 105 boys and girls with ADHD aged 6 to 12 that were randomized to either atomoxetine, ATX, treatment with a target
dose of 1.2 mg/kg/day or a placebo condition over eight weeks. Ten primary measures of hyperactivity, inattention and impulsivity indicated significant improvements from baseline to week 8 and differences between conditions on most times of the day after 8 weeks. Interestingly, all of the variables showed significant improvements at the morning evaluation in the treatment condition at week 8 which supports the finding that ATX is effective after 24 hours of intake. The second study from 2012 examined the effect of ATX treatment with and without stimulant pretreatment in the same sample as before and found that ATX reduced ADHD symptoms regardless of stimulant pre-treatment, only three parameters differed between those with previous stimulant treatment and those who were stimulant-naive, these were motion simplicity ($p = 0.019$), mean reaction time ($p = 0.036$) and commission errors ($p = 0.048$), but the outcome showed no clear pattern between the groups and the authors suggested that the difference had no larger clinical relevance since the overall pattern indicated effectiveness regardless of previous treatment. In a group of older subjects, aged 7-18 years, with ADHD using the same combined measurement strategy (QbTest and QbTest-Plus), a robust treatment response, partial response and non-response was possible to predict with a moderate test-dose with stimulants (Vogt & Williams, 2011). Robust responses were found in 84 % of the sample and improvements were objectively recorded, 7 % were partial responders while the remaining 9 % were non-responders with no improvements in objective measures. Most of the responders demonstrated an effective response to the moderate stimulant test dose and was identified early on. Participants aged 13 to 18 performed the adult version of the test, QbTest-Plus, while participants aged 7 to 12 years performed the childhood version, QbTest. There were significant differences between baseline and post-MPH for both the QbTest ($F = 23$, $p < 0.001$) and the QbTest-Plus group ($F = 23$, $p < 0.001$) but no significant difference in treatment responses between these groups ($p > 0.05$). There were large and significant correlations between measures belonging to the attention and activity domain respectively, ranging from 0.53 to 0.57 and correlations between measures of hyperactivity ranged from 0.83 to 0.96. There were moderate and significant correlations between hyperactivity and impulsivity measures ($r = 0.36$ to 0.47), omission and commission errors ($r = 0.51$) but not for omission errors and normalized variation ($r = 0.15$, $p = 0.30$). These findings suggest that measures of attention and activity often co-occur but seem to form separate constructs. Another study (Ahlqvist, Silverberg, & Ulberstad, 2007) examined objective outcome in 21 children with oppositional defiant disorder, conduct disorder and/or ADHD following CBT interventions that included a “Stop-think-go” module for all of the children and additional parent management groups and teacher workshops for half of the
sample. Impulsivity yielded significant post-treatment improvements ($p = 0.03$) and inattention were close to significant ($p = 0.07$) while no improvement in hyperactivity was attained ($p = 0.58$).

Except from self-ratings, actigraphs and motion tracking systems, other measurement methods and laboratory measures also report higher levels of hyperactivity and its relations to increased motor activity in participants with ADHD across ages. A review of observational methods in ADHD (Platzman et al., 1992) included both a wide range of class-room based observations as well as laboratory observations and found high levels of consistency among the settings. In the class-room setting, gross and minor motor movement was a particularly outstanding feature of ADHD versus control groups and it was more likely to be observed in the class-room compared to the laboratory setting. Overall, observations of attention, motor activity and excessive/negative vocalization were the primary features associated with ADHD in both laboratory and naturalistic settings. Occular motor performance has also been found to distinguish adults with ADHD from controls on laboratory measures (Feifel, Farber, Clementz, Perry, & Anllo-Vento, 2004) such that they generate less efficient saccades towards peripheral visual stimuli, including significantly more premature saccades and more directional errors, which may be interpreted as deficits of fine motor behavior as well as impulsivity on task. Using the physical and neurological assessment of subtle signs for quantified motor examination including for example finger tapping, toe tapping, heal to toe tapping etc., reports are that age contributes to significant improvements on timed tasks in terms of faster responses and less overflow in ADHD but that controls are consistently faster across the age span (Cole, Mostofsky, Gidley Larson, Denckla, & Mahone, 2008). Similarly, when operationalizing hyperactivity as motor activity inhibition during an anti-saccade task and inattentional inhibition during an attentional blink task in adults, Carr et al (2006) found that motor control was equally affected in persistent and remitted forms of ADHD. The directional task of motor activity was however only affected in those subjects with persistent ADHD which indicate problems with inhibiting motor response during task. This pattern of problems with both motor control and inhibition in persistent ADHD was typical for both diagnostic subtypes and suggest similar neuropsychological deficits in both subtypes. The attentional inhibition was however not disturbed in either ADHD group or subtype using the attentional blink task. Examining motor response inhibition during lab task in adults with ADHD or bipolar disorder and controls (Passarotti, Sweeney, & Pavuluri, 2010), both clinical groups performed equally worse compared to the controls on the behavioral measure.
However, fMRI indicated differences in neural activation between clinical groups such that the ADHD group presented reduced activity in ventrolateral and dorsolateral prefrontal cortex and increased activity was found in the caudate of both clinical groups. Even though the ADHD group was impaired on the behavioral measures of motor activity, their performance was not discernible from clinical controls. On the neural level however, the ADHD group was more extensively impaired in prefrontal cortex than participants with bipolar disorder which was also accompanied with subcortical dysfunctions. This study illustrates the importance of neuropsychologic tests that are sensitive enough to underlying brain deficits as to successfully reach clinical specificity for adult ADHD. In a series of studies, Rommelse and colleagues investigated various neuropsychological measures as endophenotypes for ADHD and the most profound was the motor response deficits (Rommelse et al., 2007a, 2008a, 2008c, 2008e). During a task (Rommelse et al., 2007a) with three blocks in which the participant was expected to indicate the direction, opposite direction and both directions of a target, children with ADHD were the most severely impaired, while their affected and non-affected siblings were medium impaired and controls least impaired. However, when comparing block two and three relative to block one, i.e., baseline measures of lower-order cognitive processing operationalized as response inhibition versus higher-order cognitive processing operationalized as motor inhibition and cognitive flexibility, the ADHD group and their siblings were not regarded as significantly more affected in higher-order cognition per se. Instead, the authors suggested that deficiencies in motor response was the results of impaired lower-order cognitive functioning which in turn caused deficient motor response and cognitive flexibility in persons with ADHD or ADHD load.

The other studies (Rommelse et al., 2008a, 2008c, 2008e) with similar tasks of motor response, variability and timing suggest that deficiencies within this domain are related to underlying core deficits of ADHD and motor measures indicate these deficiencies in both affected participants and their affected and non-affected siblings which makes motor response measures suitable as endophenotypes. However, these measures were also mediated by age and gender so that older and female subjects produced closer to normal performances. Moreover, even though deficiencies in motor output were strongly associated with the disorder, it was not possible to explain all of the variation in performance, not even when adjusting for age, sex and IQ. This suggests additional deficiencies to account for and measure behavioral variations associated with ADHD.
Examining familiality in affected and non-affected children and adolescents with more direct lab measures of hyperactivity using actigraphs (Wood et al., 2009), results were elevated rates and magnitudes of activity which distinguished subjects with clinical rates of ADHD from the non-affected and explained a large proportion of the variance too. Wood and his colleagues performed a study (2008) to address the reliability of actigraphy data and found that various body loci measured the same construct and was therefore combined at the aggregated level which produced the strongest reliability coefficients, 0.52, and when data was combined for all eight neuropsychological tasks in their study, it rose to 0.66, and there were no situational or inter-machine effects on actigraphy data. The authors suggested that overactivity is a valid core symptom of the ADHD combined subtype that is possible to measure with actigraphy and notable, the actigraphy data was not significantly different between those with and without comorbid psychiatric disorders, which indicate that the measurement construct was uniquely associated with ADHD and even suitable as an endophenotype for the disorder. Another genetic study (Ilott, Saudino, Wood, & Asherson, 2010) compared actigraphy during laboratory conditions with parent ratings of activity level in home-settings in a population sample of 2 year old twins. They found high heritability for ADHD, 78%, which were similar to the heritability found for activity level in lab, 68%. The two measures were only modest in genetic correlation ($r = 0.24$) and the activity level at home correlated higher ($r = 0.50$) with an ADHD composite. The estimated genetic correlation for subjective ratings and objective measures of activity level in this population sample was high, 0.60. The authors concluded that both mechanically assessed activity level and parent ratings of ADHD behavior are independently heritable phenotypes. The fact that they correlated significantly strengthen the belief that actigraphs measure behaviors that are related to ADHD and more specifically, higher activity levels, e.g., hyperactivity.

Similarly, the use of actigraphs and its validity in measuring behaviors of hyperactivity as well as the genetic disposition towards hyperactivity in ADHD was supported by another study conducted by Wood and colleagues (Wood et al., 2007). Actigraphy measures showed a moderate degree of heritability (24 to 30%), with a common set of genes influencing activity level across lab testing and during break from testing which support the ecological validity of lab actigraphy as a means to measure hyperactivity as well as etiological factors of both genetic and shared environmental influence across situations (27 to 42%) for this behavior. Yet another study (Jucaite et al., 2005) supporting the role of hyperactivity and its relations to both objective measures of motor activity as well as dopaminergic adversities was performed.
in male adolescents with ADHD \((N = 12)\) aged 12 to 15 years and healthy controls \((N = 10)\) aged 19 to 38 years. PET was used to assess dopamine transporter/receptor binding and associations with combined CPT and MTS which revealed significant relationships between degree of hyperactivity and the level of DAT binding in the striatum \((r = 0.66, p = 0.02)\), and larger head movement than mean normal for ADHD subjects \((> 42 \text{cm}^2)\). ADHD alone was also associated with lower DAT binding in the midbrain \((16 \%, p = 0.03)\) and notably, there were no significant age effects on DAT binding in the midbrain in any of the groups. There were significant correlations between dopamine receptor binding in the right caudate nucleus that correlated significantly with increased motor activity \((r = 0.70, p = 0.01)\) in ADHD but no significant relationships were found with regard to the CPT measures of inattention and impulsivity. This finding support the role of lower dopamine receptor binding in higher levels of hyperactivity as in increased motor activity as well as the unique association between motor measures and motor activity since none of the CPT measures were associated with increased motor behavior in ADHD.

Another interesting study (Oades et al., 2010) examined potential biochemical association including metabolic and immunological markers like cytokine levels with the QbTest measures of motor activity and attention in ADHD with or without medication and controls. Here, the authors found links on the conceptual level between the activity in anti-inflammatory functions with hyperactivity and pro-inflammatory functions with cognitive control, impulsivity and inattention. Most of the investigated cytokine levels were increased in these children with ADHD combined type and all tended to normalize during psychostimulant treatment. The groups differed in many of the CPT and MTS measures, including increased area of motor activity, number of microevents, slower reaction time, higher reaction time variability and more omission errors and many of the biochemical variations were possible to predict with the MTS and CPT measures using regression analyses.
1.2 Theoretical perspectives

1.2.1 Introduction

The psychological mechanisms that underlie behavior manifestations of ADHD have been difficult to identify. Many studies have reported poorer performance on CPT tasks and other neuropsychological tasks for both children and adults as compared to clinical and normative controls but the interpretation of these group differences has been the center of debate amongst diverse theoretical perspectives including behavior, cognitive, neuropsychological and motivational centered perspectives. Empirical support for theoretical perspectives has been derived from studies of children primarily and to a lesser extent from studies of adolescents and adults although age-related assumptions are commonly made. There are five major theoretical perspectives of ADHD in this thesis, (1) response inhibition deficit (Barkley, 1997), (2) working memory impairment (Pennington & Ozonoff, 1996; Pennington, Bennetto, McAleer, & Roberts, 1996), (3) the cognitive-energetic model (Sergeant, Oosterlaan, & van der Meere, 1999; Sergeant 2000, 2005), (4) delay-aversion (Sonuga-Barke, Taylor, Sembi, & Smith, 1992; Sonuga-Barke, Houlberg, & Hall, 1994; Sonuga-Barke, 2002, 2003, 2005), and (5) dopamine hypofunctioning (Sagvolden, Aase, Johansen, & Russell, 2005). The theories are briefly summarized in this section but comprehensively reviewed in the original works of the authors.

1.2.2 The response inhibition deficit theory

A neuropsychological hybrid model

Barkleys (1997) neuropsychological hybrid model of executive (self-regulatory) functions (figure 1) combine constructs from earlier theories regarding the internalization of speech for the control of behavior and for creation of novel goal-directed behaviors (Bronowski, 1977), with theories of prefrontal functions for the formation of cross-temporal structures of behavior that have a unifying purpose or goal (Fuster, 1989, 1995). Both Bronowski and Fuster distinguished the critical function of the working memory in configuration of hindsight, forethought, anticipatory behavior, and goal-directed purpose-driven action, along with the unique capacity of humans to create complex behaviors and analytic-synthetic structures in
the purpose of attaining future goals and they assigned these capacities to the prefrontal cortex which gave rise to the belief that both the syntax of behavior and speech is the function of the prefrontal cortex. Barkley builds upon these ideas and develops the hybrid model of executive function which specifies that the essential impairment involved in ADHD is deficits of response inhibition. The model is hierarchical in the sense that deficits of response inhibition is defined as the precursor of secondary impairments involving the following four neuropsychological abilities, (a) working memory, (b) internalization of speech, (c) self-regulation of affect-motivation-arousal, and (d) reconstitution. In turn, these secondary impairments lead to decreased control of motor behavior by internally represented information, symbolization and self-directed action, which is referred to as motor/control/fluency/syntax. So the appearance of poor sustained attention in ADHD for example is the consequence of a successive chain of impairments in which the four executive functions depend upon response inhibition for their own effective performance, and in which improvement of response inhibition should successively normalize and ultimately improve executive functions and sustained attention. The whole theory would be described as generally belonging to developmental psychology and the domain of self-regulation, as well as neuropsychology with respect to executive functions.

Behavioral inhibition as the precursor to executive function

Barkley describes behavioral inhibition in terms of three inter-related processes in which (a) there is an inhibition of the initial and prepotent response, (b) there is a stopping of the ongoing response so that the decision to respond is delayed, and (c) the stopping period and the self-directed actions occurring within it are protected from disruption of competing responses and events, which is termed interference control. Thus, the initiating of self-regulation must begin with behavioral inhibition or interruption of ongoing ineffective response patterns so that a delay is created in which the executive functions can occur. However, this behavioral inhibition does not directly cause the executive and self-directed actions to occur, but rather they provide the necessary delay for them to occur. The executive self-directed behaviors are not necessarily observable although they may often be so during early development and over the course of life they tend to become increasingly more private, internal-cognitive in their style by means of internalized and self-directed speech. However says Barkley, even though they become private (cognitive), they still remain self-directed forms of behavior that contribute to executive functions and self-regulation. According to
Barkley's theory, the five executive functions are, (a) 
self-directed actions, (b) organization of behavioral episodes over time, (c) utilization of self-directed speech, rules or plans, (d) deferral of gratification, and (e) purposive, goal-directed, future-oriented and intentional acts. These executive functions all depend upon response inhibition and may be most obvious and also most needed in those situations where (a) the delay of consequence is imposed during task, (b) a conflict between immediate and delayed consequences of response is imposed, and when (c) generation of novel responses is required to solve a problem, which all has the potential to initiate executive functions. So for example, tasks that require resistance to temptation or deferred gratification requires the most activation of what Barkley labels behavioral inhibition, executive function and self-regulation. The four executive functions influences the fifth neuropsychological ability that Barkley calls motor control-fluency-syntax, which emphasize control of both the motor system as well as the synthetic capacity to generate novel and complex responses in a goal-directed approach and all of which originate from the motor system of the brain, broadly interpreted as the frontal and prefrontal cortex. However, several other non-executive brain systems (subfunctions) may be influenced by the effects of the motor system if they are necessary for the execution of goal-directed behavior, including for instance systems involving sensory-perceptual, spatial, memory, language, and emotional components (Figure 1).
Development of executive functions and self-control

As the executive functions develop during childhood, Barkley theorizes this should create a gradual shift from those things that guide and control the child, from external to internal representations. This include, but is not limited to, the more gradual guidance of internal representations such as motivations, images and speech of which many are dealing with the future, rather than being guided by external events and stimuli, which is referred to as internal control. Also, one should notice a gradual shift from being controlled by others to increased control of the self, which is referred to as self-control. Moreover, there would be a gradual change from being aware and responsive to events in the moment and close surroundings to focus on the future. And there would also be increased value put on larger, delayed consequences and gratifications rather than immediate and smaller ones, which is referred to as deferred gratification. In adulthood, these aspects of self-regulation is according to Barkley
fully achieved (social maturity) during the normal developmental course which makes subjects primarily guided by internal information, self-control, demonstrating goal-directed behavior and concerned with maximizing the future rather than immediate consequences of actions. Barkleys’ theory predicts that persons with ADHD would be impaired in these areas relative to a normal developmental course since the executive functions occur to a lesser degree in these persons due to impairments in impulse inhibition. The areas of executive dysfunction/function are described in more detail below.

The self-regulation of affect-motivation-arousal component of Barkleys model include separation and self-regulation of affect. Emotions may be elicited but they are moderated by means of self-directed speech and actions, they may be self-generated through motivation and arousal that support goal-oriented behavior. Both the ability to regulate and induce emotional states in support of goals and plans are included and may consist of self-comforting, self-directed speech, visual imagery, and self-reinforcing behavior. Barkley specifies the following subfunctions of the affect-motivation-arousal component, (a) emotional self-regulation, (b) a capacity for objective and social viewpoints, (c) self-regulation of drive and motivation, (d) self-regulation of arousal states. The internalization of speech component is believed to provide opportunities for reflection, description, problem-solving, formulation of plans, metacognition, symbolization and self-questioning by means of language. In behavior analysis, this has been referred to as rule-governed behavior (Skinner, 1953) and so by formulating rules a person is able to construct prolonged behavioral chains and guide behavior towards future goals so that behavior is not dependent upon the immediate surrounding contexts. Self-directed rules contribute to cross-temporal organization of behavior in that they bridge temporal gaps and assist in forestalling and planning future behavior. The link to inhibitory processes is apparent in for example responses-inhibition of stimuli that compete with rules and seems to be related to the ability to hold verbal rules in working memory.

The working memory component primarily include nonverbal working memory and the covert sensory-motor action toward the self which encompass the ability to maintain internal representations in mind and to use them for control of behavior. This would include all of the senses but especially so the covert visual imagery (re-seeing to oneself), and the covert audition imagery (re-hearing to oneself) which creates what Barkley call an internal stream of information that is used to guide behavior across time and towards certain goals. The ability to envision a certain future and work towards that imagery as a guide and the sense of time is
one central piece for this capacity which deals with the linkage of passages from the past, present and future and the coordination of self-directed actions according to this linkage, referred to as the cross-temporal organization of behavior (if-then). The reconstitution component include two interrelated processes called analysis and synthesis, which relates to the ability of taking pieces of behavior sequences apart and combine them into more complex sequences of creative and novel behavior. This ability would be apparent in nonverbal fine and gross motor behaviors as well as in the syntax of speech, and provides a person with generative and inventive power in their behavior so that there are both nonverbal and verbal fluency. This also makes possible the creation of multiple potential responses, and testing of fluencies and syntaxes before they are performed, Barkley calls this a metaprocess of “planning”.

Within this model, sustained attention is believed to arise as a function of the formulation and holding in mind of task-goal and the plan for attaining that goal (working memory), so that the necessary behavior for attaining the goal may be created and performed, which would obviously include more or less all of the four executive functions. According to this theory, it is the goal-directed and internally represented behavior that is disrupted in ADHD and therefore, the measures assessed during CPT performance would be described as goal-directed behavior rather than sustained attention. The instructions on the CPT task become both a rule and a goal and the subject is supposed to sustain responding despite the lack of external reinforcement, which creates assessment of goal-directed persistence, and Barkley mention that this goal-directed form of attention with necessity includes the prefrontal cortex while the contingency-shaped type of sustained attention do not. He gives examples of neuroimaging studies and neuropsychological findings in support of the right prefrontal region activation during CPT performance (i.e., Rueckert & Grafman, 1996) and neuroimaging research on reduced volumes in this area for subjects with ADHD (i.e., Castellanos et al., 1996; Filipek, et al., 1997). The hypothesis has primarily been investigated with regard to the Stop Signal Reaction Task (SSRT), which is a measure of response inhibition based on an explicit model of inhibitory processing called the race model (Logan & Cowan, 1984) and it allows separation of inhibition and other executive processes involved during performance.
All in all, one may say that the hybrid neuropsychological theory of deficient response inhibition predicts that ADHD is a disorder of self-regulation that arises from impaired impulse control which in turn hinders the activation of executive functions and ultimately may be visible in deficiencies of the motor control/fluency/syntax, which is the inhibition of task-irrelevant responses, execution of goal-directed responses, execution of novel/complex motor sequences, goal-directed persistence, sensitivity to response feedback, behavioral flexibility, task re-engagement after disruption, and control of behavior by internally represented information (Barkley, 1997).

1.2.3 Working memory impairment

Pennington and colleagues (Pennington & Ozonoff, 1996; Pennington et al., 1996) presents an interactive framework for understanding of the prefrontal cognitive functioning that involve interactions of working memory activations and inhibitory suppression on basis of three interactive dynamics, 1) working memory resources, 2) working memory demands, and 3) the strength of prepotent but misleading action alternatives. Working memory functioning is crucial for successful inhibition suppression and the theory predicts that behavior inhibition difficulties may result directly from nonoptimal working memory functioning. Prefrontal functioning are involved in what the authors call higher-order cognitive processes or executive functions, which is a collection of related yet distinct abilities such as attention control, working memory, impulse control and set maintenance. The ability to resolve competing action alternatives result from prefrontal cognitive functioning in which the interactive processes of working memory and response inhibition are effectively operating. Working memory processes is necessary for generating and executing correct responses while response inhibition is required for suppressing incorrect prepotent actions, and these types of processes interact in the production of action. The likelihood of making errors on prefrontal tasks changes as working memory demands and prepotent response tendencies vary. Stronger incorrect prepotencies require higher and more consistent working memory activation to avoid falling prey to the prepotency.

There are three main characteristics of working memory processes within this framework, 1) capacity, which is the concurrent storage and processing of information and the activation of complex and suitable features in long-term memory, 2) maintenance, which refers to the
ability to maintain information such as elements and representations over time which relates to working memory limitations and, 3) \textit{level of moment-to-moment-activation}, which has to do with the information being directly and effortlessly retrievable over specific time periods which may be seen as the very essence of working memory. These characteristics are described as separable and defining features of working memory but may also interact with each other during task performance, and various tasks require different working memory processes. In order to make a correct response the participant needs to retain information as well as use that information to guide action appropriately. In some tasks, the participant will also need to maintain the retained information during temporal gaps, or the participant may need to maintain a rule or self-instruction that may be more or less fixed and then apply the rule at the right moment for appropriate action. Other tasks may require more demands on working memory by requiring that information is transformed or manipulated or that the results needs to be tracked in order to guide response.

Working memory thus involve both online storage of information and also using that information along with contextual specifics to generate upcoming action. The authors thus suggest that working memory involve storage, computation as well as attentional activation. Since both working memory and attention refers to control of information (Kintsch, Healy, Hegarty, Pennington, & Salthouse, 1999), they are described as related but the exact relationship between the constructs and their possible overlap is discussed with reference to perspectives that view attention as either selective control or mental energy which according to the authors needs not to be incompatible with each other. A third possible position is according to the authors (Kintsch et al., 1999) that attention is an emergent property of the underlying cognitive architecture, which is more of a perspective of the underlying and dynamic interaction of subsystems and their effects of phenomenon such as working memory and attention, rather than two fundamentally distinct classes of cognitive processing.

 Except for working memory, successful task performance requires inhibition of prepotent responses and as prepotency strengthens so does the need for higher degrees of inhibition. Although not all possible incorrect responses need to be suppressed, the authors suggest that prepotent actions require inhibition of overt behavior that has not yet occurred. When working memory processes are appropriately activated and maintained, the inhibition of alternative actions is inhibited by default. Tasks that are sensitive to prefrontal dysfunction push the competitive limits towards prepotent responding by either increasing working memory...
demand or the strength of the prepotency. From this perspective, poor performance on prefrontal cognitive tasks by persons with ADHD is the result of simultaneous demands of working memory and inhibition which are posed by competing response alternatives. A main implication of the interactive framework is that failure of working memory should result in problems with response inhibition, and that there is a continuum between normal and abnormal functioning so that the same competitive dynamics of working memory and inhibition may result in everyday task errors as well as produce the psychopathological prefrontal dysfunctions seen in patients with ADHD. The authors (Pennington & Ozonoff, 1996) present empirical support for the idea that increasing working memory load increases probability of response errors and this interaction may be examined by either increasing time of keeping information online or introducing secondary tasks that increases the load of working memory.

1.2.4 The cognitive-energetic model

An empirical approach to ADHD is put forth in the Cognitive-Energetic Model, CEM, introduced by Sergeant, Oosterlan and van der Meere (1999; Sergeant, 2000, 2005). This theoretical model advocates that behavior performance in children and adults with ADHD are dependent upon the energetic state of the person and the interplay between attention mechanisms, state factors, and cognitive management/executive functions. The unique contribution of this theoretical model is the role of the energetic state in ADHD performance and how deficiencies in state regulation and energy are essential for core symptoms of ADHD. In addition to deficiencies in state regulation and energy, the model also suggests that there may be specific deficits in inhibition that affect behavior and performance in ADHD. Thus, the model entails both “higher” neural processes, i.e., cognitive management and executive functions as well as “lower” neural processes including three state-regulating factors of effort, arousal and activation.
CEM comprises three levels (see figure two) of which the first level entails the so called computational mechanisms of attention that includes four stages labeled encoding, search and decision (central processing) and motor organization. These are all information processing stages and they have been associated with experimental task variables such as target detection and motor output during CPT and Go/No-Go performance. The second level of CEM involves the three energetic pools labeled effort, arousal and activation. Effort is the energy necessary to meet task demands. It is required when the current state of the person does not match that required by the task at hand. The level of effort also depends upon cognitive load and entails motivation and response to contingencies. During CPT performance for example, effort would entail the ability to sustain attention to stimulus and persist in self-motivation so to effortfully complete the task. Sergeant (2005) argues that the effort pool is strongly related to the hippocampus and that it has the ability to both excite and inhibit the two other energetic pools of activation and arousal and therefore, the effort pool is a fundamental deficiency in ADHD. Next, the arousal pool is defined as phasic responding and strongly affected by the stimulus processing as well as influenced by intensity and novelty of task. Its behavioral indications may be indexed by sleep and wake patterns and associated with amygdala and the
mesencephalic reticular formation. During CPT or Go/No-Go tests for example, arousal may be affected by target frequency and the target stimulus interval such that a Go/No-Go test stimulates higher levels of arousal compared to the traditional and less intense CPT. Finally, the activation pool is associated with the physiological readiness to respond and affected by task variables such as preparation, alternence, time on task and time of day. This activation pool is according to the authors associated with the striatum and the basal ganglia. The interplay between these energetic pools are important for understanding of ADHD behaviors, and so for example the effort and activation pool are greatly related and will have an effect on the actual motor output during task. Sustained effort, motivation and physiological readiness are all inter-related processes that are necessary for the effective responding to targets. Except from these energetic-arousal aspects of ADHD behavior and performance and the attentional information processing during task, the third level of CEM involves a “higher” over-riding level of processing including planning, monitoring, detection, inhibition and correction of error as well as the mental representation of a task. This level of processing are associated with the prefrontal cortex and may be described as executive functions.

The CEM idea is that ADHD involves deficits in three levels of functioning, i.e., the cognitive mechanisms and especially those related to motor output, state regulation by means of the three energetic pools and the cognitive management system. Regarding the order of deficits, the model proposes that ADHD, at least in part, is derived from underlying deficits in state regulation that in turn will create inhibition and motor output deficits. Within then CEM paradigm, the third level of information processing, i.e., executive functioning, and more specifically the inhibition deficit associated with ADHD are operationalized as for example commission errors on the Go-/No Go task and the Stroop task, which are both assessing impulsivity. The authors of CEM links their theory to both laboratory tasks of impulsivity and neuroimaging data including manipulations of stimulus-response frequencies that report decreased striatal activation in children with ADHD but neutralization with MPH. The striatum is also the area associated with the activation pool, e.g., physiological readiness to respond, according to the theory. Another line of evidence for their theory concerns studies with the Stop Signal Task which is also assumed to measure deficits in response inhibition. Here, children with ADHD as well as children with conduct disorder show equally weak response inhibition compared to controls which makes an inhibition deficit not uniquely related to ADHD. Moreover, there is also empirical evidence that other aggressive behaviors except from conduct disorder are related to equal levels of response inhibition deficits seen in
ADHD. This supports the notion that a response inhibition deficit is at least not the only primary deficit in ADHD. Other experimental data referred to by the authors suggest that children with the ADHD predominantly inattentive subtype show specific brain patterns that appear too early to be evoked by the stop-signal stimulus and therefore not a failure of inhibition, but rather a sign of inadequate brain-state for the task demand. Recent studies have also been conducted with adolescents and adults that indicate hypofrontality at the right caudate, right mesial frontal, the basal ganglia and relations to motor output. The authors point out that since ADHD, at least in boys, are associated with reduced brain volumes in cerebellum, assigning significance to specific cortical areas are problematic.

Regarding empirical evidence for the relevance of the energetic pools, the authors put forth that activation is directly related to the motor organization and output which are clearly implicated in ADHD. Further, that the effort pool involving aspects like motivation and response to contingencies are disrupted in ADHD. An example with direct affect on attentional activity is fMRI data of increased thalamic activity after consumption of caffeine. Alterations in the activation pool may according to the authors be observed through shifts of the event rate during task since event rate alters the energetic state of the subject. For example, fast compared to medium conditions may induce either over arousal or over activation and results in fast and inaccurate responding. A slow event rate condition may induce under arousal or under activation which also result in slow and inaccurate responding. A test that may track variations in the energetic state is the CPT and depending on the event rate, different patterns may evolve. Both children and adults with ADHD have been shown with their primary activation in the right middle frontal gyrus during CPT performance. Children and especially adults with ADHD have been found to perform more poorly on conditions with relatively slow event rates conditions as compared to both moderate and fast event rate conditions. An experiment comparing three CPT event rate conditions with children having only ADHD or plus tic disorder and controls are given as example. The interesting finding was that despite both clinical groups presenting equal levels of higher than control commission errors, only the ADHD group performance deficiencies was related to variations in even rate. This was clear as the level of commission errors in children with ADHD increased in the slow and fast condition but not in the medium event rate condition. The authors suggest this finding support the theoretical idea of poor response inhibition being modulated by the inability of ADHD children to adjust their energetic state. So, altogether, the authors’ main point is that findings presenting a response inhibition deficit are not
automatically ruling out other underlying explanations for this behavior like the state-regulating deficits indicated in ADHD. They present empirical evidence that the behavior deficits seen in ADHD are dependent upon the state of the subject and the allocation of energy to the task at hand and that not only anterior attentional networks but also parietal and subcortical networks are involved in the disorder.

1.2.5 Delay aversion hypothesis

Sonuga-Barke and colleagues (Sonuga-Barke et al., 1992, 1994; Sonuga-Barke, 2002, 2003, 2005) presents the dual-pathway model of ADHD (Figure 2) which states that ADHD is both a neuro-cognitive disorder characterized by executive dysfunctions (EDF) and a motivational style-characterized by attempts to avoid or escape delay, e.g., delay aversion (DEL). Poor inhibitory control underpin dysregulation of behavior and cognition while delay aversion is a central part of the motivational style-arising from fundamental disturbances in reward circuits of the brain, and these independent characteristics co-exist in ADHD but give rise to two distinct psycho-patho-physiological subtypes of the disorder with different developmental pathways, one in which poor impulse control result in the dysregulation of behavior and cognition and another in which the motivational style is characterized by alterations in a delay gratification gradient. Both subtypes are by means of experimental testing linked to separate circuits of the brain, e.g prefrontal cortex, and the nucleus accumbens respectively but the pathways are presented at multiple conceptual levels including symptomatic, neuropsychological and neurobiological. The dual-pathway model proposes that ADHD is a developmental outcome of two distinct psychological and developmental processes, and that these outcomes also represent two conceptual perspectives of behavioral disorders in general, one that deals with the site of dysfunction and one that deals with the role of function. By specifying these developmental processes as two pathways, linkages between neurobiological systems, psychological processes, behavior manifestations and testable performances are suggested.

ADHD as executive dysfunction, EDF, within the dual-pathway model include the dysregulation of action, thought and cognitive-energetic states that results in a general failure of controlling these aspects in accordance with social norms and intellectual expectations of a given situation, e.g., impairment relative to the environment. Sonuga-Barke (2003) describes
how the EDF pathway represents a family of research that emphasizes the impairment of cognitive control processes as the results of neuro-psychological dysfunctions across various domains, settings and activities. EDF are also described as top-down cognitive processes that deals with the appropriate facilitation of cognitive sets and shifts in the purpose of attaining future goals, this would include executive functions such as working memory, impulse control, planning and set shifting which are inter-related yet distinguishable and related to various developmental lines. However, Sonuga-Barke refers to Barkleys (1997) theory on impulse inhibition for executive function and other theories (Sergeant, 2000, 2005) of state-regulation for the effectiveness of executive function, and notes that the association between ADHD and executive functioning is uneven and that not all of the functions may be impaired in ADHD which makes theoretical accounts of EDF not by themselves able to explain the occurrence of ADHD seen through the dual pathway perspective. The motivational approach is put forward in terms of delay aversion in order to communicate valuable aspects of ADHD psychological processes and behavior manifestations, that is not explained satisfactorily by EDF theories alone.

The *delay aversion* pathway, DEL, represents the hypothesis of sub-optimal reward processes in which ADHD persons has higher than normal levels of delayed reward discounting which become manifest in attempts to avoid or escape delay. This is supposed to be the result of biologically-based shortened delay reward gradients which makes ADHD persons predisposed to display higher tendencies to discount future rewards and prefer immediate rewards which causes problems with waiting for desired outcomes and working effectively over extended periods of time. DEL stretches from neurobiological analytical levels through psychological processes and makes predictions about actual behavior manifestations for different conditional situations. ADHD is seen as the outcome of neurobiological impairment in the power and efficiency of signaling the potential future reward in the present situation. This leads to reduced control of present behavior with regard to future rewards and a steeper delay of reward gradient. Delay aversion is defined as a negative emotional reaction that occur during delay rich conditions and become manifest as behavioral attempts to escape or avoid delay.
Delay reduction strategies are conditional and differ in choice and no-choice situations (Figure 3) so that DEL is expressed in terms of different behavior manifestations. No-choice situations are those in which ADHD persons cannot escape or avoid actual delay, that is during fixed time conditions (i.e., CPT testing) which causes the person to maximize attention instead towards non-temporal stimulation (interesting and absorbing aspects of the environment) and systematically reduce the subjective sense of time spent which result in behaviors of inattention and over-activity. Attention is allocated to such aspects of the environment that makes the perceived passage of time to speed up so that the subjective experience of delay is minimized. If environmental aspects described as non-temporal stimulation are not present, persons with ADHD may act upon the environment to create non-temporal stimulation by themselves. Hyperactivity then (such as fidgeting) is viewed as “functional” behaviors that create non-temporal stimulation during delay, and inattention (attention off-task) is the result of focusing on non-temporal stimulation of the environment during delay. The other condition for expression of DEL are those choice situations in which the person is able to choose between immediate and delayed rewards and ADHD persons tend
to choose immediate rewards which are manifest as impulsive behavior. The significance of these behaviors relate to their possible clinical character (symptoms) and this view is consistent with findings suggesting that ADHD predisposes persons to become more hyperactive and inattentive during periods of delay.

Fig 3: A schematic representation (adapted from Sonuga-Barke, 2003) of delay aversion during choice- and no-choice conditions, resulting in core-symptom manifestations of ADHD.

DEL makes predictions relating to bottom-up processes including those attentional processes that deals with the capture of attention during initial stage of stimulus presentation, for example emotional and motivational cues in the environment that provide opportunities to escape from delay. Persons with ADHD are theorized to be hyper-vigilant to environmental cues that provide opportunities to escape from delay. Mediators are for example culturally-based influence and socialization in which a person’s willingness to wait is partly determined by social and cultural factors in their environment. Neurobiological findings in support of DEL are described but the effects of the mediators are said to be partly speculative since environmental and individual factor-interactions are not fully understood in ADHD. Within a neuro-ecological framework, delay aversion is described as associated with three developmental processes, (a) child x environment correlation, (b) person x environment correlation, and (c) individual accommodation. The first one (a) is related to predisposed
behavior responses of the child and the interaction with social environment shapes behavior, this may for example include a child with high levels of predisposed impulsive and hyperactive behavior to pose cues on the social environment which enhances response patterns that hypothetically accumulate the child’s behavior and leads to stronger expression of symptomatic patterns related to ADHD. The second one (b) include those social punitive environments that shapes the child's behavior and the emergence of more generalized delay aversion since delay evokes negative emotional response from which the child tries to escape. The third (c) process involves the personal accommodation between underlying dispositions and the constraints that this imposes on learning situations.

Sonuga-Barke (2005) also distinguishes five active developmental components. The first includes the process of neurobiological reward circuits and the impaired signaling during delay rewards which causes impulsivity. Second is the process of how impulsivity leads to ineffective operation in delay rich environments which thirdly, leads to negative response from significant other which leads to delay aversion. Fourth, the failure to engage during delay has a negative impact on the experience of management during delay activities which in turn reduces opportunities to practice on this skill. Fifth, delay aversion become both a trait of impulsivity but also extends to behavioral characteristics of activity and attention domains along with the reduced organizational skills, and these process-components will over time reinforce the type of symptoms and impairments that is defined as development of a fundamentally motivational disorder.

Opposite to executive functioning theory and the role of impaired inhibition in problems with waiting, Sonuga-Barke thus suggest that the core problem in ADHD is delay aversion since children with ADHD are able to wait even though this might involve inhibition but that they often choose not to wait even though this does not involve inhibition, so regardless of required inhibition or not, they prefer not to wait. Also, the tendency to choose small an immediate over future and potentially greater rewards during decision-making when this reduces the overall delay of task rather than merely striving to immediately increasing reward or response is supporting this theory (Sonuga-Barke et al., 1994). This latent response style in ADHD is associated with meso-limbic circuits of the brain in which dopamine has a key reward-signaling and behavioral regulating function during conditions of delayed reward and animal models demonstrate that lesions in the accumbens reduces the ability for delayed reward.
1.2.5 Dopamine hypofunctioning

The dynamic developmental theory of ADHD (Sagvolden et al., 2005) primarily outlines a behavioral analytical level since ADHD currently has no biological marker. The theory is however based upon genetic and neurobiological correlates since a majority of the findings from various research fields converge with impaired dopamine mechanisms in ADHD. According to the authors, ADHD should be analyzed on a systems level rather than by means of single- genes or synapses levels since development and severity of symptoms may be linked to the degree of dysfunction in various dopaminergic systems. The theory predicts that symptoms associated with ADHD may be caused by hypofunctioning dopaminergic loops and mediated by altered reinforcement and deficient extinction processes that are developed dynamically as the person grows up and interacts with the social surroundings.

ADHD behaviors may be related to neurobiological factors in terms of hypofunctioning in three dopamine branches, 1) mesocortical, 2) mesolimbic, and 3) nigrostriatal. A central assumption is that hypofunctioning in mesolimbic dopamine branches generate altered reinforcement of behavior and deficiencies in the extinction of previously reinforced behavior. Moreover, the hypofunctioning mesocortical dopamine branch underlies attention response deficiencies such as poor response toward targets and poor behavioral planning. A hypofunctioning nigrostriatal dopamine branch will cause impaired modulation of motor functions and deficiencies in nondeclarative habit learning and memory, which may be observed as excessive motor behavior, developmental delay, clumsiness, neurological “soft signs”, and failures to inhibit responses when quick reactions are required.

The authors suggest that behavioral processes like reinforcement and extinction may constitute the most elementary level at which universal factors of ADHD are possible to identify. Both of the main behavioral selection mechanisms of reinforcement and extinction are associated with dopamine neuron activity such that the neuronal connections are strengthened when associated with reinforced behavior, which is usually adaptive, and weakened when associated with non-reinforced behavior, which is usually maladaptive.
Reinforcement mechanisms operate within a limited time window that “opens” when behavior occurs and “closes” as the perception of its consequences emerge. The authors argue that in ADHD, there will be a narrower time window than what normally is because of the dopamine hypofunctioning. Stimuli that control behavior will be prematurely restricted and cause some of the attention problems seen in ADHD. The narrower time window will also promote short sequences of behavior which give rise to motor and cognitive impulsiveness. Also, the authors say, this hypofunctioning of dopamine leads to deficiencies in behavioral extinction processes which causes the excessive behavior called hyperactivity and increased behavior variability, i.e., failure to inhibit responses. The authors separate motor and cognitive impulsiveness since motor impulsiveness occur as bursts of responses with short inter-response times, while cognitive impulsivity implies that private events, i.e., plans and thoughts, are dealt with for short periods of time and with rapid shifts which causes problems with organizing behavior, generating and following plans, forgetfulness, and inefficient use of time. The theory predicts that poor sustained attention and hyperactivity is derived from the same source in which reduced dopamine function associated with ADHD produces shorter than normal time windows for operation of reinforcement and extinction of behavior processes, explained in theoretical terms as shorter delay gradients.

Reinforcement is described as the selection mechanism in the evolution of behavior and it increases the probability of future responding by means of reinforcers which may vary along dimensions such as density (frequency), contiguity (delay of reinforcement), predictability, and value (attractiveness). The effect of reinforcers is largest when immediately being delivered after the occurrence of a response and the more time that elapses, the weaker the effect of the reinforcer. This relation between the reinforce effect and the time gap between the response and reinforcer is known as a delay gradient. The delay gradient operates for the relation between responses and reinforcers by bridging longer time intervals. The potency of a stimulus as a conditioned reinforcer thus depends upon the time between its onset and the subsequent delivery of a reinforcer in its presence. In general, the effect of a reinforcer is stronger when delay is short than when it is long. In ADHD, the theory predicts that a shorter and steeper than normal delay gradient mainly makes the reinforcement that happens close in time to the response effective. Because of this, the reinforcer must follow quickly after stimulus onset in ADHD or else the stimulus will not become a potent reinforcer and the person will not attend to it. It is also less likely that persons with ADHD will repeat a response, since fewer of their total responses will be reinforced. Also, since reinforcers acts
upon both the response that produced it and the previously emitted responses, the chain of reinforcement mechanisms altogether will be less effective in persons with ADHD. Based on the same delay gradient principle, the theory suggests that extinction processes is less efficient in ADHD because elimination of previously established but no longer reinforced responses will take place to a lesser extent.

Predictions based on the dopamine theory of behavioral reinforcement and extinction processes include behavioral outcomes such as delay aversion, impulsiveness, hyperactivity, deficiencies in sustained attention, increased behavioral variability and failure to inhibit responses. The authors comprehensively discuss (2005) neurobiological and theoretical processes of behavioral outcomes. Hypofunctioning dopamine branches are seen as the main individual predisposition for ADHD but through dynamic interplay with the surroundings, development is influenced by factors that may have positive or negative effects on behavior/symptom development. On the neurobiological level specifically, the authors describe neurotransmitter and neuromodulator systems undergoing growth spurts and pruning several times during ontogenesis which will be associated with synaptic supersensitivity and associated with vulnerability to negative and positive environmental influences on the neurodevelopmental dynamics of ADHD. Behavior characteristics, neurobiological development during life, and the environmental circumstances are thus developmentally multidirectional within this theoretical framework.
2. THE PRESENT INVESTIGATION

2.1 Introduction

In this section the aims, designs, instruments, procedures, statistics and results of the four papers contained in this thesis will be discussed. The papers originate from a research program regarding objective markers of adult ADHD and include materials from participants with psychiatric disorders as well as participants from the normal population. Paper I-IV includes materials from 126 participants with ADHD, 36 participants assessed for but disconfirmed a diagnosis of ADHD and 45 participants with Bipolar II disorder or Borderline personality disorder as well as 202 normative participants from the general population with screened non-ADHD symptoms levels. The research program was established in 2008 and is based on collaboration between division of psychiatry in the County Council of Värmland, the psychiatric clinic in the NU health care of Västra Götaland, the clinic of neuropsychiatry and CBT-Cereb in Stockholm, as well as the department of psychology at Karlstad University, Sweden.

2.2 Paper 1. In Search for an Objective Measure

2.2.1 Aim

The purpose of this study was to investigate the levels of sensitivity and specificity for the Quantified Behavior Test Plus (QbTest-Plus) with regard to ADHD in 19 adult patients awaiting clinical assessment for ADHD.

2.2.2 Design

The criterion variable, i.e., clinical assessment, was performed by trained clinicians at the psychiatric clinic within the NU-health care. Assessments typically included observations, childhood anamnesis, self-report symptoms scales, information from relatives, psychological and/or occupational-therapeutic tests and additional batteries of well-chosen psychological
tests performed by specialists in neuropsychiatry were sometimes used. The clinic adheres to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV; American Psychiatric Association, 2000). Results of the clinical assessment were categorized into the dichotomous variable of No (not ADHD) or Yes (ADHD is established) and compared to the outcome of QbTest-plus which was either “Probably not ADHD”, “Possibly ADHD, further assessment is needed” or “Probably ADHD”.

2.2.3 Instruments

QbTest-Plus - Quantified Behavior Test Plus

This instrument (QbTech AB, 2010a, 2010b, 2010c) combines a continuous performance test (CPT), installed as a software program on a PC and an activity test during 20 minutes. While performing the CPT-test on the computer, movements of the participant are recorded using a motion tracking system. The purpose of the instrument is to provide objective information regarding cardinal symptoms of ADHD: hyperactivity on basis of motor-activity and inattention and impulsivity on basis of the CPT-test.

In the present paper, hyperactivity was operationalized with the parameter called "distance", i.e., the length of the path describing the movement of the headband reflector during the test. Inattention was operationalized using omission errors (no response is registered and the stimulus was a target) and impulsivity using commission errors (a response is registered and the stimulus was a non-target). Recommended cut-off scores, i.e., Q-score >1.3, for core items were based on 149 male and 118 female healthy normative participants from 13 to 55 years of age and was set at the 90th percentile of the distribution (QbTech AB, 2010b).

2.2.4 Procedure

Nurses at the psychiatric clinic used the approved patient information to inform participants awaiting clinical assessment about the purpose and procedure of the study and interested participants were registered for participation.

When arriving at the psychiatric center, the participant was met by a researcher in the lobby and taken to the test-room were information of the study-procedures were given. The
participant was introduced to the written informed consent and then signed and obtained a copy of it. The patients diagnosis and status was unknown to the researcher during the whole process of experimental testing. Prior testing, the participant was asked to be seated on a chair without armrests in order to ensure a non-reclining body-position in front of the PC and provided with the reflective head-band and the hand-held button. Nicotine was not consumed during the test.

Instructions on how to do the QbTest-Plus was given, verbally and then by the means of a standardized video (QbTech AB, 2010b) presenting procedures of the QbTest-Plus. The participant performed a one minute pre-test to make sure the instructions had been understood correctly. After this, the participant performed the QbTest-plus during 20 minutes. A room with minimal visual and auditory stimuli was used for the test and if any significant stimuli occurred, both what type of stimuli and the time when it occurred was documented. The researcher was present during the test but placed in such a way that it could not distract the participant. After testing, the participant answered demographic and other relevant questions regarding the psychiatric history but no questions endangering the blind design was asked. For purposes of analysis, data covering the results and methods used for clinical assessment, psychiatric history, the latest global assessment of functioning and information concerning medical treatment at the time of the study was collected from the participants' clinical record.

### 2.2.5 Statistics

In the present paper, results were analyzed using calculations of sensitivity and specificity. The three objective core items of QbTest-Plus, that is, hyperactivity measured in distance, impulsivity measured with commission errors and inattention measured with omission errors, was divided into either "No" or "Yes" relative to the predetermined cut-off level indicating moderately atypical behavior, i.e., Q-score >1.3 (QbTech AB, 2010a). Core items were then combined into a total judgment of either "Probably not ADHD" (all three No), "Possibly ADHD, further assessment is needed" (one or two Yes) or "Probably ADHD" (all three Yes) which were compared with the dichotomous criterion variable of "No" or "Yes" regarding the clinical diagnosis of ADHD.
2.2.6 Results

Sensitivity for detection of ADHD was 83 % and specificity was 57 %. Comparisons between clinical assessments and the QbTest-Plus yielded 74 % accuracy including ten true positive and four true negative cases, as well as three false positive and two false negative cases. The positive predictive value was 77 % and the negative predictive value was 66 %.

2.3 Paper II. Composite Measure of ADHD

2.3.1 Aim

The aim of the present study was twofold, first to 1) examine the predictive power of the QbTest-Plus in terms of sensitivity and specificity for adult participants with ADHD and non-ADHD normative participants, and second to 2) develop a composite measure for the entire ADHD core symptom triad on basis of the measures provided by the QbTest-Plus.

2.3.2 Design

The independent variables were Group (norm-group, ADHD-group), Gender (men, women) and Prediction of ADHD (No, Yes). There were 202 participants in the normative group and 55 participants in the ADHD-group. The total number of men was 139 and the total number of women was 118. The categorical variable “Prediction of ADHD” was conducted using qualitative analysis of Q-scores (Qb-Test raw scores) for cardinal symptoms from participants in the present study and tested on a norm-group of 84 adult persons with ADHD. The normative group with ADHD consisted of 47 men and 37 women whose mean age was 35.07 (SD = 10.36) and who had been assessed for ADHD at a neuropsychiatric clinic.

Dependent variables of the present study were ADHD core symptoms of hyperactivity, inattention, and impulsivity as well as the composite measure called the Weighed Core Symptoms scale (WCS). The dependent variables were developed statistically on basis of the core symptom measures from QbTest-Plus, i.e., hyperactivity measured in distance, inattention measured with omission errors and impulsivity measured with commission errors.
Analyses with Receiver Operator Characteristic (ROC) curves did not yield discriminant thresholds with acceptable power and analyses of the core symptom measures were also based upon practical analyses. The Q-score (Qb-test raw score) of each core symptom was transformed into percentages: 0 % indicated maximal quantity of the symptom and 100 % indicated complete absence of the symptom. The additional scale, WCS, was constructed using weighed Q-scores from the symptom scales. WCS runs from 0 which indicate maximal amount of ADHD-symptoms and 100, which indicate complete absence of ADHD-symptoms. The weighed Q-score principle was based upon practical analyses in which hyperactivity was the most predictive item of ADHD and therefore multiplied with three, inattention was the second most predictive item and multiplied with two and impulsivity was ascribed no additional weight because of its relatively low predictive value.

The categorical variable Prediction of ADHD, PADHD (no ADHD, yes ADHD), was also based upon raw scores from the measures of the QbTest-Plus (Q-scores), i.e., hyperactivity measured in distance, inattention measured with omission errors and impulsivity measured with commission errors. It was analyzed in the present study using Fisher’s exact test ($p < 0.05$) with PADHD (no ADHD, yes ADHD) and Group (non-ADHD normative group, ADHD group).

### 2.3.3 Instruments

**QbTest-Plus - Quantified Behavior Test Plus**

This instrument was also used in Paper I (please see section 2.2.3 for further details regarding QbTest-Plus).

**ASRS - The Adult Self Report Scale for Adult ADHD v1.1**

This screening instrument (Kessler & Üstün, 2004; Kessler et al., 2005b) was developed by the World Health Organization in order to provide initial information about the prevalence of ADHD-symptoms for both research and health care centers. It is derived from the criterions of ADHD in DSM-IV. Part A include the 6 most predictive items while part B holds an additional 12 items, all rated on a five-point scale (0 = never, 1 = rarely, 2 = sometimes, 3 = often; and 4 = very often). Each item has a cut-off point of either 2 (sometimes) or 3 (often), and four or more items listed above the cut-off in part A is used as inclusion/-exclusion-
criteria for clinical purposes and in research programs such as in the normative sample of the Qbtest-Plus (QbTech AB, 2010a). The internal consistency for the patient-administered version is 0.88 (Cronbachs alpha, \( \alpha \)) (Kessler et al., 2005a).

GAF - Global Assessment of Functioning Scale
The Global Assessment of Functioning Scale (Luborsky, 1962) are found in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000), estimating psychological, social and occupational functioning on a numeric continuum (0-100) of mental health and illness for adult persons (American Psychiatric Association, 2000). The first interval (0-50) describes severity of symptoms whereas the second interval (50-100) describes functional disabilities. The final score (GAF-total) of this scale ought to be the lowest score of the symptoms (GAF-symptom) and functional disability (GAF-function) estimations on the continuum. Reliability estimates for GAF scale have ranged from 0.28 to 0.90 (Söderberg & Tungström, 2007). The GAF-scores presented in the current study have been carried out by licensed clinicians and are the scores reported in the psychiatric records closest in time to QbTest-Plus.

2.3.4 Procedure
The Normative Group
A majority of the participants in the normative group (\( N = 139 \)) were recruited with the assistance of students at the department of psychology at Karlstad University in Karlstad, Sweden, and the remaining part of the normative group (\( N = 63 \)) were recruited with the assistance of the Cognitive Neuroscience Centre for Psychiatry at the University of Giessen, Germany. In Karlstad, recruiting was performed using major employers in the fields of education, transportation/industry as well as among students at the University. In Giessen, recruiting was performed via the Cognitive Neuroscience Center for Psychiatry using music organizations. Participants were informed about the purpose and procedures of the study and the QbTest-Plus was performed at the Universities of Karlstad and Giessen respectively. For further details on experimental testing with QbTest-Plus in the normative group please see the procedures described for the ADHD group below since procedures for the two groups coincide.
The ADHD Group

Diagnostic assessments had been carried out within two separate psychiatric clinics, the NU-Health Care in Västra Götaland, Sweden ($N=36$), and the psychiatric division of the County Council of Värmland, Sweden ($N=19$). The diagnostic assessments are carried out with similar neuropsychological procedures at both clinics and include for example anamnestic and structured interviews, self-ratings, interviews and symptoms ratings from relatives, tests of working memory, executive functioning and intelligence, observations and somatic examinations.

Nurses and trained clinicians at the psychiatric centers screened psychiatric records and recruited participants by mail and telephone. The study-specific procedures were explained and information on withholding ones diagnostic and medical status from the researcher as well as withdrawing from stimulant treatment 24 hours prior testing were pointed out in particular. On the day before participation, participants received a short message service on their mobile phone including reminder of the day, time and location of the study. For further details on the collection of data please see section 2.2.4, since the experimental procedures of this study correspond with the procedures of Paper I.

2.3.5 Statistics

Analysis of the study was conducted in three steps. First, the Fisher’s Exact Test was used to examine connections between Group (normative group, ADHD-group) and Prediction of ADHD (No, Yes). Second, a Pillai’s MANOVA was conducted with Group (normative group, ADHD-group) and Gender (men, women) as independent variables, and Hyperactivity, Inattention and Impulsivity as dependent variables, and a two-way ANOVA was used for analysis of WCS. Third, a one-way Pillai’s MANOVA was used with Prediction of ADHD (No, Yes) as the independent variable and Hyperactivity, Inattention and Impulsivity as dependent variables, and WCS was analyzed separately with a one-way ANOVA.
2.3.6 Results

There was a strong significant connection between the variables Prediction of ADHD and Group. A vast majority of the negative predictions was found in the normative group and a vast majority of the positive predictions was found in the ADHD group. Sensitivity was 86 percent and specificity was 83 percent when applying Prediction of ADHD in the groups.

There was a significant effect for the variable Group when investigated in relation to the core symptoms of ADHD and WCS. Significantly higher levels of symptoms on core symptom scales and WCS were found in the ADHD group compared to the normative group. A significant interaction effect was found for the variables Gender and inattention, descriptive analysis showed that women were more inattentive than men.

Significant effects were found for Prediction of ADHD when investigated in relation to the core symptoms and WCS. The group with a negative prediction scored significantly higher on the scales as compared to the group with a positive prediction. Thus, higher levels of symptoms were found in the group with positive prediction regarding ADHD. In summary, the results showed significant connections between predicted, actual and measurable outcomes related to ADHD.

2.4 Paper III. Validation among clinical groups

2.4.1 Aim

The aim of the present study was to investigate the validity of WCS and PADHD in adults with ADHD as well as in clinical groups with overlapping symptoms, i.e., borderline personality disorder and bipolar II disorder, participants assessed for but disconfirmed a diagnosis of ADHD and adult normative participants. The hypothesis of the present study: participants with ADHD have more ADHD-core symptoms than participants with bipolar II disorder, borderline disorder and participants with a disconfirmed diagnosis of ADHD, and even more core symptoms than normative participants without ADHD when assessed with PADHD and WCS.
2.4.2 Design

The independent variables of the present study were Group (norm, disconfirmed, bipolar II/borderline, ADHD), Gender (men, women) and Prediction of ADHD (no, yes). There were 179 participants in the normative group, 53 participants in the ADHD-group, 45 participants in the bipolar II/borderline group and 29 participants in the disconfirmed group. The total number of men was 149 and the total number of women was 157. Dependent variables were ADHD core symptoms of hyperactivity, inattention, and impulsivity as well as the Weighed Core Symptoms (WCS) scale.

2.4.3 Instruments

QbTest-Plus - Quantified Behavior Test Plus
This instrument was also used in Paper I and Paper II (see section 2.2.3 for further details regarding QbTest-Plus).

WCS- Weighed Core Symptoms scale
This scale summarizes the total level of ADHD core symptoms in adulthood on a scale with ten cut-points ranging from 0 to 100 where 0 indicate maximal amount of ADHD symptoms and 100 indicate complete absence of ADHD symptoms. The WCS scale is based upon raw scores from the summed and operationalized measures from the QbTest-Plus in which the results of hyperactivity has been multiplied with three, inattention with two and impulsivity with one. The ten cut-points of WCS have been developed through a procedure described in Paper II. In the present study, WCS correlated (Pearsons’ r) with hyperactivity \( r = 0.82, p < 0.001 \), inattention \( r = 0.73, p < 0.001 \), and impulsivity \( r = 0.50, p < 0.001 \) and those results were about the same also when correlations were computed separately for the ADHD group or the normative group only.

PADHD- Prediction of ADHD
This categorical predictor variable regarding ADHD (no, yes) is based upon raw scores from the operationalized measures of the QbTest-Plus (Q-scores), e. i., hyperactivity measured in distance, inattention measured with omission errors and impulsivity measured with
commission errors. PADHD was developed independently from WCS using qualitative analyses and assessment trials in which the level of sensitivity and specificity was evaluated and the procedures are thoroughly described in Paper II and in section 2.3.2.

**ASRS - The Adult Self Report Scale for Adult ADHD v1.1**
This instrument was also used in Paper II (please see section 2.3.3 for further details regarding ASRS).

**GAF - Global Assessment of Functioning Scale**
This instrument was also used in Paper II (please see section 2.3.3 for further details regarding GAF).

### 2.4.4 Procedure

**The Normative Group**
This group 
\( \text{\( N = 179 \)} \) included 99 men and 80 women from the adult normal population also described in Paper II whose mean age was 31.45 years \( (SD = 10.33, \text{range} = 18 \text{ to } 53) \). Inclusion criteria were ages between 18 to 65 years of age, willingness to sign the informed consent and complete the study-specific procedures and the exclusion criteria was any known psychiatric diagnosis. ADHD-symptoms were measured with the adult ADHD self-report scale. A majority of the participants in the normative group \( (n = 113) \) were students at Karlstad University or personnel from various companies in Karlstad, Sweden, and the remaining part \( (n = 66) \) were recruited from music organizations in Giessen, Germany.

**The ADHD Group**
The mean age for participants in the ADHD group, including 24 men and 29 women, was 35.89 years \( (SD = 12.25, \text{range} = 18 \text{ to } 64) \). Participants \( (n = 50) \) were assessed at the clinic in neuropsychiatry and CBT, Cereb, or at the neuropsychiatric clinic in the NU-health care \( (n = 3) \), Sweden, at the mean age of 35.89 years \( (SD = 12.6 \text{ range} = 18 \text{ to } 64) \) and diagnosed with ADHD according to the Diagnostic and Statistical Manual of Mental Disorders. Most of the participants had the combined hyperactive/impulsive and inattentive subtype of ADHD (314.01; \( n = 47 \)) while others had the predominantly inattentive subtype (314.00; \( n = 2 \)) or ADHD-not otherwise specified (314.9, \( n = 4 \)) because of not obtaining information from
significant others regarding early childhood. The assessments included clinical interviews, self-rating scales, information from relatives and psychological testing including the QbTest-Plus.

At the neuropsychiatric clinic Cereb, nurses screened psychiatric records from 2008, i.e., this was the time when Cereb started using computerized records, and randomly selected 150 of approximately 400 patients who had done the QbTest-Plus during their clinical assessment, oversampling those with ADHD in combined form and without severe psychiatric comorbidity. Participants were contacted via mail three times from May to June in 2011. After resending the mail, participants received compensation to a value of 100 SEK for participating in the study. At the division of psychiatry in the county council of Värmland, clinicians screened psychiatric records and recruited participants on mail and telephone. The patients diagnose and status was unknown to the researcher during the whole process of experimental testing and assessment. For further details on the collection of data please see section 2.2.4, since the experimental procedures of this study correspond with the procedures of Paper I.

The Bipolar II/Borderline Group
The mean age for participants in this group, including 13 men and 32 women, was 42.33 years ($SD = 11.63$, range = 22 to 60). The group had Bipolar II disorder ($n = 27$) or Borderline Personality Disorder ($n = 18$) and received their diagnosis at the mean age of 40.60 years ($SD = 12.05$, range = 21 to 69). Diagnostic assessments had been carried out within two separate psychiatric clinics, the NU-Health Care in Västra Götaland, Sweden ($n = 29$), and the psychiatric division of the County Council of Värmland, Sweden ($n = 16$). Clinicians screened 586 psychiatric records and recruited participants on mail and telephone. The study-specific procedures were explained and information on withholding ones diagnostic and medical status from the researcher was pointed out in particular. For further details on the collection of data please see section 2.2.4, since the experimental procedures of this study correspond with the procedures of Paper I.
The Disconfirmed Group

The mean age for participants in this group, including 13 men and 16 women, was 35.21 years ($SD = 10.31$, range = 20 to 54). Their mean age when disconfirming ADHD was 33.45 years ($SD = 10.33$, range = 19 to 52) and most of the clinical assessments ($n = 22$) concerned ADHD specifically while some also included a broader field of neuropsychiatric disorders ($n = 7$). The outcome included none ($n = 8$), one ($n = 9$) or two ($n = 12$) psychiatric diagnoses, including Aspergers syndrome ($n = 6$), dyslexia ($n = 4$), personality disorders ($n = 4$), borderline personality disorder ($n = 1$), bipolar disorder unspecified ($n = 2$), obsessive compulsive disorder ($n = 1$), post-traumatic stress disorder ($n = 1$), memory disorder unspecified ($n = 1$), as well as secondary diagnoses of depression ($n = 3$), dyscalculia ($n = 2$), attention disorders unspecified ($n = 2$), developmental coordination disorder ($n = 1$), tics ($n = 1$), social phobia ($n = 1$), dysmorphophobia ($n = 1$), and mixed substance use disorder ($n = 1$). Diagnostic assessments had been carried out within three separate psychiatric clinics, the NU-Health Care ($n = 6$), the psychiatric division of the County Council of Värmland ($n = 6$) and Cereb ($n = 17$).

Clinicians screened psychiatric records and recruited participants who had been assessed for ADHD/ADD and/or neuropsychiatric disorders including ADHD/ADD but not received such diagnoses. Study-specific procedures were explained and information on withholding ones diagnostic and medical status from the researcher was pointed out in particular. At Cereb, 50 participants who had done QbTest-Plus during clinical assessment were randomly selected and contacted via regular mail three times from May to June in 2010. For further details on the collection of data please see section 2.2.4, since the experimental procedures of this study correspond with the procedures of Paper I.

2.4.5 Statistics

Analysis of the study was conducted in three steps. First, Pearson Chi-Square was analysed with Group (normative, disconfirmed, bipolar II/borderline, ADHD) and Prediction of ADHD (No, Yes). Second, PADHD was analyzed as an independent variable with regard to WCS using a one-way ANOVA. Third, Group and Gender differences as well as possible interactions with regard to core symptoms were analyzed with a Pillai’s MANOVA, and WCS was analyzed separately for these independent variables using a two-way ANOVA.
2.4.6 Results

There was a strong significant connection between the variables Prediction of ADHD and Group and a majority of people who according to PADHD did not have ADHD were found in the normative group and a majority of people who according to PADHD had ADHD was found in the clinical groups. Sensitivity was 87% for ADHD and specificity was 85% for normative participants. Specificity was 41% for disconfirmed participants and 36% for participants with either bipolar II disorder or borderline personality disorder. Investigating PADHD with regard to WCS yielded significant results in the sense that a majority of positive predictions with PADHD fell into the lower range of WCS (indicating higher symptom levels) and a majority of negative predictions fell into the higher range on WCS (indicating low or no symptoms).

The MANOVA omnibus yielded significant effects for Group and the interaction group and gender but not for gender. Post-hoc tests indicated that the ADHD group scored lower on hyperactivity with regard to all other groups, lower on inattention than normative and the disconfirmed group but not significantly lower with regard to inattention than the bipolar II/borderline group. The ADHD group also scored lower with regard to impulsivity compared to the normative group but not compared to the other two clinical groups. The normative group scored higher on the core symptom scales for hyperactivity and inattention than all three clinical groups but with regard to impulsivity they were not significantly more (or less) impulsive than the disconfirmed group. The disconfirmed and the bipolar II/borderline group did not differ with regard to hyperactivity or impulsivity but only with regard to inattention were the latter group scored lower (had more inattention) than the disconfirmed group. The interaction of group and gender yielded significant results only for impulsivity and further analyses showed a difference with regard to gender only in the disconfirmed group were men were more impulsive than women. The WCS yielded significant effects for group but not for gender or the interaction group and gender. The ADHD group score significantly lower than all other groups on WCS and the normative group score significantly higher than all other groups on WCS. There was no significant difference between the disconfirmed and the bipolar II/borderline group with regard to WCS.
2.5 Paper IV. Objective measures of treatment response and remission

2.5.1 Aim

The aim of the present paper was to evaluate two prospective and objective measures of response and remission in adult ADHD using first-line treatment agencies for the disorder, i.e., methylphenidate.

Study one evaluates the ability of WCS and PADHD to indicate response to treatment with fast acting Central Stimulant (CS) treatment. Two hypotheses were postulated, 1) the lowest dose of fast-acting treatment with methylphenidate leads to remission according to PADHD, and 2) the lowest dose of fast-acting treatment with methylphenidate decreases ADHD symptoms according to WCS. There were 63 participants with ADHD in study one.

Study two evaluates the ability of WCS to indicate dose response and both instruments ability to indicate symptomatic remission during titration with CS and at three months follow-up. Three hypotheses were postulated, 1) CS-treatment leads to remission at follow-up according to PADHD, 2) CS-treatment leads to decreased symptoms at follow-up according to WCS, and 3) CS-treatment leads to decreased symptoms during titration according to WCS. There were 10 participants with ADHD in study two.

2.5.2 Design

Study one

In study one, the levels of sensitivity and specificity for Prediction of ADHD (PADHD) were investigated using frequency distributions before (no, yes) and after (no, yes) treatment. A mixed design with analyses of variances was used with dependent variables of Hyperactivity, Inattention, Impulsivity and the Weighed Core Symptom scale (WCS). The independent variables were Treatment (before, after) and Gender (men, women). There were 31 men and 32 women in the study.
Study two

In study two, PADHD before treatment (no, yes) and PADHD at follow-up (no, yes) were analyzed using descriptive data and reported in terms of sensitivity and specificity. Dependent variables were objective measures of Hyperactivity, Inattention, Impulsivity and WCS. Measures were collected before treatment (baseline) and at each dose level (18/20, 36, 54, 72) as well as three months after identifying the optimal dose level (follow-up). Wilcoxon signed rank test (5 % level) was used to analyze baseline and follow-up measures for each dependent variable. The same test was also employed to investigate subjective behavior ratings before treatment and at the follow-up.

2.5.3 Instruments

QbTest-Plus - Quantified Behavior Test Plus
This instrument was also used in Paper I – III (see section 2.2.3 for further details regarding QbTest-Plus).

WCS- Weighed Core Symptoms scale
This instrument was also used in Paper III (see section 2.4.3 for further details regarding WCS).

PADHD- Prediction of ADHD
This instrument was also used in Paper III (see section 2.4.3 for further details regarding PADHD).

ASRS - The Adult Self Report Scale for Adult ADHD v1.1
This instrument was also used in Paper II (please see section 2.3.3 for further details regarding ASRS).

GAF - Global Assessment of Functioning Scale
This instrument was also used in Paper II (please see section 2.3.3 for further details regarding GAF).
WRASS 1 - Wender Reimherr ADHD Symptoms Scale for Patients
WRASS (Ward, Wender, & Reimherr, 1993) estimates symptoms of ADHD from the adult patients point of view on a 5-point scale (0= not at all/only a little, 1= to some extent, 2= a lot, 3= severely, 4= completely). The scale covers areas of attention difficulties (4 items), hyperactivity, instability of mood, temper outbursts, organizational difficulties, sensitivity to stress and impulsivity. WRASS provides a score for every separate area as well as a total score including all symptoms of ADHD. The internal consistency of the Wender Reimherr Interview is 0.82 (Cronbachs alpha, \( \alpha \)), its inter-rater reliability is 1.0 (Kappa coefficient), and the convergent validity with the WRASS-self report version of the scale is 0.65 (Spearman’s coefficient) (Rösler et al., 2008).

WURS - The Wender Utah Rating Scale
This scale (Ward et al., 1993; Wender, 1985) retrospectively measures the severance of symptoms regarding ADHD in the childhood of adult persons on a 5 point scale (0= not at all/only a little, 1= to some extent, 2= a lot, 3= severely, 4= completely). In total, adult subjects rate 61 items related to relevant aspects of cognitive abilities, social interaction, emotional stability, behavioral functioning and somatic aspects. A cut-off score of 46 for the 25 most predictive items was used in the current study which is in line with previous results (Ward et al., 1993) in which 86 % of patients with ADHD (\( N = 81 \)), 99 % of normal subjects (\( N = 100 \)) and 81 % of depressed subjects (\( N = 70 \)) were correctly classified using this technique.

CAARSS – Conners Adult ADHD Rating Scale- Short version
This self-report scale (Conners, Erhardt, & Sparrow, 1999) measures 26 items related to four areas of adult ADHD: Inattention problems, Hyperactivity/restlessness, Impulsivity/emotional lability and Problems with self-concept, all on a four-point scale (0 = never, 1 = sometimes, 2 = often, 3 = very often). Psychometric data on the Conners Adult ADHD Rating Scale (full version) has previously been reported to be 82 % sensitivity, 87 % specificity and the inter-rater reliability was 0.69 (kappa coefficient). Significant correlations (pearsons’ \( r \)) were found for WURS and the four factors of CAARS and ranged from, \( r = .37 \) (\( p = <.001 \)) to \( r = .67 \) (\( p = <.001 \)) (Erhardt, Epstein, Conners, Parker, & Sitarenios, 1999).
2.5.4 Procedure

Study one

Assessment of ADHD had previously been carried out within the Clinic of Neuropsychiatry and CBT- Cereb (n = 51), the psychiatric division in the County Council of Varmland (n = 11) or the psychiatric clinic in the NU-health care in Vastra Gotaland, Sweden (n = 1). The clinical assessments were carried out with similar neuropsychological procedures at the psychiatric clinics and included for example childhood and clinical anamnesis, behavior rating scales from relatives and the patient, structured interviews with the patient and sometimes with close relatives, psychological tests of memory and attention. In most cases (n = 51), the assessment also included the QbTest-Plus with its original report and the unstandardized interpretation. Vital inclusion criterions for the ADHD group was 18 to 65 years of age, diagnosis of ADHD according to DSM-IV, described chronic course of ADHD symptoms from childhood to adulthood with some symptoms present before seven years of age and continue to meet DSM-IV criteria at the time of assessment.

At the neuropsychiatric clinic Cereb, nurses screened psychiatric records from 2008, i.e., this was the time when Cereb started using computerized records, and randomly selected 150 patients who had done QbTest-Plus during their clinical assessment, oversampling those with ADHD in combined form and without severe psychiatric comorbidity. The nurses were unaware of the results of the report that had been generated from QbTest-Plus. At this time, there were about 400 patients who had done QbTest-Plus during their clinical assessment at Cereb. Participants were contacted via regular mail three times from May to June in 2011. In total, 51 participants joined the study from Cereb. After resending the mail, participants received compensation to a value of 100 SEK for participating in the study. Participants were informed about how to ask questions and contact the researchers and the clinic during the whole process and afterwards.

At the division of psychiatry in the county council of Varmland and at the psychiatric clinic in the NU-health care in Vastra Gotaland, clinicians screened psychiatric records and recruited participants that had been diagnosed with ADHD and were to begin with central stimulant treatment. The study-specific procedures were explained and information about the freedom to terminate participation without this affecting contact or continuous treatment at the clinic was pointed out in particular.
Post- and pre- central stimulant treatment measures with QbTest-Plus was administered at the same day at an approximate mean time of 103.16 minutes ($SD = 55.36$) from the oral intake in most of the cases ($n = 51$). In the remaining cases ($n = 12$), the second QbTest-Plus was administered some days after the baseline-measure with an approximate mean of 193.43 minutes ($SD = 122.51$) from daily intake of stimulant treatment. The patients were ordinated fast-acting central stimulant treatment from their doctor at the smallest possible dose, on average 13.69 mg ($SD = 6.97$, range = 10 to 54). Participants were informed that participating in the study was optional and that termination would not affect the treatment or the contact with the clinic. For further details on the collection of data please see section 2.2.4, since the experimental procedures of this study correspond with the procedures of Paper I.

**Study two**

The time of the titration process was individual but decisions made by patients and doctors regarding shifts of dose levels were often taken within a couple of week’s interval. Measurement of dose changes was often taken some days after the change in dose level. The time from identifying the optimal dose level to collecting follow-up measures was standardized to three months. QbTest-Plus was administered with an approximate mean time of 103.16 minutes ($SD = 55.36$) from oral intake. Patients were ordinated OROS-methylphenidate central stimulant treatment from their doctors, starting at the smallest possible dose, often being 18 but sometimes 20 mg. Increases in dose levels was entirely dependent upon communication between the doctors and the patients regarding effects and potential side-effects. Neither the participants of the present study, nor the treating professionals were aware of the results from QbTest-Plus. Participants were informed that participating in the study was optional and that termination would not affect the treatment or the contact with the clinic. Participants received compensation at a value of 100 plus 50 SEK per test session for joining the study and they were informed how to ask questions and contact researchers and the clinic during the whole process of testing and afterwards. The reader is also referred to the methods section of Paper I further back in this thesis since the procedures for the two studies coincide.
2.5.5 Statistics

Study one
Analysis of the study was conducted in three steps. First, Fisher’s Exact test was used to analyze treatment (baseline, follow-up) and PADHD (no, yes). Second, a Pillai’s MANOVA was conducted with treatment (before, after) and gender (men, women) with regard to core symptoms of hyperactivity, inattention and impulsivity. Third, WCS was analyzed with a mixed ANOVA with regard to treatment condition and gender.

Study two
Effects regarding sensitivity and specificity for PADHD at baseline (no, yes) and follow-up (no, yes) were descriptively analyzed using frequency tables. The Wilcoxon signed rank test (5 % level) was employed to analyze WCS and core symptom measures with regard to treatment (baseline, follow-up) and to assess WCS and core symptom measures during titration with 18, 36, 54 and 72 mg of methylphenidate. The Wilcoxon signed rank test was also employed to assess subjective ratings (WRASS, ASRS self-rating, ASRS interview, CAARSS) with regard to treatment (baseline, follow-up).

2.5.6 Results

Study one
The lowest dose of fast-acting treatment with methylphenidate resulted in symptomatic remission for 62 % of the cases according to PADHD. The variable classified 87 % of participants as having ADHD at baseline and 62 % of participants as not having ADHD at follow-up. The lowest dose of fast-acting treatment with methylphenidate decreased ADHD symptoms according to WCS (from 10 to 47). All pre- and post- treatment results for the core symptom measures yielded improvements in symptom scores after treatment, hyperactivity improved from 26 to 58, inattention from 34 to 52 and impulsivity from 60 to 74. This means that the treatment targeted all of the core symptoms in this group with the combined subtype. WCS yielded gender differences since men had less ADHD symptoms than women, men were also faster responders than women and even though both genders gained roughly the same amount of improvement from treatment according to WCS, men manifested less total ADHD symptoms after treatment. PADHD was proposed as a measure of remission since the post-treatment performance made by participants that were classified as not having ADHD
equaled that of non-ADHD normative participants. There was a clear difference in WCS-value at baseline and follow-up which indicated progress as in response to treatment.

**Study two**

Individually optimized CS-treatment resulted in remission for 90% of the cases according to PADHD at follow-up. At baseline, the variable classified 80% of the sample as having ADHD and at three months follow-up, 10% was classified as having ADHD. Results were confirmed by subjective behavior ratings made by patients. The suitability of PADHD as a measure of remission was strengthened since both clinicians and patients considered the treatment optimal with regard to ADHD core symptoms. Individually optimized CS-treatment resulted in decreased symptoms at follow-up according to WCS, from 31 at baseline to 69 at follow-up. WCS also indicated response to treatment during titration with 18/20 mg of methylphenidate and a further response when increasing the dosage to 36 mg. WCS did not indicate a response when increasing the dosage from 36 to 54 mg, from 54 to 72 mg or from 72 mg to follow-up. None of the core symptom measures alone were sensitive enough to detect responses to changes in dose level.

Altogether, the ability of the instruments to calibrate treatment for adults with ADHD was supported in the sense that WCS quantified significant symptoms decline at baseline, during titration and at follow-up and PADHD correctly classified participants ADHD status at baseline and follow-up.
3. GENERAL DISCUSSION

3.1 Introduction

The aim of this thesis has been to examine objective laboratory measures of ADHD in adult persons and to develop composite measures that could aid in clinical practice. The results of Paper I-IV show that ADHD predisposes adult persons to perform poorer on continuous performance tasks and to have higher levels of motor activity while performing these tasks as compared to normative participants without ADHD and participants with bipolar II disorder, borderline personality disorder and participants assessed for but disconfirmed a diagnosis of ADHD described in Paper II-III. Even though ADHD had the highest level of hyperactivity, inattention and impulsivity, the cognitive symptoms were marked among the other clinical groups too. The most specific symptom of men and women with combined or inattentive subtypes of ADHD was the level of hyperactivity as measured with an infrared motion tracking device during cognitive task. Paper IV also shows that the performance is improved with minimal doses of fast acting methylphenidate and normalized using individually optimized titration and at three months follow-up. On basis of this information, objective composite measures of ADHD may be developed and a few suggestions, i.e., WCS and PADHD, have been put forward in the present thesis. Paper IV investigated these measures during titration with stimulants to examine their responsiveness to changes in dose-levels and possible response and remission criteria for adult ADHD. Results from Paper IV suggest that the measures are sensitive to adjustments in dose levels and correspond with subjective ratings made by patients, medical considerations taken at the clinics as well as provide tools for evaluation of treatment effectiveness. Notably, Paper IV report that the WCS composite outperforms single core symptoms measures when it comes to discerning small changes in dose levels. PADHD classified 62 % of participants as being remitters after minimal doses of methylphenidate and and 90 % of the cases reached remission according to PADHD with optimized titration. Furthermore, PADHD correctly classified 87 % of participants with ADHD and 83 % of non-ADHD normative participants. Paper III also suggests that WCS has higher clinical specificity than core symptom measures alone and the ADHD group scored significantly lower (indicating higher symptom levels) than all other groups on WCS with a mean WCS of 12, non-ADHD normative participants scored significantly higher (indicating lower symptom levels) than all other groups with a mean WCS of 68, and the other clinical
groups with disconfirmed ADHD and bipolar II/borderline disorders scored intermediate on WCS with means of 42 and 39 respectively. Additional studies are needed in order to test these tentative suggestions with regard to the complexity of the disorder as well as its clinical manifestations during adulthood. In this discussions section, an overview of empirical findings in association with current theoretical and research perspectives of ADHD is provided and findings are discussed also with respect to their practical and methodological implications.

3.3 Theoretical accounts

Several general theories have been proposed to account for the etiology, symptoms and possible mechanisms of ADHD. The purpose of this thesis has not been to test any specific theory but to generate empirical findings of test performance from a clinical perspective which by definition is related to the symptom level of the disorder. The theories may however promote understanding of possible mechanisms that underlie behavior manifestations of ADHD in adults and perhaps also something about how the measures derived from the test may be related to both clinical and etiological perspectives of ADHD. Theoretical conceptualizations of ADHD have recently begun and there is no exact or unifying theory of this complex disorder. Nor are there any theory specifically devoted toward explaining symptom manifestations and developmental pathways into and throughout adulthood. Accordingly, theories from somewhat different scientific perspectives will be discussed with regard to the results. Interpretation of experimental data with regard to theoretical perspectives is complex with many alternative explanations of performance deficits and behavioral symptoms, some of which are more reflective of the context and task at hand, e.g., state regulation difficulties and motivational deficits, and some of which are more into the cognitive deficits concerned with executive dysfunctions and working memory impairments that are generally reduced in ADHD and noticeable during for instance tasks requiring response inhibition, sustained attention and rule-governed behavior. The study of behavioral problems associated with ADHD is also related to the broader question of causal pathways and plausible endophenotypes for genetic and etiological explanations of the ADHD phenotype.
From a neuropsychological executive function perspective (Barkley, 1997), ADHD is a disorder of self-regulation that arises as a result of poor response inhibition. Impaired sustained attention during CPT performance for example, arises from poor goal-directed persistence and internally represented behavior. The instructions on the CPT become a rule and a goal but the executive processes are hindered by impaired response inhibition which leads to impulsive and inattentive behavior to a level that is developmentally inappropriate as seen in Paper I-IV. ADHD impairments of sustained attention in Paper I-IV are thus assumed to arise as a dysfunction of the formulation and holding-in-mind of task-goal so that the necessary behavior for attaining the goal may be created and performed. Accordingly, the poor performance on QbTest-Plus reported in Paper I-IV is described in neuropsychological terms as poor goal-directed behavior rather than sustained attention, and includes the processes of prefrontal cortex which are generally considered the site of executive dysfunctions.

This theory is general and inclusive in that the function called “motor control/fluency/syntax” is assumed to summarize the executive dysfunctions characterizing ADHD and manifested during basically any type of situation, including CPT tasks and motor performance. The behavior outcome that is likely to occur as a result of the predictions made within the response inhibition deficit theory may well explain, from a general neuropsychological perspective, why problems with sustained attention and excessive motor behavior, i.e., poor goal-directed behavior, are more common in adults with ADHD during QbTest-Plus in Paper I-IV as well as why a subgroup of the normative participants exhibit tendencies of these behaviors while most participants do not. However, Paper III is very interesting in this regard as the clinical groups who shared behavior manifestations with ADHD, i.e., especially inattention and impulsivity, are also impaired on the measures derived from QbTest-Plus although to a lesser total extent than ADHD. Actually, their problem too may be explained in terms of deficiencies in response inhibition and goal-directed behavior and therefore it seems unlikely that this theory is giving a specific enough account for the essential ADHD causal pathways, although from a phenomenological perspective the theorized behavioral “output” may well match clinical indications. In line with this is the finding that impulsivity is equally pronounced in ADHD and the other clinical groups in Paper III and a relatively unspecific marker of ADHD throughout in Paper I-IV.
The response inhibition deficit theory is somewhat limited for it mainly facilitates understanding of empirical findings from a neuropsychological perspective while not all of the executive functions mentioned in the theory may be disordered in ADHD and the empirical associations between ADHD and executive dysfunctions have been uneven as well (Andrés, 2003; Nigg, 2006). It is not clear for example whether primary symptoms such as inattention and hyperactivity are the result of executive dysfunctions or if executive dysfunctions are merely describing a collection of the secondary difficulties sometimes seen in clinical cases of ADHD, such as poor organization, time management, planning and working memory. The executive function paradigm is applicable in most neuropsychiatric disorders, and may explain the occurrence of some or all behavior problems seen in ADHD depending on the person at hand, but this hybrid-theory is rather inclusive and vague when it comes to defining the very essence of ADHD core problems which are supposed to be both necessary and sufficient for the disorder. Also, the executive function paradigm is much concerned with the site and role of dysfunction from academic and abstract angles and not so much concerned with the role of implicit behavior which would make this type of theory challenging to falsify as well. However, there have been some good empirical accounts for falsification of this theory in the literature and continuous performance tests have been one of the methodological approaches applied here. For example, it is well-known that not all subjects with ADHD suffer from executive dysfunctions (Hinshaw et al., 2002; Nigg et al., 2005a) and patients with executive dysfunctions may not suffer from ADHD but there may of course be an overlap between EF and ADHD whose frequency is boosted by referral biases since people who carry both impairments may be more likely to be referred for assessment and treatment, as well as more prone to develop secondary psychiatric problems which is also likely to inflate the occurrence of executive dysfunction problems among clinic-referred adults with ADHD. Pennington and Ozonoff (1996) have made an overview of EF studies with ADHD versus controls and the only non-difference was found in a population-based comparison. Therefore, even though many children and adults seems to suffer from EF deficits, it may be problematic to apply a strict executive functioning paradigm to ADHD when examining psychometric properties of neuropsychological tests since EF dysfunctions may not be necessary for the disorder or not sufficient enough to pinpoint the very core essence of the disorder. The functional impairment is likely to be greater when ADHD is accompanied with extensive executive dysfunctions which have been documented in youths with ADHD and disruptive disorders (Biederman et al., 2004b). Except from defining what tests are valid measures of the broad construct of executive functions, another obstacle when
interpreting findings from measures defined as belonging to the EF paradigm are causality. The occurrence of EF deficits are not necessarily a reflection of primary problems with response inhibition even though the presence of response inhibition is possible to operationalize and test. Instead, the presence of response inhibition and other mechanisms described by Barkley such as slow and variable response rates, attention deficits, poor rule-governed behavior and inability to delay response may be explained partly by suboptimal states of activation (Sergeant, 2005), motivational styles (Sonuga-Barke, 2005) and/or alterations in a delay-of-reinforcement gradient (Sagvolden et al., 2005). Such processes may well forerun response inhibition or account for distinct causal pathways of the disorder as Sonuga-Barke (2005) has pointed out in his dual-pathway model. Even though CPT and go/no-go tasks has been identified as capable of assessing sustained attention and response control in children (Börger & van der Meere, 2000) and adults with ADHD, i.e Paper I-IV, it is not clear why this is so and many possible explanations exists while some of them are impossible to falsify using CPT data. There are however a lot of data, including CPT when interpreted from an EF perspective (section 1.1.4), that can confirm the involvement of broad executive dysfunctions as described by Barkley during poor task performance for both ADHD and other psychiatric disorders and if not providing an explanation of causal links to behaviors so at least descriptions of some skills involved for successful task performance in neuropsychological terms.

The working memory deficit theory would be placed within the EF domain by some researchers (Pennington & Ozonoff, 1996; Pennington et al., 1996) and is similar to the neuropsychological hybrid model in the use of higher-order cognitive functions for explaining the interaction of working memory and response inhibition during task. Although in this theory, working memory is assumed to forerun response inhibition and to be the originator of successful CPT performance with response inhibition as the end-result of effective working memory. ADHD is seen as a disorder of working memory which is a broad construct involving storage, computation and attentional activation. There is a continuum between normal and abnormal functioning since tasks that are sensitive to working memory deficits push the competitive limits by either increasing working memory demands or the strength of the response prepotency. In Paper I-IV the level of response inhibition measured with commission errors, is the weakest signature of ADHD and does rarely occur during task performance. The working memory load may be increased by means of including manipulations of rules or tracking of results during task, which according to this theory would
result in higher levels of impulsive responding. Studies investigating the effect of manipulating the ISI-rate on go/no-go tasks, e.g., Uebel et al., 2010, have empirically confirmed this assumption since the density of go-conditions during shorter ISI experiments is much higher than for longer ISI, triggering prepotency of responding and thus response inhibition deficiencies to a higher extent. It is possible, and data suggest, e.g., Kuntsi et al., 2009, that this principle is true also with increased age in ADHD but the presentation rate should be increased even further for adults in order to trigger the, according to this particular theory, underlying working memory impairment with observable response inhibition deficiencies. From this working memory perspective, QbTest-Plus mainly facilitates holding information online during small temporal gaps (200 ms) and applying a fixed rule (XX-CPT) for effective responding with little demand of working memory capacity, maintenance and activation. A small subset of the ADHD group exhibited excessive levels of deficient response inhibition along with other core features of ADHD but it seems like operations of working memory and response inhibition alone would not be sufficient to either detect or explain all core symptom manifestations of ADHD that are distributed on the abnormal-normal continuum by means of the Qb-test Plus. However, it may well be that the test is not optimal for testing working memory deficits since the competitive limits of working memory and response inhibition are not elevated sufficiently. Indeed, QbTest-Plus is intentionally designed not to put a heavy demand upon working memory since it is assumed not to be central for the etiology of the disorder, instead attentional and inhibitory deficits are assumed to be effectively tapped using this test and highly related to ADHD diagnosis. Instead, according to this theory, a main component of the measures derived from Paper I-IV would perhaps be the attentional activation, i.e., lack of attention, which is assumed to underlie the cognitive architecture of working memory, and which in turn argues for the working memory impairment as a “theoretical complement” or additional deficiency that some people with for example ADHD suffers from, but it may also concern persons with neuropsychological deficits in general such as borderline personality disorder (Soler et al., 2012) or bipolar disorder (Addington & Addington, 1998) but these cognitive deficits may also exist as functional disabilities in many psychiatric disorders. Paper III reported equal but higher than normal levels of impulsivity among participants with ADHD, bipolar II disorder, borderline disorder and participants with disconfirmed ADHD and so response inhibition during this particular task was not effectively pinpointing ADHD. Whether methodological or theoretical foundations underly this finding is not apparent though and the postulated connection between working memory and response inhibition made within this framework is not possible to
falsify or verify by means of the findings from Paper I-IV. However, an interesting and related study conducted within the CPT paradigm (Halperin et al., 2009) used identical pair versions and put substantially more demand upon working memory by means of applying four-digit stimulus twice in a row as criterion for stimulus in adulthood. The cohort was followed into adulthood and compared among persisters and remitters. Effortful processes constituting the basis for theoretical assumptions of working memory impairment in ADHD were impaired in their childhood and in adult persisters but no longer in adult remitters. This finding suggests that the postulated working memory impairment put forth within this framework is not central to the etiology of ADHD, but instead described as an epiphenomenal characteristic. Moreover, these findings remind us that theoretical assumptions are crucial to verify in adulthood by means of enough challenging tasks such as the test employed by Halperin et al (2009) and future studies will be more disposed to put heavier demands upon working memory in adulthood so to examine if the findings are possible to verify or not.

From a motivational perspective (Sonuga-Barke et al., 1992, 1994; Sonuga-Barke, 2002, 2003, 2005), ADHD is a disorder of delay aversion in which an abnormal level of delayed reward discounting becomes manifest in attempts to avoid or escape delay. The theory is applicable in the present thesis and places the results of Paper I-IV in a theoretical context by means of neurobiological and psychological empirical findings from other experimental studies, e.g., Marco et al., 2009. A great contribution of this theory is that its predictions should be possible to test experimentally by means of QbTest-Plus. One assumption made within this framework is that delay reduction strategies are conditional and differ in choice and no-choice situations with regard to behavior manifestations. The no-choice condition would explain the behaviors during experimental testing with QbTest-Plus since it would stimulate behaviors of inattention and hyperactivity because of the inability to escape delay during fixed time and task conditions. The no-choice condition would cause the person to maximize attention towards non-temporal stimulation and systematically reduce the subjective sense of time spent during testing. Persons with ADHD may act upon the environment to create non-temporal stimulation such as fidgeting which is in line with the most predictive and clinically specific behavior of ADHD in Paper II-IV. Also, persons with ADHD would focus on non-temporal stimulation of the environment during delay, i. e., inattention, which was the second most predictive but the most common behavior of adult persons with ADHD in Paper II-IV. The theory would explain the low quantities of impulsivity during QbTest-Plus as well since a no-choice situation per se does not trigger
impulsive behavior. Instead a choice situation in which the person is able to choose between immediate and delayed rewards would trigger persons with predisposed delay aversion to act impulsively and to choose immediate rewards. The significance of these behaviors is related to their possible clinical character so that not only the occurrence of behavior but also the amount of behaviors would be assessed with regard to clinical significant levels of behavior manifestations during no-choice conditions. The amounts of hyperactivity/inattention in adult persons with ADHD in Paper I-IV are parallel to the high levels of clinically defined symptoms and Paper III also illustrates higher quantities of ADHD core behaviors relative to clinical controls. Even though the motivational theory proposed by Sonuga-Barke has been developed primarily for childhood conditions, the findings of Paper I-IV support the relevance of a delay aversion theory in adulthood too and suggest further study within this framework.

From a developmental perspective, which is highly relevant given the adult sample studied in Paper I-IV, the delay aversion theory would suggest that ADHD symptom manifestations in a given situation are influenced by socialization and cultural factors in the environment as well. A developmental outline is offered in three steps in which a) predisposed behavior responses of the child and the interaction with social environment shapes behavior, b) social punitive environments shapes the childs behavior and the emergence of more generalized delay aversion since delay evokes negative response from which the child tries to escape, and c) personal accommodations of the underlying disposition and the constraints that this imposes on learning situations are influencing behavior. Applying these principles to adult conditions would suggest that behavior is influenced by social environment into more characteristic behavior dispositions in adults by means of personal accommodation. Even though ADHD was early on believed to be a childhood disorder and later on merely generalized across ages, its behavior manifestations are defined in developmentally inappropriate levels. The QbTest-Plus is an advancement of a similar test for children called QbTest, i.e., X-type CPT during 15 minutes, to minimize ceiling effects and low levels of sensitivity by means of increasing the complexity of the task for adults. Results from Paper I-IV suggest that a majority of persons with ADHD found the QbTest-Plus difficult to perform relative to their developed at-present disposition and with regards to adult normative behavior. A subgroup of normative participants found the test difficult too which according to this theory would suggest that hyperactivity and inattention during no-choice conditions is the
result of behavior dispositions and development, involving management of constraints and personal accommodation that are relevant for adult conditions as well.

ADHD is a collection of symptoms (traits) that are found along a continuum and the level of symptoms are used to define a clinical condition. The symptoms would thus be present not only in persons with ADHD but in persons with predisposed behavior manifestations of hyperactivity, impulsivity and/or inattention as well. QbTest-Plus is according to a delay aversion theory sensitive to quantities of these symptoms in adults during a specific no-choice condition so that the psychiatric disorder may be identified and separated from non-significant levels of behavior manifestations in adulthood. According to Paper I-IV, the QbTest-Plus seems to have a somewhat lower threshold than clinically significant levels of ADHD behaviors, i.e., lower negative predictive power. This discrepancy is reflected in levels of sensitivity and specificity in all of the papers but Paper II-IV illustrates the abnormal-normal continuum of behaviors on a scale so that the amount of behaviors in both clinical and non-clinical groups becomes evident. Low points on WCS thus indicate statistically significant amounts of difficulties with regard to test-domains but not necessarily indicate clinically significant levels of difficulties in each case. The delay aversion theory assumes that ADHD is a developmental and motivational disorder that is affected by learning situations throughout life and becomes manifest as core symptoms of ADHD at developmentally inappropriate levels. The latent response style in ADHD is associated with mesolimbic reward circuits in which dopamine has a key reward-signaling and behavioral regulating function during conditions of delayed reward. Because of the predisposition towards delay aversion in persons with ADHD during no-choice conditions, and because they present more of these behaviors than non-ADHD normative and other clinical participants, behaviors of hyperactivity and inattention described in Paper I-IV are according to this theory assumed to be manifestations of a developmentally inappropriate motivational style called ADHD.

A cognitive-energetic and state-regulation perspective of ADHD (Sergeant, 2000, 2005) would suggest that the behavior manifestations of ADHD reported in Paper I-IV are primarily the result of specific deficiencies of energetic states, as well as the result of interplay between state factors, attention mechanisms and cognitive management in ADHD. During QbTest-Plus, the disorder would present itself at all three stages of the theoretical model. During computational mechanisms of attention including stages of labeled encoding, search and decision (central processing) and motor organization, ADHD would manifest itself
as decreased target detection and abnormal motor output because of inefficient information processing. Second, regarding the energetic pools of effort, arousal and activation, the ADHD specific deficit would result in inability to meet task demands. Poor performance seen in Paper I-IV is according to this outlook because of the energy state and state regulation does not match that required by the task at hand. More specifically, the effort pool is dependent upon cognitive load and entails motivation and response to contingencies. Lack of this effort, which is a fundamental deficit in ADHD according to Sergeant et al. (2005), is theorized to result in deficiencies of sustained attention as well as the inability to self-motivate during task. This is clearly the case for most of our ADHD participants in Paper I-IV as most of them are unable to respond and persist attentively during task. Further, the arousal pool is defined as phasic responding and strongly affected by the stimulus processing and influenced by intensity and novelty of task. This energetic pool may be influenced by target frequency and ISI and studies suggest that shorter ISI will induce higher levels of arousal compared to less intense CPTs (Kuntsi et al., 2009; Uebel et al., 2010). It is according to my understanding likely to think that aspects of novelty and intensity are greatly affected by age given the central nervous system basis for disorder and development of state-regulation as well as the assumption of state-regulation as the fundamental deficit of ADHD. Within this framework, Paper I-IV suggest that the ISI of 200 ms with a 25% target probability is effectively stimulating the underlying weakness of the arousal pool in a majority of adults with ADHD and still not exceeding the normal range performance assumed to be at hand in the non-ADHD normative group without a supposed deficiency. The last pool concerning activation is associated with the physiological readiness to respond and affected by task variables such as preparation, alertness, time on task and time of day. So, the theory postulates that poor state regulation and/or weak arousal mechanisms are explaining ADHD behaviors in Paper I-IV. The reduction and normalization of these behaviors after stimulant therapy in Paper IV also strongly suggest that the behaviors are true symptoms of ADHD and not just general behaviors of impaired neurobehavioral functioning.

Is then the same type of errors made by participants without ADHD but with another distinct theoretical/clinical construct also because of problems with state-regulation? According to this framework, deficiencies during CPT tasks may be due to many factors that are not accounted for by state-regulating, energetic and attentional factors. However, what according to the authors is specific to ADHD is an inefficient state-regulation, which may or may not be accompanied with additional deficiencies in each individual. Therefore, poor CPT
performance indirectly support state-regulating deficiencies in participants with ADHD but suggest that the same deficiencies in cases of non-ADHD is due to other than state-regulating factors. Specific CPT output that Sergeant et al. suggest be directly reflecting state-regulating factors and are at the core of ADHD is $d'$, which may reflect arousal mechanisms or readiness to receive information, whereas beta may reflect activation mechanisms such as readiness to respond and other authors (Castellanos et al., 2006b) suggest that RTSD also reflects state-regulating aspects. Regarding the output in Paper I-IV, one may note that additional parameters except from the core symptom operationalizations are attained from QbTest-Plus, these are for example RTSD, normalized RTSD and $d'$ along with a number of parameters reflecting motor activity. Most of these parameters are more or less deficient in ADHD compared to non-ADHD normative participants but the parameters that have been chosen to reflect hyperactivity, inattention and impulsivity because of clinical purposes in Paper II-IV, are the top most deficient measures of ADHD and provides the highest separation from non-ADHD participants. It seems reasonable to interpret the occurrence of omission errors as a simpler-than-$d'$ form and reflection of an arousal mechanism concerning the readiness to receive information. It also seems to me like the occurrence of commission errors might be reflective of an over- alternatively under- activation of the activation pool such that the participants’ readiness-to-respond is abnormal, alternatively that the readiness-to-receive-information is inflated or under-activated in the sense that persons with ADHD are not able to remember or attend to stimulus-information. When it comes to the inflated motor output presented by participants with ADHD in Paper I-IV, it may be interpreted as a general lack of state-regulation, or more specifically as reflecting the activation pool, e.g., physiological readiness to respond in which impaired state regulation is compensated by hyperactive behavior and secondary to attentional and readiness-to-receive-information inabilities indicating that hyperactivity is reflective of weak arousal mechanisms. Sergeant (2005) says the interplay between these energetic pools are important for understanding of ADHD behaviors, and so for example the effort and activation pool are greatly related and will have an effect on the actual motor output during task. It is my interpretation of data from Paper I-IV too that hyperactivity is the result and/or compensating strategy of an interplay between state regulating factors involving the incapacity to effectively receive- and respond to stimulus. Sustained effort, motivation and physiological readiness are all inter-related processes that are necessary for the effective responding to targets. Interestingly in this regard, it is very rare in Paper I-IV that participants’ present hyperactivity without deficiencies in motor output as in inattentive and impulsive errors. On the other hand, there are both ADHD
but especially non-ADHD cases that present response errors without elevated levels of hyperactivity. Therefore, hyperactivity seems to be tightly related to a true state regulating deficit and specific to ADHD. The above theory also goes well along with the motivational framework for task performance presented by Sonuga-Barke and also the many neuroimaging and psychopharmacological evidence relating to especially dopamine impaired neural branches in ADHD, e.g., Sagvolden et al., 2005. It is also possible to relate empirical findings of executive dysfunctions within a state-regulating paradigm since it targets both higher- and lower order of cognitive processing and relations to state factors. Lower order nervous system processes involving parietal and subcortical networks seems to be accompanied with cognitive deficits that are more directly related to anterior networks during certain contexts and in more severe and comorbid cases so that poor response inhibition is being modulated by the inability of ADHD children to adjust their energetic state (Halperin et al., 2009). **Paper IV** is in line with neuroimaging studies that report decreased striatal activation in children, adolescents and adults with ADHD during CPT and other neurocognitive performance and neutralization with MPH (Rubia et al., 1999, 2007, 2009; Teicher et al., 2000; Vaidya et al., 1998, 2005). **Paper I-IV** is also in line with neuroimaging and laboratory measures of children, adolescents and adults that indicate hypofrontality at the right caudate, right mesial frontal, the basal ganglia (Castellanos, 2002; Castellanos & Tannock, 2002; Castellanos et al., 2002; Filipek et al., 1997) and their relations to motor output according to state-factors which is clearly implicated in **Paper I-IV**. According to my understanding, the lower order cognitive processing put forth by Sergeant et al and the dynamic interplay between neural processes and environmental factors proposed by Sonuga-Barke et al seems to be highly relevant for ADHD and its manifestations in adulthood. Several interesting studies in childhood ADHD (Kuntsi et al., 2001, 2006; Marco et al., 2009) suggest unique contributions by these theoretical proposals and developmental aspects should be investigated further in youth and older subjects.

From a neurobiological perspective of ADHD (Sagvolden et al., 2005), etiological mechanism that underlie behaviors during QbTest-Plus explains ADHD by means of dysfunctions in three dopamine branches that are mediated by altered reinforcement and deficient extinction processes and developed dynamically as the person grows up. Hypofunctioning in the mesocortical branch result in poor response toward targets and poor behavioral planning while the hypofunctioning nigrostriatal dopamine branch causes impaired modulation of motor functions. A central assumption is that mesolimbic hypofunctioning generate altered
reinforcement and extinction processes of behavior. A narrower time window for the reinforcement mechanism to occur will cause attention problems seen in ADHD and promote short sequences of behavior which give rise to hyperactivity and failure to inhibit responses. The delay gradient operates so that the potency of a stimulus as a conditioned reinforcer depends upon the time between its onset and the subsequent delivery of a reinforcer in its presence. Most of the stimulus (75 %) presented during QbTest-Plus are not followed by a reinforcer (target) and therefore the stimulus will most often not become a potent reinforcer and the participant will not attend to it but instead become inattentive, hyperactive and impulsive which is reflected in the result of Paper I-IV. The XX-type CPT with a 25 % target probability used in this thesis is one example of a condition in which the short and steep delay gradient explaining ADHD behaviors is being tested. Many research findings, including pharmacological (Biederman et al., 2006b), neuroimaging (Castellanos et al., 2002) and neuropsychological (Bush et al., 1999), would support the dopamine hypofunctioning explanation of behavior problems seen in ADHD. Paper IV also presents support for the dopamine theory in the sense that stimulant mechanisms decreased core symptoms of ADHD and the dopamine theory presents validity for the measures as directing ADHD core symptoms. Further support for this framework is put forth by the investigations of dose level changes accompanied by a gradual decrease in behaviors of inattention, hyperactivity and impulsivity in study two Paper IV. This neurobiological foundation is highly implicated in empirical findings throughout this thesis since hypofunctioning in the mesocortical branch is postulated to result in poor response toward targets and poor behavioral planning while the hypofunctioning nigrostriatal dopamine branch is postulated to cause impaired modulation of motor functions and also possible to moderate with dopamine targeting therapy.

In summary, the above theories support the general notion that performance deficits presented during QbTest-Plus are manifestations of ADHD core symptoms since hyperactivity, inattention and impulsivity are proposed as overt behavior manifestations resulting from various underlying deficits that are ultimately being evident during challenging tasks and situations. Since ADHD core symptoms may also be present in other clinical groups as in Paper III, the total quantity of these symptoms with a special emphasis on hyperactivity and inattention are measurable characteristic of ADHD versus other psychiatric disorders in adulthood and this finding is reflected with the WCS measure. The exact underlying deficits causing hyperactivity, inattention and impulsivity in adult ADHD are not made testable within this thesis since causality has not been accounted for and manipulations of test properties has
not been implemented because of the overarching aim of a clinical rather than theoretical application of data. However, the postulated underlying psychological, neurobiological, motivational and cognitive mechanisms that trigger ADHD behaviors and are made within various theoretical perspectives generate several plausible suggestions for the core symptom occurrence in adults and the way in which QbTest-Plus trigger these behaviors, as well as ideas for future research.

3.3 Empirically derived measures for the clinical practice

Objective composite measures for the core symptom triad in adult ADHD have rarely been examined in previous research. In recent years, the importance of objective quantification of psychiatric diagnoses like ADHD has been increasingly noted. Application of empirical methods facilitates consideration of conceptualizing and assessing ADHD and relates to discrete and continuous paradigms of the disorder. The upcoming diagnostic development of ADHD (DSM Taskforce, 2012) proposes changes that relate to removal of the current categorical subtypes of ADHD in favor of more continuous models of diagnosis. Efforts are being made to define developmentally appropriate symptom thresholds for adults as to better account for developmental pathways into adulthood and associated endophenotypes. In this regard, current and future diagnostic considerations anticipate methodological advances and greater adherence to empirical investigation and quantification of continuous distributions of ADHD in adulthood. Our overall aim in Paper I-IV has been to facilitate more objective measurement and quantification of continuously distributed ADHD in adults using core symptom measures from laboratory testing with the Quantified Behavior Test Plus, QbTest-Plus. The goal of this test is to provide objective measures of ADHD core symptoms by means of combined CPT and motion tracking technologies.

In psychiatric practice, qualitative approaches like interviews and behavior check-lists are documented to be reliable during clinical assessment of ADHD when it comes to retrospectively evaluating development and assessing the present life situation in adulthood (Nylander, Holmqvist, Gustafson, & Gillberg, 2009). However, qualitative methodologies are also associated with limitations including subjective bias, interview and halo effects and they are mediated by subjective experience and the level of awareness of behavior manifestations and functional disability (Culpepper & Mattingly, 2010; Ramos-Quiroga & Casas, 2011).
These limitations along with the possibilities of more appropriate diagnosis for adult ADHD motivates methodological approaches allowing for high-quality assessment using complementing and more objectively derived approaches and especially when there are inconclusive material or when the assessment is complicated. Multiple sources of clinical data-collection including psychometric techniques are one strategy to minimize the effects of potential predispositions and to increase reliability, which have been documented to assist clinicians in several studies (McGough & Barkley, 2004; Nylander et al., 2009). Psychometric measures also provide quantification of symptom severity and validation of ratings made by patients and family members so that their experiences may be understood and assisted as much as possible.

Moreover, there is a lack of reliable measurement techniques to adjust and evaluate the effectiveness of treatments for ADHD and to optimize the titration process despite its crucial role for effective treatment (Kooij et al., 2010). Given the lack of objectively derived measures that are calibrated specifically towards the clinical presentation of ADHD symptoms in adulthood, our overarching aim in Paper I-IV has been to work from an empirically driven methodological approach in order to develop reliable and complementing measures that are applicable during clinical assessment and treatment of ADHD in adults. Except from the practical contributions and lines for future clinical investigations suggested here, the present work is also well-positioned to make contributions to theoretical and academic areas of inquiry, including conceptualization and measurement of diagnosis, proposition for remission criteria as well as suggestions for future endophenotypes.

In Paper I we started searching for objective measures of ADHD manifestations in adulthood and the aim here was to assess the level of correspondence between QbTest-Plus and clinical diagnosis. We were curious to see if there were any correspondence at all and whether adults with ADHD presented a typical profile on the test. Previous research findings has clearly indicated that adults with ADHD are inclined to perform poorly on CPTs as compared to non-clinical controls, e.g., Boonstra et al., 2005, and studies of actigraphy strongly suggest heightened frequencies of movement in laboratory and real-life settings (Boonstra et al., 2007; Halperin et al., 2009). Previous research findings also support the notion that ADHD behaviors in adulthood may not be in line with the current diagnostic criteria (McGough & Barkley, 2004), as well as not apparent during experimental conditions due to ceiling-effects and the underlying mechanisms of ADHD involving for example psychological development.
and personal accommodation (Sonuga-Barke, 2005). Hyperactivity for example may appear as subtle peripheral behavior manifestations that are not extraordinary or abnormal for persons with a life-history of restlessness and over-active behavior and may therefore be reported less often than in childhood. **Paper I** reported abnormal behavior and cognitive functioning for our ADHD participants as well as for those participants who were assessed but disconfirmed a diagnosis of ADHD. Except from confirmed/disconfirmed ADHD, these groups had multiple psychiatric disorders as well. From a research perspective, we found it difficult to examine the test when the number of potential sources of symptoms was adding up and we also did not know very much about behaviors of normative general population participants. We found that the QbTest-Plus provided plenty of separate measures supposedly relating to symptom domains of ADHD as well as overlapping with other disorders which made interpretation of test statistics rather challenging. Since the QbTest-Plus was not calibrated specifically for adult ADHD at that time, we concluded that this motivated further examination of calibrated and composite measures.

**Paper II** was designed to investigate predictive and composite measures of ADHD and here, behavioral measures from the symptom domains were firmly operationalized to represent the cardinal symptoms. We included participants who had already been assessed for ADHD and applied exclusion criteria for some diagnoses like for instance acute bipolar disorder and obsessive-compulsive disorder. We also included normative participants to increase the chances of understanding true behavior manifestations of ADHD. Results from **Paper II** found hyperactivity as measured in distance (meters) with the motion tracking system to be the most significant measure for singling out ADHD from normative participants. Operationalized continuous performance measures of inattention and impulsivity were the second and third most significant measures of ADHD. Here, the WCS composite scale ranging from zero to hundred was constructed to represent this relationship and express the continuum of ADHD behavior quantities. Predictive values of the test were examined on basis of cardinal symptoms and the composite using the categorical measure PADHD. A majority of the participants with clinically defined and predicted ADHD coincided with low points on the scale (indicating high symptom levels) and the normative participants generally scored high on the scale (indicating low symptom levels) which yielded good predictive values. Thus, in opposition to the common belief that hyperactivity outgrows with age, **Paper II-IV** suggest that the level of motor activity are the most predictive and specific behavior manifestation of ADHD in adults during performance with QbTest-Plus, and this parameter
offers the highest separation from non-ADHD normative participants in **Paper II** and from other psychiatrically diagnosed participants as well as participants assessed for but disconfirmed a diagnosis of ADHD in **Paper III**. The more motor activity during the test, the greater was the likelihood of ADHD and this was the case for both the hyperactive and the inattentive subtypes and regardless of gender.

**Paper II** had some methodological limitations. One was related to the number of participants on which the predictive and composite measures were calibrated. There were relatively few participants with ADHD, some of which had comorbid psychiatric disorders. However, a normative group of adults with ADHD independently confirmed the findings. The study did not make apparent though whether participants were representative for adult persons with ADHD in general. A similar situation is apparent for the normative group and for the time being the results are preferably tested for replication in future studies. Another limitation is that the measures have not yet been specifically tested together with common instruments for ADHD but is primarily compared to the results of the clinical assessments even though our behavior-rating scales correlate strongly with the results of the new measures. A majority of our participants had the combined subtype which is the most commonly diagnosed in psychiatric practice (Murphy & Barkley, 1996).

In adults, clinical interventions may be complicated since ADHD from a life-course perspective is associated with development of other psychiatric disorders that may trigger additional and other primary symptoms than those of ADHD, i.e., substance use, mood, anxiety, and disruptive behavior disorders (Biederman et al., 2004a). A person with ADHD may often self-refer or is remitted also because of other psychiatric problems (Faraone, Spencer, Montano, & Biederman, 2004), of which some are likely to be secondary to ADHD frustration and failure. In a situation like that, multifaceted interventions including also the underlying neuropsychiatric disorder may help the person to develop more healthy behaviors and reduce the risk of additional distress since untreated ADHD severely increases the risk for multiple and lifelong comorbidity (McGough et al., 2005). However, in order to minimize influences from comorbid disorders and attain more direct measures of ADHD-related behaviors so to adjust standards accordingly we intentionally over-sampled participants with as few as possible additional disorders in **Paper II-IV**. Many of our participants in especially **Paper II** did however have additional disorders as it is almost impossible to find adults with “only” ADHD in clinical samples. Participants in **Paper III** had minimal comorbid disorders.
Therefore, since the new instruments have been calibrated on participants with relatively low levels of disorders, it is likely to think that cases with more severe comorbidity will have an impact on test outcome since most psychiatric disorders involve cognitive symptoms of inattention and/or impulsivity.

Females in Paper II, regardless of them having ADHD or not, turned out to be more inattentive than males but females with ADHD were significantly more inattentive than non-ADHD females. We think that gender-related issues are worth investigating further since Paper II-IV presented somewhat conflicting results in this regard and gender is not well understood in connection with ADHD presentation in general. It is possible that age has moderating effects upon potential gender-differences in ADHD. Even though potential gender differences with regard to hyperactivity and impulsivity tend to persist with growing age (Brocki et al., 2010), it is not clear whether additional effects of comorbid disorders and developmental pathways are at work in adulthood. It has been suggested that the impact of gender differences upon ADHD presentation decreases with age since overt hyperactivity and impulsivity becomes less manifest in older subjects in general (Kooij et al., 2010). However, Paper II-IV strongly suggests that adults with ADHD, regardless of gender, are clearly and equally impaired in these aspects and with regard to non-ADHD subjects. The main gender difference found in Paper II and Paper IV is that women were more inattentive than men, but this was however not reported in Paper III. Previous authors have suggested (Biederman et al., 2004a) that a referral and diagnosis bias exist which causes women to be less frequently identified even if women who are diagnosed tend to have higher-than-normal-ADHD-symptoms-levels. Also, the higher levels of internalizing disorders among women may affect symptoms presentation in ADHD and/or mask their impairments. However, in Paper II-IV we have worked, for better and worse, with the intention of minimizing comorbid disorders as well as over-sampling those with combined subtype, i.e., Paper III-IV. This may have created a recruiting bias which is specific for our studies and not reflective enough of an actual gender bias. On the other hand, results may be more directly related to ADHD specific deficiencies and less inflated by common gender-related biases found in clinical samples with higher levels of comorbidity. It may also seem like the non-significant gender-difference with regard to hyperactivity in Paper III-IV may be associated with the strategy of primarily recruiting combined subtypes. However, Paper II, upon which the new instruments were calibrated, did not over-sample any subtype found the same results with regard to equal levels of hyperactive and impulsive behaviors among men and women with combined or inattentive...
subtype. The question is definitely intriguing and worthy of further examination since a true and clinically meaningful gender difference would suggest gender-based standards. In this regard it may also be worth noticing that the QbTest-Plus, which generates raw data for WCS and PADHD, relates to both age and gender-based standards in their normative data-set. Since gender differences among adults with ADHD in clinical samples may be related to referral- and diagnosis biases, results vary across studies, and more studies are needed to draw firmer conclusions about possible gender related differences in symptom presentation and subtype frequencies and especially concerning development of standards for more objective measures.

A general dilemma of CPT measures is the interpretation of test scores, and this is true for the QbTest-Plus for example. To begin with, the significance of various test scores was not clear and we wished to support more reliable interpretation of ADHD from a clinical perspective. We also found that from a quantitative perspective, the symptoms had different impact for detecting ADHD and extracting abnormal-normal behavior manifestations. The combination of symptom measures created a more reliable tool for quantification of ADHD than looking at separate symptom representations, which is in line with studies on childhood ADHD (Rommelse et al., 2008a; Wood et al., 2008) supporting the use of composites at the aggregated level both for predictive power and statistical reliability such as reduction of error terms. Also, we found that the abnormal-normal continuum became more explicit when adding measures up in a composite measure, which again is found to work well for ADHD measures at younger ages. However, since this relationship was not clear in the Qb-test report we thought that a complementing scale would make it easier to use the valuable information attained from the test. Results of Paper II-IV suggest that the composite measure is more reliable than using separate measures as was done in Paper I. More specifically, the level of specificity with regard to ADHD is increased by doing so which might be helpful when considering clinical methods for ADHD including for example screening, assessment, pedagogical approaches and treatment programs. The test is specifically developed for adult conditions and the clinical manifestations of ADHD in adulthood and in Paper II we decided to work with the total level of ADHD symptoms as a supplement to the valuable test statistics made possible with QbTest-Plus.

There have been many studies of impaired performance on CPT tasks with especially children but also with adults having ADHD. The results of Paper I-III are in line with previous results that adult persons with ADHD have more cognitive deficits than adults without the disorder
(Boonstra et al., 2005; Hervey et al., 2004; Schoechlin & Engel, 2005). There are previous studies with measures of motor activity in adult ADHD using actigraphy techniques (Boonstra et al., 2007; Tuisku et al., 2003), and one study with combined cognitive and motor measures using QbTest-Plus in adult ADHD (Lis et al., 2010), and several studies combining motor and cognitive measures in childhood ADHD with reliable results (Rommelse et al., 2007a, 2007b, 2008c). Especially interesting are the findings showing that except from the many studies indicating various cognitive deficits as plausible endophenotypes for ADHD, motor activity may also serve for such purposes (Andreou et al., 2007; Bidwell et al., 2007; Rommelse et al., 2007a, 2007b, 2008c; Slaats-Willemse et al., 2005). The results of Paper II-IV are encouraging in this regard and suggest that motor activity measures are suitable for further examination as possible endophenotypes in adulthood too. Altogether, these findings support the notion that ADHD is a combined collection of behavior manifestations that may be measured in adults and increased reliability is attained at the aggregated level of measurement. It seems like measures of motor activity are one valuable aspect of understanding behaviors in adult ADHD and perhaps a serving ground for future studies regarding heritability traits for the disorder. It also seems like the combination with calibrated cognitive measures may facilitate responsiveness towards problems that adults with ADHD are facing, so that the opportunities of getting support and not develop other psychiatric disorders increase.

In Paper III we wished to challenge the measures with regard to complex psychiatric disorders often mimicking ADHD in adult psychiatric patients as well as testing the measures on a new pool of participants with ADHD but having as little of comorbidity as possible. Here we chose to include participants with bipolar II disorder, borderline personality disorder and participants assessed for but disconfirmed a diagnosis of ADHD as they are symptomatically overlapping, may be demanding to discriminate from as well as co-exist with ADHD. Bipolar disorders for example often include the attention symptom domain such as low attention span, forgetfulness and distractibility as well as the activity symptom domain with increased psychomotor activity, impulsiveness, subjective restlessness as well as affective symptoms such as irritability, emotional lability and tantrum outbursts which may be found in ADHD as well (Giedd, 2000; Kent & Craddock, 2003). Borderline personality disorder may include cognitive symptoms such as difficulties with sustained attention and vigilance, high levels of impulsivity and distractibility as well as the motor symptom domain with restlessness and hyperactivity because of easily getting bored and being impatient as well
as affective symptoms that may be present in ADHD and altogether make the test profile look like ADHD. Except from the group with bipolar and borderline disorders, the second clinical group was more heterogeneous in their clinical character but all shared the common feature of presenting symptoms that was initially addressed as ADHD but later on, after thorough neuropsychiatric assessment, was found to be due to other problems such as autism spectrum disorders including organizational difficulties and low functioning in everyday life, dyscalculia or dyslexia which may co-exist with ADHD but in itself also create secondary attentional and organizational problems during challenging situations, personality disorders which may create dysfunction especially with regard to cognitive deficits and some of the participants in this group had solely been disconfirmed an ADHD diagnosis and was receiving further screening and assessment.

In Paper III, WCS generated consistent differences between ADHD and all other groups as well as between the normative and all other groups. Our measure suggest that participants with ADHD have a larger amount of “global ADHD” than bipolar II, borderline and disconfirmed participants and even more so than the normative participants. This is especially interesting since we know from clinical experience that the other groups do not lack behaviors that are typical of ADHD, and Paper III indeed confirm the occurrence of especially inattention and impulsivity in these other clinical groups. The difference between ADHD and these clinical groups seems to be one about the total frequency of symptoms which was possible to measure and quantify during laboratory-based testing. As far as we are concerned, there has been previous research reports of high levels of cognitive symptoms during CPT performance for both participants with bipolar (Addington & Addington, 1998) and borderline (Soler et al., 2012) disorders but none that has been comparing the quantity with ADHD participants and none that has been accounting for motor activity levels as a separating factor. A continuous and composite instrument like the WCS seems to be fruitful when examining differences between ADHD and clinical groups with shared symptoms since the total level of symptoms constitute a major difference between these groups, and if the motor activity domain had not been included in the composite it would not have been possible to separate ADHD from the bipolar or borderline disorders in Paper III.

There is however limitations with Paper III and one of them concern the possibility of hyperactivity as the strongest marker of ADHD versus other clinical groups because of a majority of ADHD participants having the combined subtype. In Paper II however we had a
better mix of the ADHD subtypes and hyperactivity results did not differ between the two studies but this on the other hand may be due to the fact that combined subtypes are more common in adults as well as among children which is represented in Paper II as well. However, this is not a guarantee that each individual case with the ADHD inattentive subtype will be successfully identified within the lower and more ADHD-like zone on the scale and one should add that each individual case of ADHD will probably not be representative for the levels of behaviors characterizing this group in Paper II-IV. This is a good example of how statistical approaches to behavior manifestations on any single scale or instrument is not enough to secure quality of assessment in clinical practice and therefore a multimodal approach (Kooij et al., 2010) for every person is really necessary for good results with this complex behavior disorder.

On the same topic and in line with Paper II, most of the ADHD and normative participants in Paper III were correctly classified with PADHD but clinical specificity for the bipolar II/borderline group was 36 % and for the disconfirmed ADHD group it was 41 %. This involves clinical logic through and suggests that there are greater similarities between these groups than between the normative and the ADHD group with regard to core symptoms of ADHD. However, this relatively low clinical specificity of PADHD illustrates that the measure is not calibrated with regard to any specific clinical differential diagnosis but merely with regard to the ADHD normal–abnormal continuum presented in Paper II. Another weakness of PADHD is the inability to represent ADHD behaviors in continuous terms although higher levels of core symptoms in the ADHD group were represented as a higher general level of sensitivity for this group. To separate ADHD from other clinical groups it seems like a good idea to look more into the quantitative measurement of behavior and especially regarding motor activity since a major difference between the bipolar II/borderline and the disconfirmed participants on the one hand and the ADHD participants on the other hand is the total level of behavior manifestations during the test as measured in meters.

In Paper IV we wanted to investigate the ability of the test to detect dose changes and response towards stimulant treatment. We found that both of the composite measures identified small changes in dose level and the ADHD cut-off marker PADHD was proposed as a criterion for remission as it had been developed within a broad pool of normative participants as well as tested with regard to complex clinical groups with documented results. In Paper IV we found hyperactivity to be the symptom with the most marked response towards low doses of stimulant treatment and this holds true especially for our male
participants. In order for females to have response on hyperactivity using stimulants, our studies suggest they need a somewhat higher dose level. **Paper IV** is in line with the broader literature (Kooij et al., 2010) suggesting that even though gender differences may be discernible during diagnosis and treatment, it is not a sufficient principle for attaining the goal of remission since the optimal dosing is still highly individual. Is then attaining a state of remission the same as an optimal dose level? In **Paper IV** we found that the decisions made by patients and clinicians, which was based on daily functioning and symptom decline, as well as the self-reported questionnaires used to assess current state of functioning and symptom levels were highly correlated with the first time of attaining an optimal dose level according to both of our composite measures and also constant during prolonged treatment and follow-up. PADHD was informative in the sense that it clearly stated if remission had been attained or not and WCS illustrated the development and change in symptom level that was apparent during experimental conditions. In study one **Paper IV**, a typical patient with ADHD started off with a WCS value of 10 and attained remission at a WCS value of 47 after lowest dosage. After optimal titration in study two **Paper IV**, participants typically attained a WCS value of 69. This value matched the mean of the normative sample, i.e., 64, and equaled a highly individualized and optimal dose level. Therefore, a reasonable WCS value indicating remission is suggested to be around WCS > 64.

PADHD offers the opportunity to test achievement of remission during treatment and the variable classified 62 % of the cases in study one **Paper IV** as being remitters after the lowest dose of fast-acting treatment with methylphenidate. After individually optimized titration in study two **Paper IV**, PADHD indicated remission for 90 % of the cases. In study two **Paper IV** WCS was sensitive to small dose level adjustments and results suggest that WCS is suitable for optimizing dose response. WCS yielded gender differences regardless of experimental condition which is confirmed by previous reports of WCS in clinical and non-clinical samples. Men had less ADHD symptoms than women and previous reports from **Paper II** propose that men are generally less inattentive than women. In **Paper IV**, men were also faster responders than women and even though both genders gained roughly the same amount of improvement from treatment according to WCS, men manifested less total ADHD symptoms after treatment and thus, are likely to need a lower general optimal dosage. As previously noted though, a gender factor may be biased by referral and diagnostic factors and warrants further study. Even though, all of the pre- and post- treatment results for the core symptom measures yielded improvements in symptom scores after treatment in **Paper IV**.
they did not identify small changes in dose level as investigated in study two Paper IV. Only the composite measure, WCS, made dose level changes possible to measure.

Whether using behavior rating scales or other measures of symptoms, Steele and colleagues (2006) suggest a reasonable remission cut-off should be found in matched control populations without ADHD for calibration of efficient standards using well-founded and age-dependent remission criteria. Not all of the participants in Paper IV attained a state of remission and those patients also did not benefit from the treatment and made few if any progress in responding. Some of them did not have initial values that corresponded with ADHD on the WCS and sometimes only subtle markers of inattention on the QbTest-Plus and self-ratings. Our general experience from the two studies in Paper IV is that the response and the optimal dose level may vary but in ADHD, a state of remission according to PADHD equals WCS values found in the general population sample. It is crucial to obtain and extend that state of remission for good treatment outcome documented in Paper IV.

However, since WCS and other laboratory measures are often based on ADHD core symptoms alone it is crucial also to be responsive towards secondary psychiatric and/or psychological problems. This is indeed very common for adults with lengthy undertreatment of ADHD symptoms and it therefore needs to be attended to in order to provide full service and work holistically, hinder escalation of suffering, risks and costs associated with prolonged undertreatment of ADHD and associate impairments. Several authors have noted (Kooij et al., 2010; Nutt et al., 2007) that complementary techniques for improvement and enhancement of cognitive and coping strategies in cases of comorbid psychiatric disorders may be of great help to achieve remission as in quality of life for that person, and especially when ADHD has triggered severe secondary problems such as addictive behavior, self-injury, conduct and personality problems. Many studies (Biederman et al., 2009; Hechtman & Greenfield, 2003) also suggest that treating ADHD effectively will not only result in symptomatic improvement but will also be accompanied with functional development. There is much empirical support for the correlation between symptomatic and functional improvement in ADHD and the earlier the onset and duration of remission the greater functional recovery will be achieved (Barkley et al., 2006a; Biederman et al., 2006a; Murphy et al., 2002; Ramos-Quiroga & Casas, 2011). The use of quantifiable metrics with objective outcomes and standardized interpretation permit reliable estimation of treatment effectiveness and comparisons which may be helpful to attain good results in clinical practice.
4. CONCLUSIONS

In this thesis we have examined objective laboratory measures of Attention Deficit Hyperactivity Disorder (ADHD) in adult persons and we have developed measures for diagnosis and treatment using the psychometric instrument called the Quantified Behavior Test Plus. Paper I concluded that the instrument needs to be calibrated with regard to adult ADHD and emphasized the importance of a composite measure for the disorder. Paper II generated two new measures, the Weighed Core Symptom scale (WCS) - a composite measure of adult ADHD ranging from 0 to 100, and Prediction of ADHD (PADHD) - a categorical variable that indicate diagnostic status with good predictive power. A majority of participants with ADHD had low points on WCS (indicating high levels of symptoms) and a majority of non-ADHD normative participants had high points on WCS (indicating low levels of symptoms). Paper III examined WCS and PADHD among clinical groups with shared symptoms vis-à-vis ADHD. Here, participants with ADHD presented higher level of symptoms than other clinical participants with bipolar II disorder, borderline personality disorder, participants with disconfirmed ADHD and even higher levels of symptoms than non-clinical participants. In Paper IV, the measures are proposed as indications of response to treatment and remission after titration with stimulant treatment and WCS indicates response to small changes in dose level.

The major findings of the present thesis may be summarized as the construction of two new objective measures for ADHD in adult persons with practical implications for diagnosis and treatment. Hyperactivity is the most specific marker for ADHD in both men and women, followed by the cognitive markers of inattention and impulsivity. PADHD and WCS may not replace a thorough neuropsychiatric assessment and further studies that promote diagnostic subtype stratification are suggested. Future studies may want to consider these measures in outcome-based investigations of treatment efficacy as well in the study of neuropsychological endophenotypes. Practical implications include clinical strategies to enhance objectivity during assessment, optimizing beneficial effects of treatment, attaining remission as well as improving the quality of life for adults with ADHD.


155


158


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178


182


184


190


Global Assessment of Attention Deficit Hyperactivity Disorder

The aim of this thesis is to examine objective laboratory measures of Attention Deficit Hyperactivity Disorder (ADHD) in adult persons and to develop measures for diagnosis and treatment using a psychometric instrument called the Quantified Behavior Test Plus. The instrument objectively quantifies cardinal symptom manifestations in adult ADHD using motion tracking devices and continuous performance testing.

Papers I-IV suggest that ADHD predisposes adult persons to perform poorer on continuous performance tasks and to have higher levels of motor activity while performing these tasks as compared to other clinical as well as non-clinical groups. Performance by adults with ADHD is normalized following stimulant treatment and measures of response to treatment and remission are suggested.

The major findings of the present thesis may be summarized as the construction of two new objective measures for ADHD in adult persons with practical implications for diagnosis and treatment. The Weighed Core Symptom scale (WCS) – a composite measure of adult ADHD ranging from 0 to 100, and Prediction of ADHD (PADHD) – a categorical variable of diagnostic status with good predictive power. Practical implications include clinical strategies to enhance objectivity during assessment, optimizing beneficial effects of treatment, attaining remission as well as improving the quality of life for adults with ADHD.