Cognitive functioning in adult ADHD

Fuermaier, Anselm B.M.

Cognitive functioning in adult ADHD

Measurement, treatment and public perception

Anselm B.M. Fuermaier

Publication of this thesis was financially supported by:
University of Groningen (RuG)
School of Behavioral and Cognitive Neuroscience (BCN)

ISBN (book): 978-90-367-6894-8
ISBN (e-pub): 978-90-367-6895-5

Paranymphs: Peter **F**ürmaier, Felix Schirmann
Cover design: Herbert Stahl
Layout and printing: Gildeprint, Enschede

university of groningen

Cognitive functioning in adult ADHD

Measurement, treatment and public perception

PhD thesis

to obtain the degree of PhD at the
University of Groningen
on the authority of the
Rector Magnificus Prof. E. Sterken
and in accordance with
the decision by the College of Deans.

This thesis will be defended in public on

Thursday 19 June 2014 at 14.30 hours

by

Anselm Bernhard Maria Fürmaier
born on 25 April 1985
in Munich, Germany

Supervisor
Prof. O.M. Tucha

Co-supervisors
Dr. L.I. Tucha
Dr. J. Koerts

Assessment committee
Prof. A. Aleman
Prof. E.A. van der Zee
Prof. J. Thome

CONTENT

1. General introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most frequent neurodevelopmental childhood disorders with a prevalence rate of about 5% of children worldwide (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). Behavioral characteristics of ADHD can be divided into three groups of symptoms, i.e. symptoms of inattention, hyperactivity and impulsivity (American Psychiatric Association, 2013). Symptoms of inattention manifest in daydreaming, distractibility, loosing things and difficulty focusing on tasks, whereas symptoms of hyperactivity/impulsivity are usually expressed as fidgeting, restlessness, excessive talking and inappropriate premature behavior (American Psychiatric Association, 2013; Biederman, 2005). Consequently, a high proportion of children with ADHD suffer from considerable impairments which often have serious consequences, such as a higher chance for being involved in accidents, problems in interpersonal relationships and reduced academic performance in school (Biederman, 2005; Booster, DuPaul, Eiraldi, & Power, 2012; Daley & Birchwood, 2010). Historically, ADHD had been understood as an exclusive childhood disorder, which grows out by adolescence and is nonexistent in adulthood (Klein & Mannuzza, 1991; Ross & Ross, 1976). However, a large body of research in the last two decades demonstrated that ADHD persists up into adulthood as a valid and reliable disorder (Barkley, Fischer, Smallish, & Fletcher, 2002; Biederman, 2005; Faraone et al., 2000; Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1998; Rasmussen & Gillberg, 2000). The extent to which symptoms of ADHD persist from childhood to adulthood is difficult to estimate due to a high heterogeneity of methodology and design between studies. Therefore, estimations of persistence rates of children with ADHD who still suffer from symptoms of ADHD in adulthood vary between 30% and 60% (Biederman, 1998; Biederman, Mick, & Faraone, 2000; Seidman, Valera, & Makris, 2005). A recent epidemiologic study performed by Barbaresi and colleagues (Barbaresi et al., 2013) reported a persistence of ADHD into adulthood in 29% to 38% of cases. Regarding the developmental trajectory, it is notable that the clinical picture of ADHD in adulthood differs from the clinical picture as described in children with ADHD. Motor symptoms of hyperactivity/impulsivity were shown to be less dominant in adult ADHD, whereas cognitive dysfunctions (such as inattention and disorganization) were found to become more pronounced in adult ADHD (Biederman et al., 2000; Davidson, 2008). Moreover, symptoms of ADHD in adulthood were demonstrated to be closely linked to academic failure, social dysfunction, low self-esteem and reduced quality of life (Agarwal, Goldenberg, Perry, & IsHak, 2012; Biederman, 2005; Canu & Carlson, 2007; Canu, Newman, Morrow, & Pope, 2008). In addition to the impairments associated with ADHD, it has been shown that more than two thirds (77%) of adults with ADHD suffer from at least one comorbid psychiatric disorder (Biederman et al., 1993). High prevalence rates (between about 27% and 50% of comorbid diagnoses among adults with ADHD) were found for anxiety disorders,

mood disorders, antisocial disorders and alcohol/drug dependence (Biederman et al., 1993; Biederman, 2005).

The etiology of ADHD has been examined extensively and still attracts much controversy (Thapar, Cooper, Eyre, & Langley, 2013). Potential risk factors of ADHD currently discussed are genetic predispositions (i.e. genes associated with dopaminergic neurotransmission), pre- and perinatal factors (e.g. maternal substance misuse, maternal stress, low birth weight or prematurity at birth), environmental toxins (e.g. organophosphate pesticides or lead), dietary factors (nutritional deficiencies such as polyunsaturated fatty acids and nutritional surpluses such as artificial food colorings) and psychosocial adversity (such as parent-child hostility or severe early deprivation) (Thapar et al., 2013). No single risk factor has been identified as the explicit cause for ADHD so that it has been concluded that both inherited (genetic) and noninherited (environmental) factors contribute to ADHD. However, it must be emphasized that genetic and environmental factors do not work independently but interact with each other regarding their effects on ADHD (Nigg, Nikolas, & Burt, 2010; Thapar et al., 2013).

The attempt to understand the neurobiology of ADHD resulted in a large body of research applying various methodologies (Cubillo & Rubia, 2010; Durston, 2003; Faraone et al., 2005; Pliszka, McCracken, & Maas, 1996; Solanto, 2002). Converging evidence from genetic, psychopharmacological and neuroimaging studies suggested dysfunctioning of the dopaminergic system in fronto-striatal brain circuits as the primary biological basis of ADHD (Durston & Konrad, 2007). For example, studies on the genetics of ADHD considered several candidate genes of the catecholaminergic neurotransmitter system to play a role in the neurobiology of ADHD. The majority of these genes are associated with dopaminergic neurotransmission, such as genes for dopamine receptors or the dopamine transporter (Faraone et al., 2005). In addition, the hypothesis of a catecholaminergic dysregulation in ADHD is supported by the effectiveness of stimulants (such as methylphenidate and amphetamines) in the treatment of ADHD (Wigal, 2009; Wigal et al., 1999; Wilens, Spencer, & Biederman, 2002). These drugs are believed to stimulate the release of catecholamines (i.e. dopamine) from the presynaptic neuron and to inhibit the reuptake back to the presynaptic neuron and thereby to increase the level of dopamine in the synaptic cleft (Volkow et al., 1998). In a model linking dysfunctions of the dopaminergic system with symptoms of ADHD, cognitive impairments (such as inattention) were associated with a *hypo*dopaminergic state in the prefrontal cortex, whereas symptoms of hyperactivity/impulsivity were associated with a *hyper*dopaminergic state in the striatum (Pliszka et al., 1996; Solanto, 2002). Moreover, neuroimaging studies have been performed focusing on both the baseline resting-state brain activation and on changes in brain activation related to those cognitive tasks in

which individuals with ADHD are often found to be detrimental (i.e. tasks measuring cognitive control) (Cubillo & Rubia, 2010; Durston, 2003). Increasing consensus of these approaches suggests a changed brain activation pattern in individuals with ADHD compared to healthy individuals. More specifically, a considerable number of studies reported decreased neural activity in fronto-striatal and fronto-cerebellar brain circuits in individuals with ADHD compared to healthy individuals (Durston & Konrad, 2007; Valera, Faraone, Biederman, Poldrack, & Seidman, 2005). Decreased neural activity was, in particular, found in functional neuroimaging studies showing an association between decreased brain activation in fronto-striatal and fronto-cerebellar areas and decreased performance in tasks assessing cognitive control (Durston & Konrad, 2007; Valera et al., 2005).

Various strategies and approaches were applied in the treatment of ADHD which can be best described by distinguishing between pharmacological interventions and nonpharmacological interventions. Pharmacological interventions involve stimulant drug treatment (e.g. using methylphenidate) which is the most common pharmacological treatment in ADHD, whereas treatment with non-stimulants (e.g. atomoxetine or tricyclic antidepressants) is considered if stimulant drug treatment is contraindicated or has proven to be unsatisfactory (Wigal, 2009; Wigal et al., 1999; Wilens et al., 2002). Nonpharmacological treatments encompass various strategies, including psychotherapeutic interventions (e.g. cognitive behavioral therapy) (Mongia & Hechtman, 2012; Philipsen, 2012; Vidal-Estrada, Bosch-Munso, Nogueira-Morais, Casas-Brugue, & Ramos-Quiroga, 2012), cognitive training (e.g. training of attention and working memory functions) (Klingberg et al., 2005; Tamm et al., 2010), neurofeedback (Butnik, 2005; Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003), or dietary control (Sonuga-Barke et al., 2013). However, first-line choice of treatment strategies is often a stimulant drug therapy using methylphenidate in combination with cognitive behavioral therapy, which were both shown to effectively improve symptoms and cognition of adults with ADHD (L. Tucha et al., 2011; O. Tucha et al., 2006; Verster et al., 2010; Vidal-Estrada et al., 2012; Wigal, 2009).

Whether specific interventions are indicated is largely dependent on the individual's impairments as determined in the diagnostic assessment. The diagnostic criteria of ADHD in adulthood require both the assessment of current symptoms but also a retrospective assessment of symptoms in childhood, as ADHD is considered to be a developmental disorder with an onset before the age of 12 years (American Psychiatric Association, 2013; Barkley & Murphy, 1998). Current symptoms of ADHD in adulthood are assessed by applying an adaptation of the diagnostic criteria as they are used for childhood ADHD. Consequently, three subtypes can be distinguished for ADHD in both childhood and adulthood, i.e. a predominantly inattentive subtype (if criteria of inattention are

fulfilled), a predominantly hyperactive/impulsive subtype (if criteria of hyperactivity/impulsivity are fulfilled) and a combined subtype (if criteria of both inattention and hyperactivity/impulsivity are fulfilled). In order to establish the diagnosis in childhood, parents' and teachers' reports represent the main source of information, whereas such information is not always available for adults presenting for clinical evaluation. The diagnostic process for ADHD in adulthood is therefore primarily based on the patients' self-reports of symptoms. In this respect, several self-report questionnaires for ADHD symptoms have become available, and their usefulness in the diagnostic process has been demonstrated (Barkley, 2006; Kooij et al., 2008).

Neuropsychological Assessment of Cognitive Functions: An Objective Approach

A clinical evaluation of symptoms and impairments related to ADHD benefits from an objective assessment of neuropsychological functions using standardized psychometric tests. As ADHD has been described as a disorder of cognitive control and behavioral inhibition (Barkley, 1997; Castellanos, Sonuga-Barke, Milham, & Tannock, 2006), neuropsychological research in adults with ADHD primarily focused on aspects of attention and executive functions (Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Boonstra, Kooij, Oosterlaan, Sergeant, & Buitelaar, 2010; Dinn, Robbins, & Harris, 2001; L. Tucha et al., 2008; L. Tucha et al., 2011; O. Tucha et al., 2006). Other aspects of cognition, such as memory functions, received significantly less attention. However, theoretical considerations imply that executive dysfunction may also adversely affect memory functions of adults with ADHD. This is confirmed by the results of the meta-analyses performed by Hervey and colleagues (Hervey, Epstein, & Curry, 2004) as well as Schoechlin and Engel (2005) demonstrating that adults with ADHD suffer from disturbances of both verbal memory as well as figural memory as indicated by medium to small effects. The majority of studies, however, explored aspects of *retrospective memory*, such as encoding and retrieval processes (Kaplan, Dewey, Crawford, & Fisher, 1998; Muir-Broaddus, Rosenstein, Medina, & Soderberg, 2002; Pollak, Kahana-Vax, & Hoofien, 2008), whereas other qualities of memory, such as *prospective memory* and *source memory* have largely been neglected. *Prospective memory* is a term referring to the memory that an intended action is performed at a particular point in the future and can also be described as 'the delayed execution of an intended action' (Ellis, 1996; Martin, Kliegel, & McDaniel, 2003). Tasks of prospective memory in daily life involve keeping an appointment or giving a message to a friend or colleague. *Source memory* comprises all information about *where* and *when* an event took place and *how* information was acquired (Johnson et al., 2001; Schacter, Kaszniak, Kihlstrom, & Valdiserri, 1991). Detailed information about the source of events represents a crucial quality of human memory, since events of episodic memory become vivid and rich by detailed source information.

Elaborated context information may also be responsible for an emotional connotation and personal evaluation of biographical events. Successful completion of tasks of both prospective memory and source memory have been found to be strongly associated with executive functions and can therefore be hypothesized to be impaired in adults with ADHD (Craik, Morris, Morris, & Loewen, 1990; Janowsky, Shimamura, & Squire, 1989; Martin et al., 2003; McFarland & Glisky, 2009). Thus, ***Study 1*** and ***Study 2*** examined functions of prospective memory as well as source memory of adults with ADHD.

Self-evaluation of Cognitive Functioning: A Subjective Approach

Objective measurements of cognitive functions on standardized neuropsychological tests can be distinguished from individuals' *subjective* self-evaluations of their cognitive abilities and impairments (e.g. in self-report questionnaires). This is relevant in terms of the ecological validity of assessments, because a poor predictive validity of objective measures of executive functions was revealed when judged against direct observations of executive functioning in natural settings (Acker, 1990; Barkley & Murphy, 2010; Barkley, 1991; Sbordone & Long, 1996). For this reason, self-ratings of cognitive functioning receive particular significance in predicting impairments in real life settings. For example, the diagnostic process for ADHD in adulthood is primarily based on the patients' self-reports. Surprisingly, current knowledge on the self-evaluation of cognitive functioning in adults with ADHD is scarce, emphasizing the need for further research on patients' experiences of functioning in various aspects of cognition in daily life as presented in ***Study 3***. Moreover, concerns about the validity and reliability of the different approaches used in neuropsychological assessment underlines the necessity of research addressing the relationship between subjective and objective measures of cognition. Further knowledge about this relationship might facilitate the diagnostic process and both the selection and evaluation of treatment strategies. Therefore, ***Study 4*** was performed addressing the predictive validity of subjective self-reports and objectively defined cognitive impairments.

Treatment of Cognitive Dysfunctions: Whole Body Vibration

Cognitive impairments of a majority of adults with ADHD can be effectively treated with stimulants using methylphenidate, which is often regarded as the first-line choice of treatment (Vidal-Estrada et al., 2012; Wigal, 2009; Wigal et al., 1999). However, stimulant drug treatment is also associated with several disadvantages, such as adverse clinical side effects (e.g. headache, dry mouth, insomnia) or high financial costs (Adler, Spencer, McGough, Jiang, & Muniz, 2009; Wigal et al., 1999; Wilens et al., 2002). Consequently, there is a need for additional treatment strategies which (1) can be given in addition to the effective treatments (e.g. no interaction with stimulant drug treatment),

(2) are time and cost effective, (3) have no detrimental side effects and (4) are effective on symptoms that are most detrimental to the patients' functioning, such as executive dysfunctions. To address this issue, Whole Body Vibration (WBV), the exposure of the whole body of an individual to low frequency environmental vibration, becomes subject of interest. WBV was shown to have beneficial effects on various physiological measures (including balance, mobility and posture control) (Bogaerts, Verschueren, Delecluse, Claessens, & Boonen, 2007; Cochrane et al., 2008; Lam, Lau, Chung, & Pang, 2012). Support for the potential value of WBV in improving cognitive performance was provided by studies in mice, demonstrating improved maze learning and enhanced neuronal activity following the application of WBV (Keijser et al., 2011; Van der Zee et al., 2010). Clear evidence of the effects of WBV on cognition in humans, however, could not be revealed yet (Ljungberg, Neely, & Lundstrom, 2004; Ljungberg & Neely, 2007; Sandover & Champion, 1984; Sherwood & Griffin, 1992; Sherwood & Griffin, 1990). This thesis contains two studies which were carried out in order to explore the potential value of WBV in the treatment of adults with ADHD. *Acute effects* of WBV treatment on attention were explored in a study on a large group of healthy individuals as well as in a group of individuals with ADHD (***Study 5***). Furthermore, in order to explore *prolonged effects* of WBV on cognitive functions, a case study of an adult diagnosed with ADHD receiving WBV treatment in a longitudinal design was performed (***Study 6***).

Public Perceptions and Beliefs about Adult ADHD: Stigmatization

Study 1 to Study 6 focus on individuals with ADHD, their neuropsychological impairments, the (subjective and objective) measurement of these impairments as well as their treatment. The cognitive symptoms of ADHD, together with symptoms of hyperactivity/impulsivity, result in highly externalized behavior which can easily be recognized by the environment in most situations. This may induce misperceptions of and misunderstandings about the condition in the general public and may lead to stigmatization. Stigmatization can be defined as the expression of a discrediting stereotype deriving from assumed associations between a group of people and unfavorable characteristics, attributes or behaviors (Demaio, 2006). For instance, there is evidence that externalizing and norm-violating behaviors of persons with mental disorders such as ADHD can, in particular, lead to discrimination, isolation and social rejection (dosReis, Barksdale, Sherman, Maloney, & Charach, 2010; Koro-Ljungberg & Bussing, 2009; Pescosolido, Fettes, Martin, Monahan, & McLeod, 2007). In order to identify stigmatizing beliefs and associated factors, a review of empirical research on stigmatization in ADHD was performed (***Study*** 7). In this review, it was concluded that stigma associated with ADHD is an underestimated risk factor, affecting treatment adherence, treatment efficacy, symptom aggravation, life-satisfaction and mental well-

being of individuals with ADHD. However, despite the fact that stigmatization in ADHD is widely prevalent (Canu et al., 2008; Martin, Pescosolido, Olafsdottir, & McLeod, 2007), there is a lack of knowledge about the content of stigmatizing attitudes. This lack of knowledge can be explained by a shortage of available assessment tools for the specific assessment of stigmatization towards ADHD. ***Study 8***, therefore, describes the development of a new, disease specific questionnaire for the measurement of stigmatization towards adults with ADHD. The psychometric properties and the sensitivity of new dimensions of stigmatization towards adults with ADHD were explored. Finally, ***Study 9*** presents the application of this newly developed questionnaire on a sample of teachers. In the educational and academic setting, individuals with ADHD can be assumed to be at high risk of being stigmatized. Teachers have a crucial role in this environment, given their task to teach students and to assess and evaluate students' academic performance and social skills. Therefore, teachers' attitudes on adults with ADHD represent a meaningful source to evaluate current beliefs and behavioral tendencies towards adults with ADHD in the educational setting. Furthermore, the contribution of (1) knowledge about ADHD and (2) the frequency of contact with adults with ADHD to stigmatization were explored in order to gain knowledge for the development of effective intervention strategies against stigmatization towards individuals with ADHD.

Short Outline of the Thesis

The present thesis can be divided into four parts, each examining a different subject related to adult ADHD and thereby applying different methodologies. In the first part (2.1 *Neuropsychological assessment of cognitive functions: An objective approach*), objective neuropsychological assessment tools, i.e. neuropsychological test procedures, were applied in order to assess cognitive functions and by this to determine cognitive impairments of adults with ADHD. Two studies were performed focusing on different aspects of memory which were rather neglected in the field of ADHD, i.e. prospective memory as presented in ***Study 1*** and source memory as presented in ***Study 2***. In the second part (2.2 *Self-evaluation of cognitive functioning: A subjective approach*), neuropsychological functioning was assessed by subjective self-reports (by applying standardized self-rating scales and questionnaires). Healthy individuals and adults with ADHD were compared on a comprehensive self-evaluation of cognitive functioning in ***Study 3***. Furthermore, the relationship between subjective and objective measures of cognition was explored in ***Study 4***. In the third part of the thesis (2.3 *Treatment of cognitive dysfunctions: Whole Body Vibration)*, subjective as well as objective measures were applied in order to examine the potential value of WBV in the treatment of cognitive dysfunctions of adults with ADHD. A group study explored acute effects of WBV treatment on attention in both healthy individuals and individuals with ADHD as presented in ***Study 5***. Moreover,

prolonged effects of WBV treatment on cognitive functions of an individual diagnosed with ADHD were explored in ***Study 6***. In the fourth part of the thesis (2.4 *Public perceptions and beliefs about adult ADHD: Stigmatization*), the perception of ADHD and attitudes towards ADHD by the general public was examined (stigmatization). ***Study 7*** presents a review of the existing literature on stigma in ADHD in which the need for disease specific assessment tools was highlighted. Consequently, the development of a questionnaire to measure stigmatization in adults with ADHD is presented in ***Study 8***. ***Study 9*** demonstrates the sensitivity of the developed questionnaire in a study of stigmatization in teachers towards adults with ADHD. Finally, a concluding discussion of the studies and findings presented in this thesis is provided.

2. Empirical studies on cognition in adult ADHD

2.1 Neuropsychological assessment of cognitive functions: An objective approach