NEED, QUEST & EVIDENCE

resting-state oscillations, neurofeedback, and working memory training in ADHD

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Promotor

Prof. dr. J.K. Buitelaar

Copromotor

Dr. D.I.E. Slaats-Willemse

Manuscriptcommissie

Prof. dr. E.L.J.M. van Luijtelaar
Prof. dr. I. Tendolkar
Prof. dr. P.J.M. Prins *(Universiteit van Amsterdam)*

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I

General Introduction

General Introduction

Attention-deficit/hyperactivity disorder (ADHD) affects about 5% of the children worldwide (Polanczyk, de Lima, Horta, Biederman & Rohde, 2007) and is associated with a high risk for adverse psychiatric outcomes in adult life (Biederman et al., 2006), poorer educational and vocational outcomes (Kuriyan et al., 2013), parental strain (Hinojosa, Hinojosa, Fernandez-Baca, Knapp & Thompson, 2012), and elevated financial costs by burden on health, social care, and justice systems in society (Pelham, Foster & Robb, 2007).
The essential feature of children with ADHD, defined by the *Diagnostic and Statistical Manual of Mental Disorders (fifth ed.; DSM-5*; American Psychiatric Association, 2013) is a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with adaptive functioning or development. Children presenting with these symptoms have been described since almost three centuries. Due to variable opinions and increased knowledge, the nomenclature of the clustered symptoms has been changed over time. Today, the literature on ADHD consists of around twenty-three thousands papers worldwide with more than half of these published the last decade. This amount demonstrates an extraordinary effort by researchers to investigate the clinical concept, the etiological factors, the underlying pathophysiology, and potential effective treatment modalities. Despite this effort, there are still gaps in our knowledge about ADHD.

This general introduction comprises a historical overview of the clinical concept of ADHD, the state of the art of resting-state oscillations in ADHD, and a preface of two non-pharmacological interventions in children with ADHD, i.e., neurofeedback (NF) and working memory training (WMT). Then, the aims and outline of this thesis will be presented. In the subsequent chapters (**Chapter II–VI**), five studies are presented, addressing the aims of the thesis. These chapters will be followed by the summary (**Chapter VII**), the general discussion, the main conclusions, clinical implications, and directions for future research (**Chapter VIII**).

"See the naughty, restless child
Growing still more rude and wild,
Till his chair falls over quite.
Philip screams with all his might,
Catches at the cloth, but then
That makes matters worse again.
Down upon the ground they fall,
Glasses, plates, knives, forks, and all.
How Mamma did fret and frown,
When she saw them tumbling down!
And Papa made such a face!
Philip is in sad disgrace."

Figure 1 Fragment of the poem about Fidgety Philip by Hoffmann (1844).

The clinical concept of attention-deficit/hyperactivity disorder from a historical perspective

Zappel-Philip (in English Fidgety Philip, *Figure 1*) was among the first references to a hyperactive child, described in a German children's book with poems about misbehaving children (Hoffmann, 1844). However, the first scientific description of a condition in children that most closely resembles the currently concept of ADHD, has recently been awarded to Weikard (1742-1803) (Barkley & Peters, 2012). Weikard's book in which lack of attention was discussed, dated from around 1770-1775. It mainly comprised a description of the illness, causes, and treatment. Especially the description of the inattentive symptoms has remarkable similarities with the current conceptualization of inattentive symptoms in ADHD (Barkley & Peters, 2012).

In 1798, Crichton published a chapter on disorders of attention in his medical textbook dealing with an inquiry into the nature of mental disorders (Crichton, 1798; Lange, Reichl, Lange, Tucha & Tucha, 2010).

A century later, three lectures to the Royal College of Physicians were published in which Still described children with problems in sustained attention, hyperactivity, defiant and aggressive behavior, and an excess of emotions; all in relation to a deficit in "inhibitory volition" (Still, 1902). He assigned these problems to a major defect in "moral control" in their behavior, and suggested the role for biological determinants (Still, 1902; Barkley, 2006b).

From 1917 to 1928, the focus was further shifted towards the underlying pathophysiology of the earlier described problems, when an outbreak of encephalitis in the United States and Europe caused major cognitive and behavioral problems among children, who survived this disease. This 'post-encephalitic hyperkinetic syndrome' included -among others- the cardinal features (i.e., inattention, hyperactivity, and impulsivity) of what is today called ADHD. Since these features were observed in children who had experienced actual disease-related neurological impairments, it provided evidence that behavioral problems could have biological causes (Ebaugh, 1923).

In 1932, the German physicians Kramer and Pollnow reported "Uber eine hyperkinetische Erkrankung im Kindesalter" (Kramer & Pollnow, 1932). They made the point that symptoms of this 'hyperkinetic disease' had previously been observed, but not distinguished from other diseases with similar symptoms, such as the residual effects of the epidemic encephalitis. Kramer and Pollnow established a concept of the hyperkinetic disease that closely resembles the current concept of ADHD by recognizing the three core behavioral symptoms of ADHD, together with an early onset and the persistence of the disorder into adulthood (Rothenberger & Neumärker, 2005).

A rising number of reports on brain damage in children with hyperactivity hypothesized that brain damage was the cause of this symptom. This idea was supported by the "Frontal Lobe Ablation Studies of Monkeys" (1930-1940) in which frontal lobe lesions often caused excessive restlessness, inability to sustain interest in activities, and behavioral disorganization

(Barkley, 2006a). This resulted in the development of the concept 'minimal brain damage' which stated that hyperactive behavior may be caused by minimal damage to the brain, even when this could not be objectified (Ross & Ross, 1976; Barkley, 2006a).
In the 1960s, the idea that every child with hyperactivity had brain damage was challenged. It was argued that children did exist with hyperactivity but without any classically traumatic or infectious factor in their historical background and so a dysfunction of the diencephalon was suggested (Denhoff, Laufer & Solomons, 1957). Therefore, the Oxford International Study Group of Child Neurology advocated a shift in terminology by replacing the former term by 'minimal brain dysfunction'. Although this concept persisted until the 1980s, its custom declined already in the 1960s when severe concerns arose (Rothenberger & Neumärker, 2005). It was found that many cases of known brain damage or dysfunction did not show hyperactivity or other symptoms postulated by the concept of minimal brain damage or dysfunction. Furthermore, the concept was criticized to be too general and heterogeneous.
In 1968, a definition of the concept of hyperactivity (at that time seen as the core feature of the clinical concept) was incorporated in the *DSM-II*. It was labeled as 'Hyperkinetic Reaction of Childhood', characterized by overactivity, restlessness, distractibility, and a short attention span, especially in young children with the notification that the symptoms usually diminished in adolescence. This definition was of great importance because it replaced the etiological hypotheses of the past with a simple description of observable behavior.
In 1971, the Canadian psychologist Douglas presented in a Presidential Address to the Canadian Psychological Association her theory that deficits in sustained attention and impulse control were more likely to account for the difficulties of these children than hyperactivity. Her landmark paper shifted the focus of research within the field from hyperactivity to attention deficit (Douglas, 1972).
With the release of the *DSM-III* in 1980, the disorder was renamed by 'attention deficit disorder (with or without hyperactivity)', based on the recognition that both inattention and impulsivity were significant symptoms in establishing a diagnosis (Barkley, 2006a). However, the two subtypes were believed to correlate so highly that the disorder was regarded as a one-dimensional construct. This led to the abolition of these subtypes, and so the name was changed into 'attention- deficit/hyperactivity disorder (ADHD)' in the *DSM-III–R*.
Next, however, critics argued that this one-dimensional construct could increase rates of diagnostic errors (Atkins, Pelham & Licht, 1985, 1989). A multi-dimensional construct was hypothesized and studies showed that two dimensions of ADHD consistently emerged in exploratory factor analytic studies, i.e., an inattention factor and a combined impulsivity-hyperactivity factor (Pelham, Gnagy, Greenslade & Milich, 1992; Healey et al., 1993). This led to the implementation of three subtypes of ADHD - predominantly inattentive, predominantly hyperactive-impulsive, and a combined type - in the *DSM-IV* (Lahey et al., 1994). *The DSM-IV-TR* did not modify the diagnostic classification of ADHD.

The *International Statistical Classification of Diseases and Related Health Problems (10th rev. ICD-10*; World Health Organization, 1992), until recently the most common used classification system of psychiatric disorders, had almost identical criteria for inattention, hyperactivity, and impulsivity compared to the *DSM-IV(-TR)*. However, there are differences; the *ICD-10* uses the term 'hyperkinetic disorder', and only recognizes a combined type. Furthermore, the diagnosis demands the presence of criteria in each domain (inattention, hyperactivity, and impulsivity), requires all necessary criteria to be present in two settings and direct observation of the symptoms. Furthermore, the *ICD-10* is stricter in the exclusion criteria. For the differences between the *DSM-IV* and the *ICD-10* in detail, see for example, the paper by Tripp, Luk, Schaughency & Singh (1999).
In the *DSM-5*, special attention is given to guide clinicians in diagnosing adults with ADHD with the ultimate goal that all people with ADHD can get care throughout their lives if needed. In light of this purpose, the threshold criterion of at least five actual symptoms after the age of 17 for the diagnosis was added. Furthermore, the subtypes were held but renamed into presentation subtypes, rather than subtypes, the disorder was placed among the neurodevelopmental disorders, the criterion for the age of onset was expanded from 7 to 12 years, and the possibility to specify the severity was included.
In sum, a behavioral pattern similar to what today is called ADHD, has been described for centuries. After the first reference to a hyperactive child, more than 250 years ago, and after more than 50 years of research, ADHD is still based on a description of symptoms, established by classification systems.

Resting-state oscillations in ADHD

Resting-state oscillations

Electroencephalography (EEG), a method to examine brain cortical activity was introduced by Berger (1929). An electroencephalogram (EEG) represents summed oscillations arising from synchronous firing of large collections of neurons measured by electric field differences on the scalp. The electrodes are often located far from the region from which the signals originate, thereby causing a relatively poor source localization and spatial resolution. Oscillations are characterized by their amplitude, phase, and frequency.
Oscillatory frequencies are clustered by temporal and functional similarities in frequency-bands. Definitions of the boundaries of these bands vary, but are generally determined as; delta (<4 Hertz [Hz]), theta (4-7 Hz), alpha (8-12 Hz), beta (13-30 Hz; often split into beta-1/ sensorimotor rhythm [SMR], 13-16 Hz, and beta-2, 17-30 Hz), and gamma (30-up to 200 Hz) (Onton & Makeig, 2009; Loo & Makeig, 2012; Saby & Marshall, 2012). In childhood, boundaries of the corresponding bands appear to be lower (Saby & Marshall, 2012). Slow oscillations (delta, theta, and alpha) have been supposed to be related to higher levels of the hierarchy regarding brain processes (meaning they are linked to more basic and general

processes) than the fast oscillations (beta and gamma) (Engel et al., 2010). Slow oscillations span relatively large cortical regions, hypothesized to serve the purpose of integration across diverse cortical sites by synchronizing coherent activity and phase coupling across widely spatially distributed neural assemblies (Nunez, 1995). Fast oscillations are distributed over a smaller area, seen as elementary signals of the brain, and functionally related to various brain processes (Schurmann, Demiralp, Basar-Eroglu & Basar, 1999). Although clear-cut knowledge about the implications of frequency-bands is still topic of research, they are supposed to represent certain neurocognitive processes and levels. In rest, delta power has been related to a state of deep sleep. Together with theta power, they are hypothesized to represent activity in brain systems that regulate behavior on the basis of motivational drives and emotional appraisal, and involved in salience detection and emotional learning (Knyazev, 2012). Alpha power has typically been associated with inhibition of brain areas and may be involved in cognitive processes associated with attention and memory (Jensen, Gelfand, Kounios & Lisman, 2002). According to the inhibition hypothesis, alpha has been shown to play a role in the cortex by a selective increase of power when that region is task irrelevant, while inhibition is released where reduced alpha power is measured (Klimesch, Sauseng & Hanslmayr, 2007). Furthermore, alpha power has been stated as a measure for resting-state arousal (Barry, Clarke, Johnstone, Magee & Rushby, 2007). The three slow bands together (delta, theta, and alpha) are thought to be reciprocally connected in a way that relative prevalence of alpha oscillations is associated with inhibition of behavioral patterns peculiar to the delta and theta power (Knyazev, 2007). Beta power has been hypothesized to play a role in motor networks (Mackay, 1997; Jenkinson & Brown, 2011) but also in cognitive processes, like executive functioning (Buschman, Denovellis, Diogo, Bullock & Miller, 2012; Groppe et al., 2013). Gamma power has been associated with a wide variety of higher cognitive processes including attention, perception, memory, and language (Benasich, Gou, Choudhury & Harris, 2008).

Resting-state oscillations in ADHD

Oscillations in ADHD during rest (i.e., awake but without directed cognitive and motor activity) have been widely investigated.

First reports in children with behavioral problems (among them problems corresponding with those seen in the currently concept of ADHD) indicated 'EEG slowing' (Jasper, Solomon & Bradley, 1938), later labeled as 'theta' (Walter & Dovey, 1944). Nowadays, elevated theta power is the most consistent finding in children and adults with ADHD (Mann, Lubar, Zimmerman, Miller & Muenchen, 1992; Matsuura et al., 1993; Janzen, Graap, Stephanson, Marshall & Fitzsimmons, 1995; Chabot & Serfontein, 1996; Clarke, Barry, McCarthy & Selikowitz, 1998; Lazzaro et al., 1998; Bresnahan, Anderson & Barry, 1999; Lazzaro et al., 1999; Clarke, Barry, McCarthy & Selikowitz, 2001d, 2001c; Bresnahan & Barry, 2002; Clarke, Barry, McCarthy & Selikowitz, 2002, 2003a; Clarke et al., 2003b; Hermens et al., 2004;

Hermens, Kohn, Clarke, Gordon & Williams, 2005a; Hermens et al., 2005b; Bresnahan, Barry, Clarke & Johnstone, 2006; Clarke et al., 2006; Clarke, Barry, McCarthy, Selikowitz & Johnstone, 2007a; Hobbs, Clarke, Barry, McCarthy & Selikowitz, 2007; Clarke, Barry, McCarthy, Selikowitz & Johnstone, 2008; Koehler et al., 2009; Barry et al., 2010; Woltering, Jung, Liu & Tannock, 2012; Clarke et al., 2013). This is in line with the conclusion of a recent meta-analysis in children with ADHD (Arns, Conners & Kraemer, 2012).

Diminished beta power has also been found in ADHD (Callaway, Halliday & Naylor, 1983; Mann et al., 1992; Matsuura et al., 1993; Clarke et al., 2001c; Bresnahan & Barry, 2002; Barry et al., 2010; Woltering et al., 2012), but far less consistently (i.e., not always a difference was found between ADHD and controls) (Lazzaro et al., 1998; Lazzaro et al., 1999; Clarke, Barry, McCarthy & Selikowitz, 2001a; Bresnahan et al., 2006; Hobbs et al., 2007; Barry, Clarke, Johnstone & Brown, 2009; Koehler et al., 2009; Liechti et al., 2013). Further, several studies have identified a subgroup (13-20%) of children with ADHD (Arns, 2012) with excess beta power (Chabot & Serfontein, 1996; Kuperman, Johnson, Arndt, Lindgren & Wolraich, 1996; Clarke et al., 1998; Chabot, Orgill, Crawford, Harris & Serfontein, 1999; Clarke et al., 2001d; Clarke et al., 2013).

Research on the alpha power during rest also yielded inconsistent findings. This may partially be explained by the great individual differences in alpha power and the choice of analyzing and reporting data. The absolute power, the actual measured power in a frequency-band, can be elevated, while the relative power, the percentage of power in a frequency-band compared to for instance the overall power, can be diminished in the same individual. This may partially clarify that some studies reported elevation for the absolute alpha power (Bresnahan & Barry, 2002; Koehler et al., 2009) or for relative alpha power (Chabot & Serfontein, 1996), one study reported an elevation for both absolute and relative alpha (Lazzaro et al., 1999), another study reported elevation of absolute alpha and diminished relative alpha in the same sample (El-Sayed, Larsson, Persson & Rydelius, 2002). Further findings include absolute as well as diminished relative alpha power (Woltering et al., 2012), diminished relative alpha power, without difference in absolute power (Clarke et al., 2001a; Barry et al., 2010), or without a clear description whether relative or absolute alpha was obtained (Clarke et al., 2001d), and diminished alpha power without reporting if the results referred to absolute or relative power (Loo et al., 2009). Finally, some studies did not find any difference regarding alpha power (absolute and relative) (Bresnahan et al., 1999; Bresnahan et al., 2006).

In addition, elevated delta power has been found in ADHD (Matousek, Rasmussen & Gillberg, 1984; Clarke et al., 1998, 2001a, 2001c; Barry et al., 2010).

Recently, gamma power was shown to be reduced in ADHD children (Barry et al., 2010).

Two main underlying neurobiological hypotheses have been proposed about the findings regarding resting-state oscillations in ADHD:

1) *The hypo-arousal theory.* This theory, first proposed by Satterfield & Dawson (1971), was initially based on the reduced skin conductance in hyperactive children. Lubar

(1991) further developed this theory, linking Satterfield and Dawson's (1971) report of hypo-arousal with Jasper and colleagues' report (1938) that normal resting EEG power is dominant in the theta and alpha bands, but shifts to the beta band during activity. He hypothesized that the ability to produce beta power is diminished in subjects with ADHD, and instead theta power is produced. Based on this hypothesis, a decrease of beta power together with an increase of theta power (elevated theta/beta power ratio) was supposed to represent a hypo-aroused state. However, an elevated theta/beta power ratio was later found not to be directly related with arousal in ADHD (Barry, Clarke, Johnstone, McCarthy & Selikowitz, 2009). The former hypothesis was expanded with the suggestion that an excess of beta power reflects a hyper-arousal state (Clarke et al., 2001d). A recent study further investigated this hypothesis by dividing children with ADHD into an "excess beta group" and an "excess theta group" and measuring the skin conductance level (SCL) as a marker of central nervous system arousal. Both ADHD groups had a significant reduced SCL compared to the control group, but the two groups did not differ from each other on SCL, indicating that ADHD children with excess beta power are not hyper-aroused and that the theta/beta power ratio is not associated with arousal (Clarke et al., 2013).

2) *The maturational lag model* (Gasser, Verleger, Bacher, & Sroka, 1988). This model refers to the hypothesis that ADHD shows a lag in the normal timetable for development (Burke & Edge, 2013). This model is based on findings that there is a decrease in the relative contribution of low-frequency rhythms and an increase in higher-frequency rhythms during the child's development (Gibbs & Knott, 1949; Corbin & Bickford, 1955; Matousek & Petersen, 1973; John et al., 1980). This model expects elevated amount of slow waves (i.e., delta, theta, and alpha) and diminished fast waves (beta and gamma) often found in ADHD.

The use of resting-state oscillations for diagnostic and prognostic purposes

The use of resting-state oscillations as diagnostic tool in ADHD has a long history. The idea of the theta/beta power ratio for diagnostic purpose was introduced to discriminate healthy children from children with ADHD and learning disorders (Lubar, 1991). Elevation of this ratio in ADHD has been replicated frequently with a large mean effect size (ES) of around 0.7. Nevertheless, caution in its interpretation is recommended, because ES has shown a decrease across the years, due to an increase of the theta/beta power ratio in controls (Arns et al., 2012). In line, a recently published large study on the theta/beta power ratio, did not find any difference at all between ADHD and controls (Loo et al., 2013). An analysis, taking into account both the sensitivity and specificity, showed an accuracy of 58% in discrimination on the theta/beta power ratio between children with and without ADHD (Ogrim et al., 2012). So, the theta/beta power ratio cannot be regarded as a reliable diagnostic tool in ADHD. Furthermore, the lack of deviation in the theta/beta power ratio when using individual frequency-bands rather than fixed frequency-bands has been explained by

mediation of a low alpha peak frequency (APF) (Arns, Gunkelman, Breteler & Spronk, 2008; Lansbergen, Arns, van Dongen-Boomsma, Spronk & Buitelaar, 2011a). This suggests the existence of two subgroups in ADHD; one group with an actual excess of theta power without any mediation of the APF, and a second group with alpha peaking at a lower frequency, thereby 'leaking' into the theta band causing the fixed theta band estimate to be falsely interpreted as inflated (Arns et al., 2012).
In addition, effort has been made to differentiate subgroups of ADHD based on resting-state oscillations; greater abnormalities in the combined subtype compared to the inattentive subtype have been found (Chabot & Serfontein, 1996; Clarke et al., 1998, 2001a; Clarke, Barry, McCarthy & Selikowitz, 2001b; Barry & Clarke, 2009). Furthermore, several studies have shown additional deviated oscillations in ADHD patients with comorbidity (e.g., learning disorders, see for example Barry, Clarke, McCarthy & Selikowitz (2009).
Resting-state oscillations have also been examined as potential predictive markers by attempting to identify subgroups to predict treatment-response. Excess of beta, frontal theta, and frontal alpha power have been supposed to predict a better stimulant treatment response. In contrast, a slow individual APF has been proposed as a marker of treatment resistance (Arns, 2012).

Resting-state oscillations and neurocognitive and behavioral correlates in ADHD

Research on the relationship between resting-state oscillations and neurocognitive and behavioral correlates in ADHD is sparse. Apart from the study described in this thesis (**Chapter II**), neurocognitive correlates of resting-state oscillations have only been studied in children. An elevated theta power has been found to correlate with less accuracy on an auditory oddball task (Hermens et al., 2005b), lower reaction time in an attention task (i.e., the Test of Variables of Attention [TOVA]) (Swartwood et al., 1998; Swartwood, Swartwood, Lubar & Timmermann, 2003), and increased response variability on a continuous performance task (CPT) (Loo & Smalley, 2008). Elevated alpha power was correlated with less inhibition on a CPT (Loo & Smalley, 2008), slower reaction time, more variability on the TOVA (Swartwood et al., 1998; Swartwood et al., 2003), and impaired attention in a Go/No-Go task (Lansbergen et al., 2011a).
Furthermore, research on the relationship between resting-state oscillations and the core behavioral symptoms of ADHD is also limited. Besides the study described in this thesis (**Chapter II**), only one other study was performed in adults (Koehler et al., 2009), reporting a positive relationship between theta power and inattention scores on the Adult ADHD Self-Report Scale (Kessler et al., 2005). Furthermore, diminished gamma power was correlated with higher inattention scores on the Conners' Parent Rating Scale-Revised (CPRS-R) (Conners, Sitarenios, Parker & Epstein, 1998; Barry et al., 2010). In another study, beta power correlated positively with inattention and the total symptom-score on the CPRS-R (Ogrim, Kropotov & Hestad, 2012). In yet two other studies, beta power was positively correlated with impulsivity (Swartwood et al., 1998; Swartwood et al., 2003) and

negatively with inattention (Swartwood et al., 1998). Theta power correlated positively with inattention and negatively with hyperactivity and impulsivity on the Conners' Rating Scale Revised (Ogrim et al., 2012). For the theta/beta power ratio, a weak correlation was found with inattentive symptoms (Loo et al., 2013).
Inconsistency of these findings and the small amount of studies reporting correlations between resting-state oscillations and neurocognitive and/or behavioral measures in ADHD make firm conclusions not yet possible. The small amount of studies may be even smaller than it seems at first sight; the studies by Swartwood and colleagues (1998; 2003) have possibly used the same data set, suggested by exactly the same results.

So, despite the robust evidence for elevated theta power and - to a lesser degree - diminished beta power, the findings on resting-state oscillations, and their correlations with neurocognitive and behavioral measures in ADHD are inconsistent. This may have different causes and those will be further addressed in the discussion (**Chapter VIII**). This inconsistency has led to - among other reasons - innovating technical aspects of the EEG, such as independent component analysis (Loo & Makeig, 2012). Furthermore, research has been expanded to other electrophysiological approaches. Slow cortical potentials (SCPs), for example, also used as target for NF (see later in this introduction), are slow event-related direct-current shifts of the EEG, originating from the upper cortical layer (Birbaumer, Elbert, Canavan & Rockstroh, 1990). They are not oscillatory in nature but occur as a consequence of external or internal events (Strehl et al., 2006). It has been suggested that SCP shifts in the negative direction reflect increased excitability, while shifts in the positive direction reflect reduced excitability (Birbaumer et al., 1990; Hinterberger et al., 2003). The contingent negative variation, a SCP associated with cognitive preparation, has found to be reduced in children with ADHD in several ERP studies suggesting dysfunctional regulation of energetically resources in ADHD (Sergeant, 2005; Banaschewski & Brandeis, 2007). Other examples of electrophysiological approaches are coherence analyses (Clarke et al., 2007b) and event-related potentials (see for a review Johnstone, Barry & Clarke, 2013).
These approaches may have different purposes, like 1) to understand more about the neural mechanism underlying ADHD and its relationship with the clinical concept of ADHD, 2) to detect a diagnostic or prognostic tool that sufficiently discriminates on individual level, or 3) to detect an electrophysiological target suitable for treatment modalities.

Non-pharmacological interventions in children with ADHD; neurofeedback and working memory training

National and international guidelines describe a multimodal, stepped-care treatment plan with an individual approach for children with ADHD (Taylor et al., 2004; Landelijke Stuurgroep Multidisciplinaire Richtlijnontwikkeling in de GGZ, 2005; National Institute of Mental Health

[NIMH], 2009). Psycho-education (for parents, older children, and their teachers) is seen as the first step in treatment. It includes information about the etiology, clinical course, and prognosis of ADHD, together with information about the various treatment options, possible community supports, and school resources. Further treatment depends on the level of disability, the context in which the problems exist and the age of the child. In sum, when the child is below the age of 6, or has a mild expression of ADHD symptoms, first-line treatment consists of behavioral interventions, parent training, and/or school liaison. If these interventions have shown insufficient improvement, the use of medication has to be considered. For children older than 6 years with severe and pervasive disabilities, first-choice treatment is medication. Combined therapy (i.e., stimulants and behavioral therapy) has shown additional benefits (e.g., improvement of symptoms other than the core behavioral symptoms of ADHD, parent-child interaction, parental satisfaction, and social skills) compared to stimulants alone (MTA Cooperative Group, 1999b, 1999a). However, the general recommendation is to indicate combined therapy only if stimulant treatment alone has shown insufficient improvement of the ADHD symptoms or in case of comorbidity with other psychiatric disorders, such as oppositional defiant disorder (ODD) and conduct disorder. Currently, the most effective treatment for severe ADHD is medication, with placebo-controlled large ESs on the core ADHD symptoms for amphetamine, methylphenidate (Faraone & Buitelaar, 2010) and atomoxetine (Michelson et al., 2002; Banaschewski et al., 2008). Although large ESs, interpretation of the implication for the individual patient, asks for cautiousness; reanalysis of the NIMH-funded Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA) data showed that only 56% of the patients in the medication group met the definition of success at the end of treatment (Swanson et al., 2001). Furthermore, some concerns accompany the use of medication in children. First, side effects have been reported and for some serious and life-threatening side effects, the risk is still not fully known and will likely to stay uncertain due to their rarity (Graham et al., 2011). The leading cause of negative attitudes in children with ADHD and their parents is based on concerns regarding (negative) long-term effects (Berger, Dor, Nevo & Goldzweig, 2008). Second, there is insufficient evidence of long-term efficacy of medication for ADHD (van de Loo-Neus, Rommelse & Buitelaar, 2011). Third, the symptoms of ADHD reappear after discontinuing drug treatment (Jensen et al., 2007; Murray et al., 2008). Based on these concerns children with ADHD and their parents may be reserved about pharmacotherapy.
Therefore, non-pharmacological treatment modalities are needed. Currently, NF and WMT are two of the most studied non-pharmacological treatment options in ADHD. In the following part of this introduction these two interventions will be discussed regarding the efficacy in children with ADHD.

Neurofeedback

After the first introduction of recording brain oscillations in humans by Berger in the 1920s, it took decades until the first published experiments took place in modulating these

oscillations. These experiments started in the 1950s, leading to the first publication on frequency NF (F-NF) in humans, showing control over their brain activity by entering the 'alpha-state', associated with a state of relaxation (Kamiya, 1968). In the same period, in 1965, Sterman accidentally discovered that cats could be trained to produce SMR and that these trained cats had built resistance against a toxic substance known to provoke seizures (Sterman, Wyrwicka & Howe, 1969). Sterman replicated this discovery successively in monkeys, in humans, and finally in patients with epileptic symptoms (Sterman, Macdonald & Stone, 1974). Eventually Lubar and Shouse were the first to report F-NF in a child with a hyperkinetic disorder (Lubar & Shouse, 1976).

NF is a form of biofeedback targeting brain oscillations, including the conventional F-NF and SCP-NF, and is defined as a process, in which sensors are placed on the scalp and devices are used to monitor and provide moment-to-moment information about the physiological brain activity, that is fed back to the individual to improve brain functioning (Hammond et al., 2011). F-NF has been hypothesized to aim at tonic aspects of cortical arousal, while SCP-NF has been hypothesized to aim at phasic excitability (Gevensleben et al., 2009). The idea is that NF works via operant learning, in which simultaneous and contingent feedback is given by positive reinforcement through visual and/or acoustic signals when changes in the brain oscillations are made in the desired direction, leading to voluntary modulation of these oscillations and controlling their underlying processes and thereby enhancing the self-regulation (Gevensleben, Rothenberger, Moll & Heinrich, 2012). In children with ADHD, F-NF protocols usually target the deviations of the resting-state oscillations found in children with ADHD. For example, the child trains to increase the production of beta activity while suppressing the production of theta activity, whereby the feedback consists of rewarding the production of the desired frequency activity (Monastra et al., 2005; Gevensleben et al., 2012). The SCP-NF protocol targets the hypothesized impaired regulation of cortical excitation in ADHD (Sergeant, 2005; Banaschewski & Brandeis, 2007) by practicing to produce positive and negative shifts (Moriyama et al., 2012). Feedback consists of rewarding the changes in the polarity (i.e., positivity vs. negativity) of the EEG over the sensorimotor cortex (Arns, de Ridder, Strehl, Breteler & Coenen, 2009).

The first review addressing the efficacy of F-NF in children with ADHD concluded that F-NF was 'probably efficacious' in children with ADHD (Monastra et al., 2005). This conclusion was based on The Guidelines for Evaluation of Clinical Efficacy of Psychophysiological Interventions (LaVaque et al., 2002), accepted by the Association for Applied Psychophysiology & Biofeedback as well as the International Society for Neurofeedback and Research, and similar to those from the American Psychological Association. These guidelines contain five levels of classification, ranging from 'Not empirically supported' to 'Efficacious and Specific'. The authors of this review further stated that although they reported beneficial effects, studies with a more robust methodological design are needed (Monastra et al., 2005), further underscored in the review by Loo & Barkley (2005). Since then, studies with

a better methodological design were performed and today's literature on this topic counts more than 20 randomized controlled trials. Using the same guidelines (LaVaque et al., 2002), the meta-analysis by Arns and colleagues (2009) concluded that NF in children is 'efficacious and specific'. However, this conclusion was based on both randomized and non-randomized studies, but not on placebo-controlled trials (not available at that moment). Most of the more recently published reviews are more reserved about the efficacy of NF in children with ADHD due to methodological shortcomings of the studies (e.g., lack of large samples and a double-blind, placebo-controlled design) (Lofthouse, Arnold, Hersch, Hurt & DeBeus, 2012; Lofthouse, Arnold & Hurt, 2012; Moriyama et al., 2012). Furthermore, conclusions about the state of F-NF as monotherapy are regarded as presumptive, since the great majority of studies investigated F-NF as an adjunctive treatment, and for ethical reasons other treatments were usually not discontinued (Moriyama et al., 2012). The review by Gevensleben and colleagues (2012) is characterized by a more positive line with the suggestion that negative results may be ascribed to certain study shortcomings (such as the lack of transfer strategies into daily life) and some directions for future research to optimize NF studies, based on the use of common variables of earlier performed trials with positive results (e.g., age 7-14, standard protocols instead of personalized protocols, block wise treatment, two or three times a week, including transfer trials, simple and clearly represented feedback, and 25-40 sessions) (Gevensleben et al., 2012).

Despite a rise of the number of randomized controlled trials (RCTs) by time of conducting our F-NF study (in 2007), not any placebo-controlled trial was performed in children with ADHD. By now, four published papers (Perreau-Linck, Lessard, Levesque & Beauregard, 2010; Lansbergen, van Dongen-Boomsma, Buitelaar & Slaats-Willemse, 2011b; Arnold et al., 2012; van Dongen-Boomsma, Vollebregt, Slaats-Willemse & Buitelaar, 2013) describe a RCT including a placebo-condition investigating the efficacy of F-NF on the core behavioral symptoms of ADHD, among them two papers of our research group (Lansbergen et al., 2011b; van Dongen-Boomsma et al., 2013); the latter is part of this thesis (**Chapter IV**) and will be discussed later (**Chapter VIII**). The three other studies did not find a superior effect of F-NF on the core behavioral symptoms of ADHD. This conclusion was in line with the most recent systematic review/meta-analysis of randomized controlled trials of non-pharmacological interventions in children with ADHD; analyses of probably unblinded ratings for NF in children with ADHD showed an ES of 0.29 ($p = .07$) (Sonuga-Barke et al., 2013).

Thus, so far, convincing evidence is lacking for beneficial effects of NF on the core behavioral symptoms of ADHD in children. Even more, neurophysiological evidence that NF leads to improvement of neural regulation is poor, and subsequently leads to significantly positive effects on behavioral outcome measures, has sparsely been investigated. Although findings suggest normalization of neurophysiological markers in ADHD after NF (Monastra, Monastra & George, 2002; Heinrich, Gevensleben, Freisleder, Moll & Rothenberger, 2004) and even so that improved behavioral outcome measures follow improved neural regulation (Kropotov et al., 2005; Strehl et al., 2006; Doehnert, Brandeis, Straub, Steinhausen & Drechsler, 2008),

these findings should be interpreted with caution, especially due to inconsistent and weak findings, methodological limitations and the small numbers of studies.
In spite of these concerns, F-NF is widely used in Europe and the United States of America as a treatment modality for ADHD. In The Netherlands, F-NF is partly reimbursed by some health insurance companies, despite the state of evidence. So, a methodological well-designed study is needed to answer the question if daily practice F-NF merits its current position as a widely used and evidence-based treatment by investigating its efficacy in children with ADHD.

Working memory training

Decades of research on neurocognitive functioning in ADHD has yielded invaluable knowledge about the neurocognitive deficits often found in ADHD. Deficits are found in attention regulation (Losier, McGrath & Klein, 1996; Epstein et al., 2003), executive functions (EFs) (Martinussen, Hayden, Hogg-Johnson & Tannock, 2005; Willcutt, Doyle, Nigg, Faraone & Pennington, 2005), reward-related processes (Sonuga-Barke, Sergeant, Nigg & Willcutt, 2008), and timing (Noreika, Falter & Rubia, 2013). Problems in EFs are found in domains of response inhibition, vigilance, planning, and working memory (WM), with the latter found to be affected most strongly in children with ADHD (Willcutt et al., 2005). Neurocognitive deficits in ADHD may have contributed to shift the focus of identifying treatment modalities in ADHD from direct amelioration behavioral symptoms towards improvement of underlying neurocognitive functioning in ADHD. Furthermore, this shift is even more understandable by the finding that persistence of neurocognitive deficits in ADHD is strongly associated with future occupational problems and morbidity (Barkley & Murphy, 2010; Biederman et al., 2012).
An example of such a treatment modality is Cogmed WMT (CWMT). This training is based on the idea that intensive training of WM may improve WM, other neurocognitive functions, and ultimately diminish the core behavioral symptoms of ADHD. WM is defined as the ability to temporarily hold information while simultaneously manipulating the information (Baddeley, 1986), and is often regarded as a fundamental neurocognitive function underlying other EFs (Klingberg et al., 2005).
Neurophysiological studies showed that maintenance of information in WM is associated with elevated and sustained neural firing over a delay when information is kept in mind (Funahashi, Bruce & Goldman-Rakic, 1989). Neuroimaging studies have mapped WM-related activity to both sensory association cortices and the prefrontal cortex (Curtis & D'Esposito, 2003; Linden, 2007; Klingberg, 2010). Neurobiological studies indicated an important role for dopamine in WM (Luciana, Depue, Arbisi & Leon, 1992; Muller, von Cramon & Pollmann, 1998; Diamond, Briand, Fossella & Gehlbach, 2004). The past decade, research has focused on neural correlates of WMT. Increased activity of prefrontal and parietal regions (i.e., the middle frontal gyrus and the superior and inferior parietal cortices) as well as thalamic and caudate regions was found following WM training. Decreased brain activation in the right

cingulate sulcus was also found and hypothesized to reflect the decreased need for motor planning (Olesen, Westerberg & Klingberg, 2004). Furthermore, changes in the density of cortical dopamine D1 receptors, namely larger decreases in dopamine D1 binding potential, were associated with larger improvements in WM in both prefrontal and parietal cortices after WMT (McNab et al., 2009). Volumetric brain changes were also found following WM training, represented by a reduced regional gray matter volume in the bilateral frontoparietal regions and the left superior temporal regions (Takeuchi et al., 2011). These findings indicate plasticity of the WM capacity (Klingberg, 2010), however, a specific neural mechanism underlying WMT and transfer effects has not yet been indicated (Buschkuehl, Jaeggi & Jonides, 2012) and research on this aspect in ADHD is lacking. See for a comprehensive review on this topic, Buschkuehl and colleagues (2012).

So far, eight studies, among one study in this thesis (**Chapter VI**) examined the efficacy of CWMT in children with ADHD (Klingberg, Forssberg & Westerberg, 2002; Klingberg et al., 2005; Holmes, Gathercole & Dunning, 2009; Beck, Hanson, Puffenberger, Benninger & Benninger, 2010; Gibson et al., 2011; Gray et al., 2012; Green et al., 2012); all but one used an RCT design (Holmes et al., 2009). The study by Gibson and colleagues (2011) showed that CWMT focuses on a component of WM that is less supposed to be affected in ADHD (primary memory rather than secondary memory). Because, this study used a modified training program, and was not designed to investigate the efficacy of CWMT in ADHD, this study will not further be included in the discussion about the efficacy of CWMT in ADHD. Our study will be presented in this thesis (**Chapter VI**), and reviewed in the discussion (**Chapter VIII**).

Four out of the six studies investigated the efficacy of CWMT on the core behavioral symptoms in ADHD. Three of them showed significant treatment effects (Klingberg et al., 2005; Beck et al., 2010; Green et al., 2012). Five studies reported improvement on at least one trained WM task (Klingberg et al., 2002; Klingberg et al., 2005; Holmes et al., 2009; Gray et al., 2012; Green et al., 2012), four studies reporting non-trained neurocognitive parameters, in which only two found significant improvement on some neurocognitive parameters (i.e., in the domains of EFs [WM, response inhibition]), and attention (Klingberg et al., 2002; Klingberg et al., 2005).

Findings of recently published reviews and meta-analyses on this topic are in line with the mixed results of the individual studies. A review/meta-analysis on non-pharmacological interventions in children with ADHD, reported no significant treatment effect (ES 0.24, $p = .34$) when probably blinded assessments were analyzed for cognitive training, including CWMT (Sonuga-Barke et al., 2013). This finding is not optimistic, but must be interpreted with caution because it represents the total mean efficacy of all included cognitive training modalities and only included one study on CWMT in children, namely the study by Klingberg and colleagues (2005). Another meta-analytic review on non-pharmacological interventions concerning children with ADHD concluded that WMT on the basis of average weighted ES across the outcome measures (i.e., core behavioral symptoms and neurocognitive

performance), did not result in greater improvement in the treatment group in contrast to the control group (Hodgson, Hutchinson & Denson, 2012). This conclusion was based solely on the study by Klingberg and colleagues (2005). Furthermore, a meta-analytic review was performed on different WMT programs, including 23 studies with clinical samples as well as samples of typically developing children and adults (Melby-Lervag & Hulme, 2013). Results indicated that WMT improved WM; however for verbal WM, these effects were not sustained at follow-up, whereas for visuospatial WM, limited evidence suggested that such effects might be maintained. In addition, there was no evidence of generalization of WMT to other neurocognitive functions. However, because of mixed included samples (i.e., clinical and non-clinical, children and adults), the inclusion of all types of WMT, and because the findings are based on neurocognitive parameters, conclusions about the clinical implication of CWMT for children with ADHD cannot be drawn. Shipstead and colleagues (2012) also reviewed different WMT programs in clinical and non-clinical samples, including all ages, and also expressed concerns about the claims for the efficacy of WMT. In sum, the authors reported the problematic tendency among researchers to define change by the use of a single measure, the use of invalid WM tasks that do not differ from the trained tasks, the use of no-contact control groups, and inclusion of subjective non-blinded measurement of change. In addition, they concluded that there is a need to demonstrate directly that WM capacity increases in response to training, and that transfer effects take place to other neurocognitive functions. Further, the authors recommended the use of a wider variety of tasks might eliminate the possibility that results can be explained by task specific learning.
A recent meta-analysis on training-modalities targeting neurocognitive functioning in children with ADHD, focusing explicitly on near vs. far transfer effects, concluded that CWMT was associated with moderate near transfer effects only (d = 0.63); far transfer effects were lacking (Rapport, Orban, Kofler & Friedman, 2013). Due to these findings, further concerns about the potential transfer effects of these training-modalities were expressed. A review including only CWMT studies in children with ADHD has been published by Chacko and colleagues (2013). They included all studies, reported earlier in this introduction, except for the study by Gibson and colleagues (2011), due to not meeting the predetermined inclusion criteria and included one extra study, the study by Mezzacappa and colleagues (2010). This latter study included children without a firm ADHD diagnosis, but with elevated scores on an ADHD Rating Scale, rated by their teacher. The four trials (Klingberg et al., 2005; Beck et al., 2010; Gray et al., 2012; Green et al., 2012) that were determined as having an Evidence Based Treatment status, espoused by the Society for Clinical Child and Adolescent Psychology (Silverman & Hinshaw, 2008), led to the conclusion that CWMT can be regarded as a 'Possibly Efficacious' treatment for youth with ADHD. Concerns like the inconsistent findings within and between studies, the weak evidence for the hypothesized underlying working mechanism, the questionable quality of the placebo condition and the differences between the sample characteristics were discussed. Future directions were mainly based on these concerns, and consisted of the recommendations to

investigate CWMT in a more heterogeneous and so more clinical sample, with a smaller and lower age range with broadening outcome measures referring functional impairment.
So far, current findings raise doubt about the efficacy of CWMT. Altogether, CWMT is (still) not a well-established treatment modality in children with ADHD. Even more, a gap in the literature exists for the young children with ADHD. Especially for the younger ADHD population, in which even more barriers may rise in the decision to start medication (e.g., due to poor efficacy [Riddle et al, 2013] and far less knowledge about side effects compared to older children), a non-pharmacological treatment option would be of great value. In addition, since WM shows a fast development throughout preschool and early school-age (Carlson, 2005), early training of WM may possibly prevent development of ADHD-related neurocognitive deficits and behavioral problems. For these reasons, stepping up the effort to investigate the efficacy of WMT in young children in ADHD is necessary.

Aims & Outline of the Thesis

For decades, resting-state oscillations in ADHD have been investigated with the most consistent finding of elevated theta in adults as well as in children. However, also significant inconsistent findings regarding resting-state oscillations in ADHD have been found. In addition, there are few studies on the relationship between resting-state oscillations on one hand and neurocognitive functioning and core behavioral symptoms on the other hand and the findings are inconsistent. Thus, the role of resting-state oscillations in ADHD and their relationship with neurocognitive and behavioral functioning is still unclear.
Furthermore, F-NF is a widely used treatment modality in children with ADHD. However, whether F-NF is efficacious for this target population is still an open question. Besides, neurophysiological evidence that NF improves neural regulation and that such an improvement significantly affects behavioral outcome measures, is scarce.
The same is true for CWMT; widely used but with an unclear state of evidence regarding efficacy in the treatment for children with ADHD. In addition, the efficacy of CWMT in younger children with ADHD has not been studied.

Therefore, the aims of this thesis are:

a. To examine resting-state oscillations in ADHD and the relationship between resting-state oscillations on one hand, and neurocognitive functioning and core behavioral symptoms of ADHD on the other hand, in adults as well as in children with ADHD. (**Chapter II and III**)
b. To investigate the efficacy of daily practice F-NF on core behavioral symptoms, neurocognitive, and global clinical functioning as well as the safety of F-NF in children with ADHD by using a stratified, semi-randomized, double-blind, placebo-controlled treatment design. In addition, the neurophysiological background is addressed.

(**Chapter IV and V**)

c. To investigate the efficacy of CWMT on core behavioral symptoms, neurocognitive, daily executive, and global clinical functioning in young children with ADHD by using a stratified, semi-randomized, triple-blind, placebo-controlled treatment design. (**Chapter VI**)

To this end, data from three different samples were analyzed.

The *first sample* consisted of 24 adults with ADHD (combined subtype), based on the *DSM-IV*, and 24 healthy controls (matched on age, gender, and IQ). Psychiatric comorbidity was allowed, as well as regular use of psychotropic medication, provided the use during the assessments. All adults performed a stop-signal task after recording of a resting-state EEG. Resting-state oscillations were analyzed and further related to the performance on the stop-signal task and the core behavioral symptoms of ADHD (**Chapter II**).

The *second sample* consisted of 41 children (age between 8-15 years) with a primary diagnosis of ADHD (all subtypes), based on the *DSM-IV-TR*, without any other psychiatric disorder (except for ODD and anxiety disorders) or any other serious medical condition. The use of a stable dosage of stimulants and/or atomoxetine was allowed, provided the presence of room for improvement on behavioral level. The children in this sample were semi-randomly assigned to F-NF or placebo-feedback for 30 sessions, twice a week. Assignment was based on stratification on age, electrophysiological state of arousal, and medication use. At baseline, resting-state oscillations were measured. Before treatment and at study end, behavioral measurements were performed and a wide selection of neurocognitive tasks was administered. Baseline resting-state oscillations were explored and analyzed in relation to the performance on the neurocognitive tasks and the core behavioral symptoms of ADHD (**Chapter III**). Efficacy of F-NF was measured by analyzing the difference between groups on core behavioral symptoms and global clinical functioning (**Chapter IV**) and neurocognitive functioning (**Chapter V**) at study end compared to baseline measurements. Furthermore, electrophysiological background was explored by analyzing the oscillations during the sessions (**Chapter V**).

The *third sample* consisted of 51, medication-free children (age between 5-7 years) with a primary diagnosis of ADHD (all subtypes), based on the *DSM-IV-TR,* without any other psychiatric disorder (except for ODD and Pervasive Developmental Disorder Not Otherwise Specified) or any other serious medical condition. Children in this sample were semi-randomly assigned to the active or the placebo condition of the Cogmed JM training program for 25 sessions, five times a week. Assignment was based on stratification on age and gender. At baseline and at study end, behavioral measurements were performed and a comprehensive set of neurocognitive tasks was administered. Efficacy was measured by analyzing the difference between groups on core behavioral symptoms, neurocognitive, daily executive and global clinical functioning at study end, compared to baseline measurements (**Chapter VI**).

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RESTING-STATE OSCILLATIONS IN ADHD

II

Relation between resting EEG to cognitive performance and clinical symptoms in adults with attention-deficit/hyperactivity disorder

Martine van Dongen-Boomsma, Marieke M. Lansbergen, Evelijne M. Bekker, J.J. Sandra Kooij, Maurits van der Molen, J. Leon Kenemans & Jan K. Buitelaar

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) in children is characterized by elevated levels of slow wave activity and reduced fast wave activity in resting-state electroencephalogram (EEG). In adults with ADHD, resting state EEG findings are scarce and inconsistent.

The present study examined whether the disparate findings are due to EEG recording conditions (i.e., eyes-open vs. eyes-closed). A second goal of the current study was to assess relations between EEG spectral indices to performance measures obtained using a stop-signal task, and to behavioral ADHD symptoms. The present study included 24 adults with ADHD and 24 control adults.

The EEG results showed a greater reduction in alpha power from eyes-closed to eyes-open (i.e., alpha attenuation) in ADHD compared to controls. In addition, the theta/beta power ratio was negatively correlated to the speed of responding to choice stimuli.

These findings were interpreted vis-à-vis a biophysical model assuming that the hypo-arousal in ADHD is due to an overdrive of the locus coeruleus resulting in inhibitory activity of the thalamic reticular nucleus.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) affects 5 to 10% of all school-aged children in European countries, and persists into adulthood in one third of the cases or more (Spencer, Biederman & Mick, 2007). According to current views, multiple cognitive deficits contribute to ADHD, such as deficient inhibitory control, impaired attention regulation, deficits in working memory, and problems related to motivation and decision-making (Castellanos, Sonuga-Barke, Milham & Tannock, 2006).

A considerable body of research focused on deficient inhibitory control in ADHD (e.g., Bekker et al., 2005; Lijffijt, Kenemans, Verbaten & van Engeland, 2005). The stop-signal paradigm is a widely used task to assess response inhibition (Logan, 1994). Meta-analyses reported significant deficits in the ability to inhibit responses in children and adults diagnosed with ADHD (mean effect sizes [ESs] range from 0.58 to 0.79) (e.g., Lijffijt et al., 2005). Moreover, it has been demonstrated that in adults with ADHD, the ability to inhibit is specifically impaired over and beyond general deficits in response activation and execution (Lijffijt et al., 2005).

Neurophysiological measures have been a major focus of research in ADHD. Brain electrical activity can be recorded during rest or while individuals perform a cognitive task. In children with ADHD, resting-state electroencephalographic (EEG) studies report elevated levels of slow wave activity, especially theta activity, reduced amounts of alpha, and beta power, as well as higher theta/beta and theta/alpha power ratios compared to control children (Barry, Clarke & Johnstone, 2003). These findings attracted different interpretations. Some authors suggested that these findings pointed to hypo-arousal in children with ADHD compared to controls (Satterfield & Cantwell, 1974; Rowe et al., 2005). Alternatively, elevated theta/beta power ratios in children with ADHD have been interpreted to suggest reduced cortical control over increased subcortical drives (Schutter, Leitner, Kenemans & van Honk, 2006).

Few studies examined resting-state EEG in older individuals with ADHD. The most consistent finding refers to elevated levels of theta activity in adolescents and adults with ADHD (Lazzaro et al., 1999; Bresnahan & Barry, 2002; Hermens et al., 2004; Hermens, Kohn, Clarke, Gordon & Williams, 2005a; Bresnahan, Barry, Clarke & Johnstone, 2006; Hobbs, Clarke, Barry, McCarthy & Selikowitz, 2007; Koehler et al., 2009). Elevated levels of alpha activity have also been reported in adolescents and adults with ADHD (Lazzaro et al., 1999; Bresnahan & Barry, 2002; Koehler et al., 2009). The findings for beta oscillations are far from consistent (Lazzaro et al., 1999; Bresnahan & Barry, 2002; Bresnahan et al., 2006; Hobbs et al., 2007; Koehler et al., 2009). Finally, all studies, except one recent study (Koehler et al., 2009), report an elevated theta/beta power ratio in adolescents and adults with ADHD as compared to controls (Bresnahan & Barry, 2002; Hermens et al., 2005a; Bresnahan et al., 2006; Hobbs et al., 2007). Summing up, the EEG literature relating to older individuals with ADHD yielded disparate findings in contrast to the relatively consistent results reported for children with ADHD.

The apparent discrepancies between children versus adolescent and adult ADHD studies of resting state EEG might be due to various factors, including developmental change, study design, EEG recording, and quantification procedures. In broad outline, it should be noted that the large majority of studies in children refer to EEG recorded when eyes were closed, whereas in three of seven adolescent and adults studies, recordings were done when eyes were open (Lazzaro et al., 1999; Bresnahan & Barry, 2002; Bresnahan et al., 2006).

In order to evaluate this potentially critical factor, the current study will analyze EEG data recorded in adults with ADHD both under eyes-open and eyes-closed conditions. In addition, few studies - and only studies in children and adolescents - examined relations between resting state EEG indices and attention/cognitive performance measures, and those that did assess such relations yielded inconsistent results. One study examining the relation between EEG theta power and performance accuracy on an auditory oddball task in adolescents with ADHD reported a negative correlation for both ADHD individuals and controls (Hermens et al., 2005b). Another study observed a positive relation between theta power and the variability of responses when children with ADHD performed a Conners' continuous performance task (CPT) and a negative relation between alpha and beta power and the incidence of response omissions (Loo & Smalley, 2008). Finally, other investigators failed to obtain significant relations between resting state EEG indices and performance measures obtained when children with ADHD underwent a CPT (Swartwood, Swartwood, Lubar & Timmermann, 2003). In view of the lack of studies examining relations between resting- state EEG and neurocognitive task performance in older individuals with ADHD, the present study will assess relations between resting-state EEG indices obtained under conditions of eyes-open vs. eyes-closed and various performance measures that can be derived from the frequently used stop-signal task (i.e., speed of responding and the efficiency of response inhibition).

A final goal of the current study is to explore the relations between resting-state EEG and behavioral symptoms observed in adults with ADHD. Recently, diminished frontal theta and elevated frontal beta activity have been related to parent behavior ratings of improved attention and hyperactivity/impulsivity in children with ADHD on methylphenidate (Loo, Hopfer, Teale & Reite, 2004). However, another study failed to observe a significant relation between theta activity and ratings of attention in children with ADHD (Swartwood et al., 1998). In conclusion, the relation between resting-state EEG and ratings of behavioral ADHD symptoms is still unclear.

In sum, based on previous studies examining stop-signal performance in individuals with ADHD, we predicted that adults with ADHD would show a slower speed of responding and less efficient response inhibition. In addition, we assumed that the apparent inconsistencies between child versus adult studies of resting-state EEG in individuals with ADHD are related to EEG recording conditions; eyes-open versus eyes-closed. Furthermore, we predicted a negative relation between slow EEG frequencies and performance on the stop-signal task based on the hypothesis that elevated slow resting-state oscillations signals hypo-arousal

(Satterfield & Cantwell, 1974; Rowe et al., 2005) and on findings suggesting reduced performance when attention is sub-optimal (Chee, Logan, Schachar, Lindsay & Wachsmuth, 1989). Finally, we will explore relations between resting-state EEG and ratings of behavioral ADHD symptoms.

Methods

In the current study, we examined data available from a previous study (Bekker et al., 2005). The methods, procedures, and materials have been described in detail elsewhere (Bekker et al., 2005). Here, we will provide only the essentials for the present study.

Twenty-four outpatient adults diagnosed with ADHD combined subtype (34.3 ± 11.68 years; range, 18-57 years; 12 men; 3 left-handed) were matched on age, IQ, and gender with 24 control participants (34.9 years; range, 18-57 years; 12 men; 1 left-handed). A semi-structured interview for adult ADHD (Kooij, 2002), four sections of the Diagnostic Interview Schedule (Robins, Cottler, Bucholz & Compton, 1995), and the computerized Composite International Diagnostic Interview (lifetime version 2.1) (Robins et al., 1988; ter Smitten, Smeets & van den Brink, 1997) were used to evaluate current and childhood ADHD symptoms and co-morbid disorders in all participants (see Bekker et al., 2005). Additionally, all participants filled out translated versions of the Brown ADD Scale (BADDS; Brown, 1996), the Conners' Adult ADHD Rating Scales (CAARS; Conners Erhardt & Sparrow, 1999) and the ADHD Rating Scale-IV (ADHD-RS) for current and childhood ADHD symptoms (DuPaul, Power, Anastopoulos & Reid, 1998). An experienced physician and nurse made the *Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV;* American Psychiatric Association, 1994) diagnosis of childhood-onset and current ADHD combined subtype. For the diagnosis of ADHD, patients must have 1) met the criteria for the diagnosis of ADHD combined subtype in childhood (i.e., 6 out of 9 *DSM-IV* criteria of inattention and 6 out of 9 *DSM-IV* criteria of hyperactivity/impulsivity in childhood), 2) met the criteria for the diagnosis of current ADHD combined subtype (i.e., at least 5 of 9 criteria *DSM-IV* criteria of inattention and 5 out of 9 *DSM-IV* criteria of hyperactivity/impulsivity in adulthood (Kooij, 2002), and 3) experienced impairment in a moderate or severe level attributed to the ADHD symptoms. Controls were excluded if currently suspected of ADHD (scores on the BADDS, CAARS, and the *DSM-IV* Rating Scale had to be below the cut-off point for ADHD), diagnosed with a developmental disorder in childhood (i.e., ADHD, oppositional defiant disorder, conduct disorder, and/or autism), reporting an ADHD diagnosis among relatives, or treated by a health-care professional. Participants gave written informed consent in accordance with the guidelines of the Ethics Committee of the University Medical Center. All further procedures were in compliance with the guidelines of the review board for Scientific Research in Humans of the Faculty of Social Sciences.

Participants performed the stop-signal task after recording resting-state EEG during an eyes-open and eyes-closed condition in a sound-attenuating cabin. The stop-signal task consisted of the presentation of square-wave, black-on-white gratings with a high (4.8 cycles per degree [cpd]) or low (0.6 cpd) fundamental spatial frequency (750 milliseconds [ms]). Participants were required to discriminate between the two gratings and press the correct (left or right) button. Unpredictably, on 40% of the trials, a tone (1000 Hertz [Hz], 80 decibel, 400 ms) was presented binaurally through earplugs, which indicated that the planned response to the grating should be withheld. The delay between go stimuli and stop signals (stimulus onset asynchrony [SOA]) was adjusted using a tracking algorithm to yield about 50% successful inhibitions, corrected for the estimated number of omissions. The time-interval between successive trials varied from 1000 to 1250 ms. There were six trial blocks that contained 76 trials without a stop-signal and 50 trials with a stop-signal. Mean reaction time (MRT) was computed for correct responses to the choice stimulus, excluding extremely fast or slow responses (i.e., < 150 ms and > 1250 ms post-stimulus). The time it takes to inhibit the response to the choice stimulus was estimated using the formalizations associated with the stop-signal task (Logan, 1994). The latency of response inhibition is dubbed stop-signal reaction time (SSRT).

The EEG data were recorded using an elastic cap with 62 tin electrodes referenced to the left mastoid. The ground electrode was placed within the cap between Fpz and Fz. Vertical electrooculogram (VEOG) was recorded from electrodes attached above and below the left eye and the horizontal electrooculogram (HEOG) from the outer canthi of both eyes. Electrode impedance was kept below 5 kOhm. EEG and EOG were amplified with a bandwidth of 0.05-50 Hz. The sampling rate was 1000 Hz. Participants were asked to sit quietly for four minutes (min), two min with eyes-open and two min with eyes-closed, during which resting-state EEG was recorded.

EEG and EOG data were analyzed using Brain Vision Analyzer software (Brainproducts, Gilching, Germany). EEG signals were re-referenced off-line to the average of all electrodes and the sampling-rate was changed to 256 Hz with a notch filter of 50 Hz. The 2-min continuous EEG data were segmented into 2-s epochs, separately for the eyes-open and eyes-closed condition. Trials with artifacts were rejected from further analysis (absolute amplitude criterion of 120 μV; low activity criterion of 0.3 μV within a 50 ms time window) and ocular artifact correction was conducted according to the Gratton et al. algorithm. The average number of EEG epochs used for the Fast Fourier Transform analyses was 51 (SD = 10.6) for the eyes-open and 49 (SD = 12.6) for the eyes-closed condition in the ADHD group and 56.2 (SD = 9.1) for the eyes-open and 57.2 (SD = 4.8) for the eyes-closed condition in the control group. EEG data were Fourier transformed (Hanning window length of 20%) and subsequently ln-transformed. Power estimates were derived from the average for the theta (4-7.5 Hz), alpha (8-12 Hz), and beta (12.5-25 Hz) frequency-bands at frontal (Fz, F3, F4), central (Cz, C3, C4), and parietal (Pz, P3, P4) sites. Theta/beta and theta/alpha power ratios were calculated between the frequency-bands by dividing the power of the lower frequency-

band by the power of the higher frequency-band. Additionally, mean alpha peak frequency (APF) was defined as the frequency at which alpha power was maximum within 7.5-15 Hz over the occipital electrodes (O1, Oz, O2) in the eyes-closed condition. Visual inspection was conducted for peak frequencies occurring at the boundaries of the search window. One adult with ADHD did not show a clear alpha peak and was excluded from the APF analysis. Separate one-way ANOVAs were conducted for MRT, SSRT, and APF to examine group differences. Separate repeated-measures analyses of variance (ANOVAs) were conducted for absolute theta, alpha, and beta power and theta/alpha and theta/beta power ratios with condition (eyes-open vs. eyes-closed), laterality (left, midline, right) and area (frontal, central, parietal), as within-subjects factors, and group (ADHD vs. control participants) as between-subjects factor. We were only interested in (interaction with) group effects. If the omnibus ANOVAs revealed significant interaction effects with group, post-hoc analyses were conducted to examine the group effect. Furthermore, parametric correlation analyses were performed to investigate the relation between task performance (MRT and SSRT) and EEG power values. Additionally, the relation between behavioral symptoms of ADHD and EEG power was examined by computing non-parametric correlation coefficients between EEG power values and the total score of the BADDS, the ADHD index of the CAARS, and the attention-deficit and hyperactivity/impulsivity items in childhood as well as in the last 6 months for the ADHD-RS. The alpha level of significance was set at .01 two-tailed.

Results

As reported in a previous study (Bekker et al., 2005), the ADHD group had longer SSRTs than the control group, $F_{(1,46)} = 7.12$, $p = .010$ (mean ± SD, 185.2 ± 38.9 ms for the control and 237.3 ± 87.2 ms for the ADHD group, respectively). The ADHD group committed more omission errors to the trials without stop-signals relative to the controls, $F_{(1,46)} = 4.24$, $p = .045$ (mean ± SD: 1.22% ± 1.18 for the control and 2.63% ± 3.05 for the ADHD group, respectively)[1], but the groups did not differ regarding MRTs, $F_{(1,46)} = 0.04$, $p = .842$ (mean ± SD, 463.3 ± 68.8 ms for the control and 467.9 ± 87.6 ms for the ADHD group, respectively). *Table 1* (see *supplement)* presents mean theta, alpha, and beta power, and theta/beta and theta/alpha power ratios at midline electrodes, for the eyes-closed and eyes-open condition, separately for the ADHD and control group. ANOVAs did not yield any significant main group effect for theta, alpha, and beta power, for theta/alpha and theta/beta power ratios or APF (all F-values < 1).

We found three significant interaction effects including group. First, a significant group (ADHD vs. control) x area (frontal, central, parietal) x condition (eyes-closed vs. eyes-open) interaction was found for alpha, $F_{(2,92)} = 4.90$, $p = .010$. Post-hoc analyses per area revealed a significant group x condition effect over parietal sites, $F_{(1,46)} = 4.69$, $p = .036$, but not over frontal or central sites. Although parietal alpha activity did not significantly differ between

groups in both conditions, the alpha attenuation from the eyes-closed to the eyes-open condition was significantly greater for the ADHD than the control group (*Figure 1*). Second, a trend for a group x laterality effect was found for theta/beta power ratio, $F_{(2, 92)} = 3.03$, $p = .053$, indicating that the theta/beta power ratio was larger for ADHD than for controls at midline compared to lateral electrodes (*Figure 2*), but group differences did not reach significance at either midline or lateral electrodes ($F < 1$). Finally, a significant group x laterality x condition effect was found for the theta/alpha, $F_{(2, 92)} = 6.73$, $p = .002$. Post-hoc analyses per laterality revealed no significant group x condition effects.

Correlation analyses were conducted to assess relations between EEG and task performance or behavioral symptoms (see *supplement*). Based on the significant interaction effects including group for alpha activity, the theta/beta power ratio, and the theta/alpha ratio, differences in power values were used in the correlation analyses. The reason for using differences in power values in the analyses is to reduce the intra-individual variability in power values. Negative correlations were observed between MRT and the theta/beta power ratio (midline minus lateral; averaged across areas and eyes-closed/open conditions) for both the ADHD and control group ($r = -0.55$, $p = .005$; and $r = -0.62$, $p = .001$, respectively). The theta/alpha ratio (midline minus lateral sites; averaged across areas) also correlated negatively with MRT; for the ADHD group in the eyes-open condition ($r = -0.52$, $p = .010$) and for the control group in the eyes-closed condition ($r = -0.52$, $p = .009$). All other correlations between EEG measures and performance measures or behavioral symptoms failed to reach an acceptable significance level.

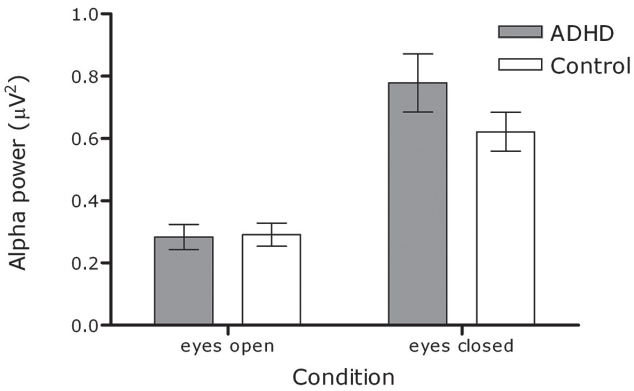

Figure 1 Mean alpha power over parietal sites in the eyes-open and eyes-closed condition for ADHD adults and matched control participants. Error bars represent the standard error of the mean.

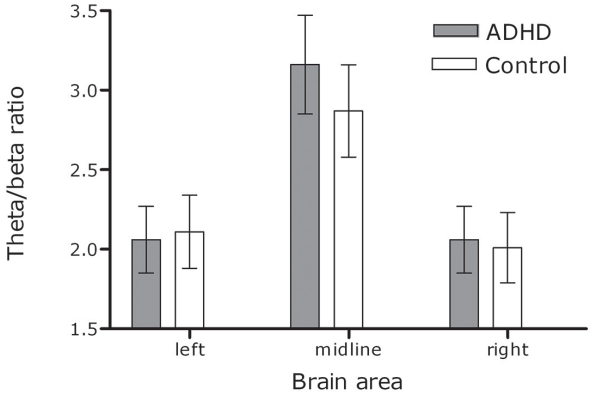

Figure 2 Mean theta/beta power ratio at left, midline and right electrode sites for adults with ADHD and matched control controls. Error bars represent the standard error of the mean.

Discussion

The current study set out to assess resting-state EEG in adults with ADHD and to relate EEG indices to performance measures obtained using a stop-signal task, and to behavioral symptoms characterizing ADHD. The data were derived from a previous report showing that response inhibition was less efficient in the ADHD group compared to controls while the speed of responding did not significantly differentiate between groups.

In contrast to previous studies examining EEG in adults with ADHD, the present study assessed potential EEG differences between individuals with ADHD and controls under both eyes-open and eyes-closed conditions. The current findings indicated that parietal alpha in either condition failed to distinguish between the ADHD group and controls, but the reduction in parietal alpha power between conditions (i.e., alpha attenuation) did discriminate between the groups. This finding seems to underscore the importance of this procedural detail (i.e., eyes-open vs. closed). Note the relatively large difference in parietal alpha power between groups in the eyes-closed, but not in the eyes-open condition. Based on the assumption that alpha activity reflects arousal state (Barry, Clarke, Johnstone, Magee & Rushby, 2007) and the current findings showing that ADHD adults had a greater difference in alpha power in the eyes-closed compared to the eyes-open condition than control adults, we may speculate that adults with ADHD are hypo-aroused during an eyes-closed resting condition (Satterfield & Cantwell, 1974). This interpretation is consistent with the hypo-arousal model of ADHD assuming that individuals with ADHD are cortically hypo-aroused and are seeking external stimulation in an attempt to normalize their arousal level.

The current study did not replicate previous findings of elevated theta power in adolescents and adults ADHD relative to controls (Lazzaro et al., 1999; Bresnahan & Barry, 2002; Hermens et al., 2004; Hermens et al., 2005a; Bresnahan et al., 2006; Hobbs et al., 2007; Koehler et al., 2009). Although theta power was larger for the ADHD than the control group at midline electrodes, these group differences did not reach an acceptable significance level. A possible explanation points to the large variability in theta power across participants, as indicated by high standard errors of the mean (*Figure 2*). The theta/beta power ratio correlated negatively with the ADHD index of the CAARS. The latter finding was unexpected given the recent observation reported by Koehler and colleagues (Koehler et al., 2009), indicating a positive relation between theta and inattention scores on the Adult ADHD Self-Report Scale. Before interpreting this apparent inconsistence, the robustness of the current finding should be established in future research.

The theta/beta and theta/alpha power ratios, although not discriminating between groups, were significantly related to performance in the ADHD and control group; larger ratios were associated with faster responding to the choice stimuli in the stop-signal task. At first glance, the observation of a positive relation between higher EEG ratios and faster responding to the choice stimuli on the stop-signal-task seems at odds with previous findings indicating that patients with ADHD are characterized by higher EEG ratios, most notably the theta/beta power ratio, and with worse performance on the stop-signal task as compared to control participants (Barry et al., 2003; Lijffijt et al., 2005). The current finding, however, should be interpreted in relation to both speed and accuracy. Although groups did not differ in the speed of responding, the ADHD group committed significantly more omission errors relative to the controls (2.63% and 1.22%, respectively). This pattern suggests a speed-accuracy trade-off in the ADHD group; that is, individuals with ADHD are inclined to respond to the choice stimulus before it is completely analyzed. Thus, the current pattern of higher EEG ratios associated with faster responding might index higher levels of impulsivity rather than improved cognitive efficiency. The relation between slow EEG frequencies and impulsivity is consistent with observations that elevated ratios of slow/fast wave EEG activity are associated with risky decision-taking (Schutter & van Honk, 2005). More specifically, it has been suggested that slow EEG frequencies are associated with 'deeper' motivational systems and fast EEG frequencies with 'higher' cognitive systems, such that a balance towards slow frequencies biases the system to response activation whereas a balance to fast frequencies would promote inhibition (Schutter et al., 2006).

To conclude, the current study showed that the alpha attenuation from the eyes-closed to the eyes-open condition was larger in adults with ADHD compared to controls. This finding was interpreted in terms of the hypo-arousal model of ADHD (Rowe et al., 2005). In addition, the current study showed a positive correlation between theta/alpha and theta/beta power ratios and the speed of responding in the stop-signal task. In adults with ADHD this pattern was associated with a higher error rate relative to the control group. This finding was interpreted in relation to previous findings suggesting a relation between an elevated theta/

beta power ratio and impulsive behavior (Schutter et al., 2006). A unified account of both findings is provided by a biophysical model presented by Rowe and colleagues (Rowe et al., 2005). This model assumes that hypo-arousal of the cortex is due to a tonic overdrive of the locus coeruleus resulting in an increase in inhibitory activity of the thalamic reticular nucleus, which in turn results in elevated EEG slow waves. The cortical hypo-arousal affects several mechanisms including the fronto-striatal circuitry implicated in the ability to inhibit pre-potent and premature responses (Bradshaw, 2001). The biophysical model proposed by Rowe and colleagues fitted data from an ADHD-medication study quite well and might open up interesting avenues for future investigations of hypo-arousal and its behavioral consequences in ADHD.

[1] *Note that the proportion of omission errors may violate the assumption of a normal distribution. To obtain more normally distributed values, proportions of omission errors were transformed using the arcsin function: arcsin(SQRT[p]).*

Supplement

Table 1 Mean power (μV^2) and mean power ratios (in parentheses standard error of the mean) at midline electrodes for the ADHD and control group.

		ADHD adults		control adults	
		eyes-open	eyes-closed	eyes-open	eyes-closed
theta	Fz	0.23 (0.10)	0.30 (0.13)	0.22 (0.13)	0.28 (0.16)
	Cz	0.21 (0.07)	0.28 (0.13)	0.21 (0.13)	0.27 (0.17)
	Pz	0.17 (0.07)	0.27 (0.17)	0.17 (0.08)	0.25 (0.14)
alpha	Fz	0.22 (0.15)	0.57 (0.35)	0.22 (0.13)	0.46 (0.25)
	Cz	0.19 (0.13)	0.49 (0.32)	0.19 (0.10)	0.40 (0.21)
	Pz	0.27 (0.17)	0.72 (0.43)	0.31 (0.20)	0.59 (0.30)
beta	Fz	0.08 (0.05)	0.10 (0.07)	0.08 (0.04)	0.09 (0.05)
	Cz	0.08 (0.08)	0.11 (0.08)	0.08 (0.07)	0.10 (0.08)
	Pz	0.08 (0.05)	0.13 (0.08)	0.08 (0.05)	0.11 (0.08)
theta/beta ratio	Fz	3.65 (1.94)	3.35 (1.37)	3.14 (1.47)	3.16 (1.31)
	Cz	3.76 (1.82)	3.32 (1.74)	3.26 (2.11)	3.02 (1.57)
	Pz	2.45 (1.07)	2.41 (1.25)	2.32 (1.09)	2.32 (1.04)
theta/alpha ratio	Fz	1.32 (0.58)	0.63 (0.26)	1.16 (0.60)	0.66 (0.30)
	Cz	1.37 (0.60)	0.66 (0.25)	1.19 (0.58)	0.70 (0.35)
	Pz	0.80 (0.43)	0.44 (0.24)	0.70 (0.41)	0.47 (0.25)

Note: Standard deviations of the mean are given in parentheses.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder.

Correlation analyses

First, parametric correlation analyses were conducted to examine the relation between brain oscillations at rest and task performance (SSRT, MRT). Second, non-parametric correlation analyses were conducted to assess the relations between EEG and behavioral symptoms of ADHD (i.e., total score of the BADDS, ADHD index of the CAARS, and attention deficit and hyperactivity/impulsivity items in childhood and in the last 6 months for the ADHD-RS).

Based on the significant interaction effects including group for alpha activity, the theta/beta ratio, and the theta/alpha ratio, differences in power values were used in the correlation

analyses for these variables to reduce the number of tests and to reduce the intra-individual variability in power values: 1) Parietal alpha power in the eyes-open condition was subtracted from parietal alpha power in the eyes-closed condition, 2) the average theta/beta ratio across conditions and lateral sites was subtracted from the average theta/beta ratio across conditions at midline sites, and 3) the average theta/alpha ratio across lateral sites was subtracted from the theta/alpha ratio at midline sites, separately for the eyes-open and eyes-closed condition. For the correlation analyses with theta and beta power, mean EEG power was calculated per area by averaging over lateral and midline electrodes. To correct for the large number of statistical tests, the alpha level of significance was set at .01 two-tailed. Bonferroni corrections were not conducted, because the test statistics were assumed to be highly dependent.

Tables 2 and *3* show Pearson's correlation coefficients for the relation between EEG and task performance on the stop-signal task. As presented in *Table 2*, a significant positive correlation was obtained for the ADHD group between central beta power in the eyes-open condition and SSRT (r = 0.54, p = .007). However, as illustrated in *Figure 1*, one outlier was mainly responsible for these results. The correlation between SSRT and beta power was not significant anymore in a post-hoc correlation analysis without this outlier (r = 0.32, p = .14).

Table 3 and *Figure 2* present the significant negative relation between MRT and theta/beta ratio for both the ADHD and control group (r = -0.55, p = .005; and r = -0.62, p = .001, respectively). Furthermore, a significant negative correlation was observed between theta/alpha ratio and MRT in the eyes-open condition for the ADHD group (r = -0.52, p = .010) and in the eyes-closed condition for the control group (r = -0.52, p = .009) (see *Table 3* and *Figures 3* and *4*).

No significant correlations were observed between EEG measures and the behavioral symptoms of ADHD.

Table 2 Pearson's correlation coefficients between cognitive performance on the stop-signal task and mean power in the theta and beta band across electrodes, for each brain area (frontal, central and parietal) in the eyes-open and eyes-closed condition, separately for the ADHD and control group.

			ADHD		control	
			SSRT	MRT	SSRT	MRT
theta	eyes-closed	frontal	0.22	0.04	-0.06	-0.16
		central	0.25	0.03	-0.02	-0.25
		parietal	0.18	-0.03	0.11	-0.02
	eyes-open	frontal	0.13	-0.09	-0.11	-0.28
		central	0.22	0.00	-0.09	-0.40
		parietal	0.27	-0.02	-0.00	-0.33
beta	eyes-closed	frontal	0.47*	0.39	0.26	0.13
		central	0.47*	0.39	0.21	0.10
		parietal	0.31	0.27	0.34	0.08
	eyes-open	frontal	0.41*	0.23	-0.12	0.13
		central	0.54**	0.34	0.14	0.09
		parietal	0.42*	0.33	0.36	0.03

* $p < .05$ (two-tailed), ** $p < .01$ (two-tailed).
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; SSRT, stop-signal reaction time; MRT, mean reaction time.

Table 3 Pearson's correlation coefficients between cognitive performance on the stop-signal task and differences in power values, separately for the ADHD and control group.

	ADHD		control	
	SSRT	MRT	SSRT	MRT
parietal alpha (eyes-closed minus eyes-open)	0.15	0.17	0.11	0.21
TB (lateral sites minus midline sites)	-0.29	-0.55**	-0.22	-0.62**
TA eo (lateral sites minus midline sites)	-0.28	-0.52**	0.03	-0.39
TA ec (lateral sites minus midline sites)	-0.15	-0.45*	-0.01	-0.52**

* $p < .05$ (two-tailed), ** $p < .01$ (two-tailed).
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; SSRT, stop-signal reaction time; MRT, mean reaction time, TB, theta/beta power ratio; TA, theta/alpha power ratio; eo, eyes-open; ec, eyes-closed.

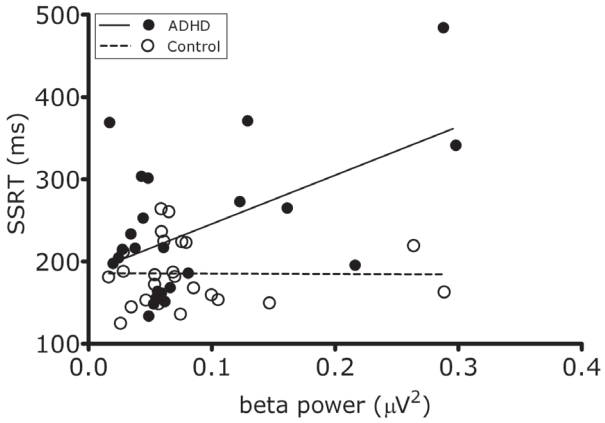

Figure 1 The relation between mean beta power at central sites in the eyes-open condition and stop-signal reaction time (SSRT) for both groups.

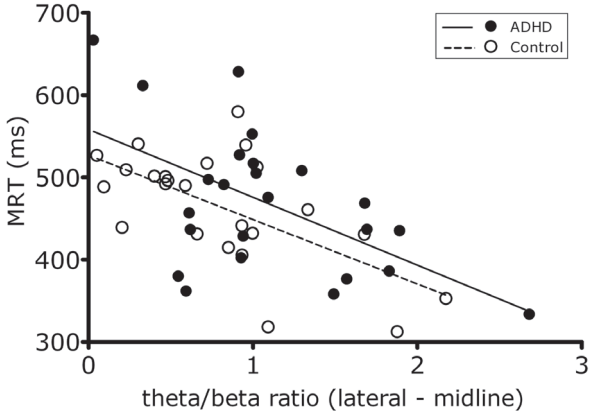

Figure 2 The relation between theta/beta ratio (averaged over conditions; midline minus lateral sites) and mean reaction time (MRT) for both groups.

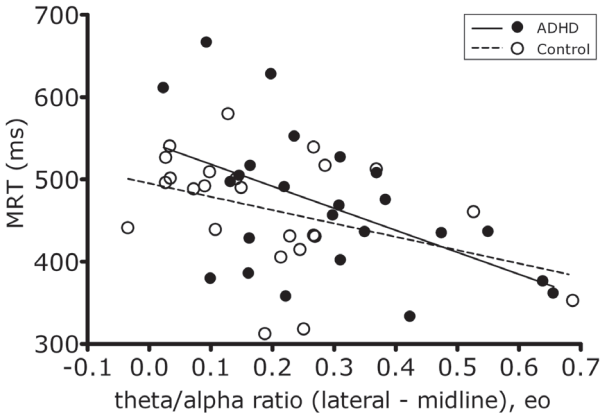

Figure 3 The relation between theta/alpha ratio (midline minus lateral sites) in the eyes-open (eo) condition and mean reaction time (MRT) for both groups.

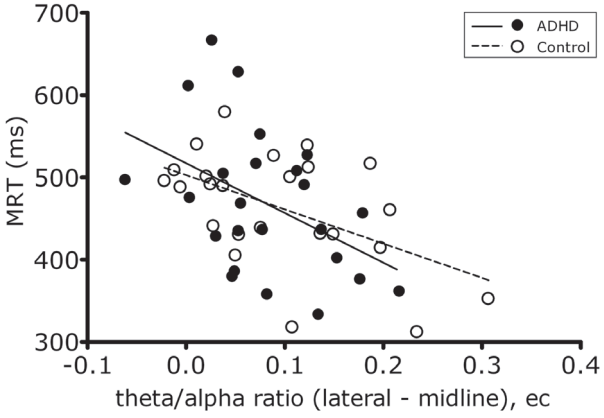

Figure 4 The relation between theta/alpha ratio (midline minus lateral sites) in the eyes-closed (ec) condition and mean reaction time (MRT) for both groups.

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III

How the individual alpha peak frequency helps to unravel the neurophysiological underpinnings of behavioral functioning in children with attention-deficit/hyperactivity disorder

Madelon A. Vollebregt, Martine van Dongen-Boomsma, Dorine Slaats-Willemse, Jan K. Buitelaar* & Robert Oostenveld*

** joint last authors*

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) has been associated with an elevated resting-state theta/beta power ratio and elevated theta power. However, the potential confounding effect of a low individual alpha peak frequency (IAPF) on the theta power estimate has often been disregarded, when studying the relationship between ADHD and the theta/beta power ratio or theta power alone. The current study assessed whether the theta/beta power ratio and relative theta power correlated with behavioral functioning in children with ADHD such as expected from previous work. Subsequently, the influence of IAPF and the amount of supposed overlap between the individually determined alpha-band and the fixed theta-band were studied.

For 38 children (age between 8-15 years) EEG data and investigator-scored ADHD IV Rating Scales were available. Additional neurocognitive data were available for 32 children.

As expected, the theta/beta power ratio and theta were positively related to the ADHD core-symptoms. This relationship strengthened when controlling for IAPF, although correlations did not significantly differ from each other. Eight out of 38 (21%) children showed a supposed overlap between their individually determined alpha-band and the theta-band. Neurocognitive performance did not show any relationship with the theta/beta power ratio or theta.

The results of this study confirmed that the theta/beta power ratio and theta indeed correlated with behavioral symptoms in children with ADHD and underscore the relevance of taking the IAPF into account.

Introduction

Children with attention-deficit/hyperactivity disorder (ADHD) display impairments in sustained attention and set-shifting (Weissman, Chu, Reddy & Mohlman, 2012), response inhibition, vigilance, working memory, and planning (Martinussen, Hayden, Hogg-Johnson & Tannock, 2005; Willcutt, Doyle, Nigg, Faraone & Pennington, 2005), reward processing (Luman, Oosterlaan & Sergeant, 2005; Luman, Tripp & Scheres, 2010), and temporal processing (Noreika, Falter & Rubia, 2013). The persistence of these neurocognitive impairments is clinically relevant for ADHD by their strong association with impairment in global functioning (Biederman et al., 2012).

The past decades, research has been conducted to understand the neurophysiological underpinnings of behavioral (i.e., symptomatic and neurocognitive) functioning in children with ADHD using quantitative electroencephalography (qEEG). A recent meta-analysis of studies on oscillatory activity at the vertex during an eyes-open resting-state condition in children with ADHD, showed that elevated absolute power in the theta-band is reported most consistently in ADHD (Arns, Conners & Kraemer, 2012). Resting-state theta power has been positively correlated with inattention on symptomatic (Loo, Hopfer, Teale & Reite, 2004; Ogrim, Kropotov & Hestad, 2012) and neurocognitive level (Swartwood et al., 1998; Swartwood, Swartwood, Lubar & Timmermann, 2003; Hermens et al., 2005; Loo & Smalley, 2008) and negatively with hyperactive/impulsive symptoms (Ogrim et al., 2012). In addition, a diminished resting-state beta power has been found, although 13-20% of patients with ADHD showed excess beta power or beta spindles (Arns, 2012). Other inconsistent findings suggest that beta power correlated positively with inattention and the overall symptoms-score of ADHD (Ogrim et al., 2012), but correlated positively with impulsivity (Swartwood et al., 1998; Swartwood et al., 2003) and negatively with inattention (Swartwood et al., 1998).

Elevation of the ratio between power in the theta- and beta-band has been regarded as a robust finding at the vertex in children with ADHD compared to controls (Arns et al., 2012). The eyes-closed resting-state theta/beta power ratio showed a weak correlation with inattention symptoms (Loo et al., 2013). Despite its robustness, caution in interpretation is warranted for several reasons (Arns et al., 2012). Firstly, the accuracy of discrimination between ADHD and controls based on this ratio is too low to serve as a diagnostic tool (Monastra et al., 1999; Ogrim et al., 2012). Secondly, although fixed frequency-bands showed a difference in theta/beta power ratio between boys with ADHD and healthy controls, this difference was absent using individual alpha peak frequency (IAPF) to determine individualized frequency-bands (Lansbergen, Arns, van Dongen-Boomsma, Spronk & Buitelaar, 2011). These results suggested the existence of a group with an actual excess of theta power without any IAPF mediation, and another group with a lower IAPF which consequently 'leaks' into the theta-band, causing the theta-band power estimate to falsely inflate when using a fixed frequency-band (Arns, 2012).

IAPF rises until the teenage years in healthy development (Chiang, Rennie, Robinson, van Albada & Kerr, 2011). Developmental change seems an important observation since ADHD is regarded as a neurodevelopmental disorder. Power in the alpha-band has been related to functional inhibition of neuronal activity and processing (Klimesch, Sauseng & Hanslmayr, 2007). A failure to suppress incoming distracting information, hence to modulate alpha power, is per definition a present core-feature of ADHD. Alpha power modulation during task performance indeed has been shown aberrant in children and adults with ADHD (Mazaheri et al., 2010; ter Huurne et al., 2013). Following the inhibition hypothesis, a low IAPF has been hypothesized to slow the process of allowance and stopping of information transfer (Grandy et al., 2013). In the literature, IAPF has been considered low if < 9 Hertz (Hz) for 9-17 and < 8.5 Hz for 6-9 years old children (Arns, Gunkelman, Breteler & Spronk, 2008). Importantly, a low IAPF has been shown to be important by its relation with non-response to stimulant medication in ADHD (Arns, 2012). Furthermore, the IAPF is thought to be trait-like and considerably heritable (Posthuma, Neale, Boomsma & de Geus, 2001; van Beijsterveldt & van Baal, 2002; Smit et al., 2010; Grandy et al., 2013) suggesting that despite changes during development, genetic factors play a lasting role.

Most research regarding these conventional electrophysiological measures focused on a dichotomous difference between ADHD and controls rather than gradual changes. The few studies that focused on gradual changes within ADHD have rather inconsistent methods and results and were not always described in sufficient detail (e.g., concerning the use of absolute or relative power and the use of correction for multiple statistical comparisons). Differences between study designs (e.g., regarding age-range, neurocognitive tasks, and medication use) further complicate comparisons.

The aim of this study was twofold. Rather than making a dichotomous distinction between ADHD and controls, the theta/beta power ratio and theta power were first correlated with behavioral functioning using a broad range of behavioral measures. Although Ogrim and colleagues (2102) found a negative correlation between absolute theta power and hyperactive/impulsive symptoms (rated by teacher), we expected a positive relationship, driven by the elevated theta power found in children with ADHD with an inherent clinical symptom-level of both inattention and hyperactivity/impulsivity. Likewise, a lower performance on neurocognitive tests, with a higher theta/beta power ratio and relative theta power was expected. Second, these relationships were studied while controlling for IAPF, comparing zero-correlations with IAPF controlled correlations. Also, the amount of children showing an IAPF for which overlap between individually determined alpha-band and fixed theta-band can be expected was determined. Taken together, the current study was designed to unravel the confounded interpretation of conventional electrophysiological measurements due to low IAPFs.

Methods

Participants

Data acquired from a clinical trial on EEG-neurofeedback in children with ADHD were examined (http://www.clinicaltrials.gov; NCT00723684). The study was approved by the Dutch Central Medical Ethics Committee (www.ccmo.nl) and conducted in accordance with the declaration of Helsinki. All parents and all children ≥ 12 years gave their written informed consent before participation; children < 12 year gave oral assent. Findings related to treatment efficacy and methodological procedures have been described in detail elsewhere (van Dongen-Boomsma, Vollebregt, Slaats-Willemse & Buitelaar, 2013; Vollebregt, van Dongen-Boomsma, Buitelaar & Slaats-Willemse, 2013). Here, we will provide the information relevant for the present study only.

Children (8-15 years old) with a diagnosis of ADHD classified according to the *Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.; DSM-IV-TR*, American Psychiatric Association, 2000) without any comorbid psychiatric diagnosis (except for oppositional defiant disorder) or any serious other medical condition. Use of ADHD-medication was allowed albeit with clinically significant remaining ADHD symptoms, i.e., at least six inattentive or hyperactive/impulsive symptoms above the clinical threshold.

Behavior

ADHD symptom rating. Total severity of inattentive and hyperactive/impulsive symptoms of ADHD, according to the *DSM-IV-TR* based ADHD Rating Scale IV (ADHD-RS; Zhang, Faries, Vowles & Michelson, 2005), was scored by the investigator in an interview with the parents, using a 4-point Likert scale (0 = never occurs, 1 = occurs sometimes, 2 = occurs often, 3 = occurs very often). The sum per subscale and the sum of all symptoms were used for further analyses.

Neurocognitive performance. Participating children underwent a neurocognitive assessment of approximately 90 minutes (min). Complete task descriptions can be found elsewhere (Vollebregt et al., 2013). Sustained attention was measured with the Sustained Attention Dots task (SA-DOTS), visuospatial memory with Visuospatial Sequencing (VSS), verbal working memory with Digit Span from the Wechsler Intelligence Scale for Children-III, verbal working and long term memory with The Rey Auditory-Verbal Learning Test (RAVLT), instrumental/operant learning with the Instrumental Learning task, precision of time perception with the Time Production task, and precision of time reproduction with the Time Reproduction task.

Electrophysiology

Instruction. EEG was acquired during 10-min eyes-open and 10-min eyes-closed resting-state conditions. Children were instructed to sit quietly and fix their eyes on one spot during the measurement. In between they had a small break.

Data processing. Data were processed and analyzed using MATLAB 2012a (The MathWorks, Inc., Natrick, MA) and the FieldTrip EEG analysis toolbox (Oostenveld, Fries, Maris & Schoffelen, 2011). Data segments showing artifacts such as vertical and horizontal EOG exceeding 100 microvolt, muscle potentials, amplifier or electrode noise, were identified using a semiautomatic routine and excluded from further analysis. When less than two minutes data remained within a dataset, the EEG signal quality was regarded inadequate and the subject was excluded from further analysis.

EEG system. EEG was recorded from 21 scalp electrodes placed according to the 10-20 system using the TruScan EEG system (DEYMED Diagnostic, Payette, ID). Electrode impedance was kept below 10 kOhm. Electrode Fpz was used as ground and the common reference was placed just anterior of electrode Fz. For all, but 8 children EEG data were recorded with a bandwidth of 0.1-102 Hz and the sampling rate was 256 Hz. For 8 children EEG data were recorded with a bandwidth of 0.1-64 Hz and a sampling rate of 128 Hz. Eye movements were not separately recorded but were detectable in the frontal EEG channels.

Electrophysiological procedure. First, spectrally resolved power was calculated using a Fast Fourier Transform. To make an informed choice of analysis parameters and to limit the number of EEG variables, i.e., minimize multiple statistical comparisons for the subsequent analysis, we used literature and a pilot analysis on independent data (see *supplement* for details). These resulted in a selection of relative theta power at the vertex for further analyses. The theta/beta power ratio was included based on literature findings. The condition, electrode position, and bandwidth of theta and beta were chosen to be consistent with (most) studies from the recent meta-analysis on the theta/beta power ratio (Arns et al., 2012); power was estimated at electrode Cz at the vertex for theta (4-8 Hz) and beta (13-21 Hz) frequency-bands in the eyes-open condition, using a time windows of 1 second (sec) and a Hanning taper. The theta/beta power ratio was calculated by dividing the average power over frequency bins within the theta-band by the average power over frequency bins within the beta-band. Theta was derived by dividing the average power over frequencies within the theta-band by the overall power of all frequencies measured at that electrode. As from here, theta/beta power ratio (Θ/β) and theta mentioned together will be abbreviated with Θ&tΘ/β.

To investigate the possibility of alpha-band power leaking into the theta-band estimate, the IAPF was determined. *Figure 1* depicts how the IAPF may confound the estimate of theta using illustrative data from two children. Obviously, higher alpha power influences the theta-band estimate more. However, to limit the number of statistical comparisons, only IAPF was a-priori selected for this study. To yield an accurate estimate of the IAPFs, we constructed a power spectrum with higher resolution than used in the standard analysis. Time windows of 3 sec were Hanning windowed and Fourier transformed, resulting in 1/3 Hz frequency resolution. The IAPF was determined by the maximum power attenuation between the eyes-open and eyes-closed condition within 6-15 Hz at the occipital electrodes (average O1 and O2). All outcomes were checked by visual inspection without prior

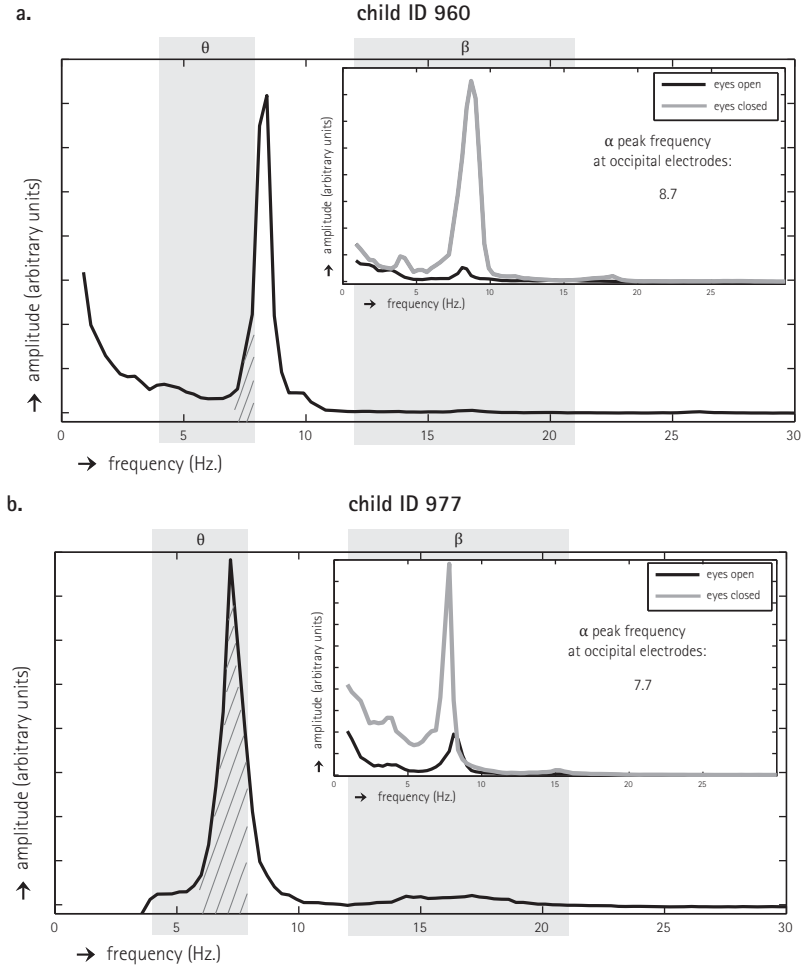

Figure 1 This figure shows two data set examples how activity from the alpha-band may lead to false interpretations of the theta-band power estimate. For illustrative purposes, the 1/f component has been removed from the power spectra in this figure. The striped area under the alpha-curve indicates the area in which alpha power may falsely be estimated as theta power. *Figure a.* depicts a case in which a – somewhat low – alpha peak frequency results in 'leaking into' the theta power estimation. Since the amplitude, hence the power of alpha is at least three times higher than of theta, this small overlap with the theta-band will inflate the theta power estimate. *Figure b.* depicts a case in which the frequency of the alpha peak is clearly low, resulting in even more 'leakage' into the theta power estimation. Note that with a same peak frequency, a higher alpha amplitude (i.e., power) would have a bigger influence on the theta power estimation.

knowledge on any of the other outcome variables. In case of multiple peaks, the peak closest to 10 Hz. was chosen. Next, recognition of the determined peak was verified at the vertex.

Statistics

Statistical analyses were performed with IBM SPSS Statistics, version 20.0 (Armonk, New York; IBM Corp.). The significance level was set at $p = .05$, two-tailed. Imputation was used to deal with random missing data to obtain the most accurate data set (Donders, van der Heijden, Stijnen & Moons, 2006). We largely avoided the multiple comparison problem by performing the partial correlations only on a few electrophysiological variables of interest, predetermined in the independent pilot study.

First, the amount of children with an IAPF < 9 Hz, thereby supposedly displaying an overlap with the fixed 4-8 Hz theta-band, and the correlation between IAPF and theta were determined. Θ&tΘ/β were then correlated with the variables of interest (i.e., variables derived from the ADHD-RS filled out by investigator and the neurocognitive tasks) while controlling for IAPF. Zero-order correlations were compared to correlations after keeping IAPF constant by determining whether a significant relation was revealed or abolished after controlling for IAPF, and by statistically comparing the correlation coefficients using a z-test. Pooled data for imputed data sets do not yield *p*-values. Therefore, for imputed data sets, correlations were reported on pooled data, while significance was determined based on the original data sets.

Results

Demographic and clinical characteristics

Forty-nine children were selected for EEG-measurement. For all children clinical information and scores on the ADHD-RS were available. Six children were excluded due to inadequate EEG-signal quality. Another five children were excluded from the main analyses because a non-comparable EEG-system was used; these data were used for pilot analyses. Hence, for 38 children (10.5 ± 2.6 years, 84.2% boys) the relationship between ADHD-RS rated by investigator and EEG data were analyzed. Six children were excluded from the treatment study, consequently lacking administration of the neurocognitive test-battery in these children. For the remaining 32 children (mean age 10.6 ± 2.2, 81.3% boys) neurocognitive measurements were available. An overview of the selection procedure is depicted in *figure 1* of the *supplement*. Descriptive characteristics can be found in *table 1* of the *supplement*. Imputation of missing data was used for the SA-DOTS and VSS (3.12%) and the Time Reproduction task (6.25%).

Overlap between individual alpha-band and relative theta power

In line with our hypothesis, eight children (21%) showed an IAPF < 9 Hz, supposedly creating an overlap between the individual determined alpha-band and the conventionally defined theta-band (4-8 Hz). Consequently, a significant negative correlation was found between the IAPF and theta (r =-.412, p = .010) which disappeared after excluding these eight children from analyses (r = -.280, p = .133). Eight additional children (another 21%) showed an IAPF of 9 Hz, potentially creating a slight overlap (see *Figure 1a*).

Partial correlations

Significant relationships were found between theta and part of the ADHD symptoms (inattentive symptoms: r = .112, p = .505; hyperactive/impulsive symptoms: r = .344, p = .034; total symptoms: r = .315, p = .054). These became stronger after controlling for IAPF (inattentive symptoms: r = .272, p = .104; hyperactive/impulsive symptoms: r = .396, p = .015; total symptoms: r = .427, p = .008). Similarly, significant relationships between the theta/beta power ratio and part of the ADHD symptoms (inattentive symptoms: r = .212, p = .202; hyperactive/impulsive symptoms: r = .312, p = .057; total symptoms: r = .335, p = .040) became stronger after controlling for IAPF (inattentive symptoms: r = .307, p = .065; hyperactive/impulsive symptoms: r = .331, p = .045; total symptoms: r = .392, p = .017). The differences between the zero-order and IAPF-controlled correlations were non-significant. Also, no significant relationships were found between the ΘεtΘ/β and any of the neurocognitive measures with or without controlling for IAPF. Results can be found in *table 2* of the *supplement*.

Discussion

In this study a gradual reference framework was used by correlating ΘεtΘ/β with behavioral functioning in children with ADHD. Furthermore, it was investigated whether IAPF influenced this correlation by keeping IAPF variability constant. The hypotheses that led us to conduct this study were twofold; 1) positive relationships between ΘεtΘ/β and clinical symptoms were expected based on the robust finding of elevated theta power in children with ADHD with an inherent clinical symptom-level of inattention and hyperactivity/impulsivity; a similar expectation was suggested regarding deviation of accompanying neurocognitive ADHD-characteristics, 2) the IAPF was hypothesized to influence these relationships by showing a supposed overlap between individually determined alpha-band and fixed theta-band in part of the children, thereby potentially falsely overestimating theta.

In line with a dichotomous difference between ADHD and controls found in previous studies (see the meta-analysis by Arns and colleagues, 2012) and as expected, a positive relationship was found between theta/beta power ratio and the total and hyperactive/impulsive symptom score on the ADHD-RS. In addition, also expected, a positive relationship was

found between theta and hyperactive/impulsive symptoms. Twenty-one percent of the children in our study showed a supposed overlap between the individually based alpha-band and fixed theta-band. Consequently, IAPF and theta correlated moderately. As hypothesized, all relationships between the Θ&tΘ/β, and core-symptoms of ADHD became stronger when controlling for IAPF. However, the differences between zero-correlations and IAPF-controlled correlations were non-significant. Still, the relationship between theta and total symptom score after controlling for IAPF changed from non-significant to a strong significant correlation. In contrast to what was expected, neurocognitive performance did not show any relationship with Θ&tΘ/β.

On symptomatic level, results confirmed our hypotheses; the Θ&tΘ/β were related to core-symptoms of ADHD and controlling for IAPF influenced these relationships. The direction of the results however, was different from what would be expected based on literature. Lansbergen and colleagues (2011) found that a dichotomous difference between ADHD and controls was *lacking* when taking into account the IAPF. To come to this conclusion, the theta frequency-band in that study was determined using IAPF as anchor point (0.4*IAPF-0.6*IAPF). A shift of IAPF however, does not necessarily imply a proportional shift of the other frequency-bands, among them the theta-band. Application of this method on the current example data sets showed that the theta-band in *Figure 1a.* would become 3.5-5.2 Hz, resulting in an estimation of the theta-band based on the theta-band as well as an additional lower peak. The theta-band in *Figure 1b.* would become 3.1-4.7 Hz, resulting in an underestimation of theta since not the entire theta-band would be covered by this new determined band. Although the results of Lansbergen and colleagues illustrated that the IAPFs differ enough from 10 Hz to shift the bands away from the dichotomous difference, the results do not necessarily imply an actual lack of the dichotomous difference from the 'normative' theta- and beta-band. The current study aimed at unraveling the influence of the IAPF-based alpha-band on the fixed theta-band of 4-8 Hz. By using a fixed theta-band comparable to the majority of previous studies (Arns et al., 2012), and an individual alpha-band comparable to Lansbergen and colleagues, we were able to show that the relationship between the conventional Θ&tΘ/β, and core-symptoms of ADHD became stronger when controlling for IAPF rather than eliminated.

The hypothesis of a relationship between Θ&tΘ/β and neurocognitive results could not be confirmed by this study, which might be explained in different ways. Although neurocognitive deficits have been recognized in ADHD, without partitioning the neurocognitive heterogeneity within the group of children with ADHD (Nigg, 2005), the measures might not be sensitive enough to detect relationships such as with Θ&tΘ/β. Furthermore, both neurocognitive and neurophysiological measurements are more vulnerable for transient state effects due to the short duration of measurement than a behavioral measurement, which is based on a significantly longer time period (Kendler & Neale, 2010). Consequently, transient state effects might be smallest in the confirmed behavioral hypotheses.

The interpretation of our findings should take into account a number of limitations. First, medication use has shown to have a large impact on the EEG activity in children with ADHD (Swartwood et al., 1998; Loo et al., 2004). The majority of the children in our sample used medication; yet, all children nevertheless displayed symptoms in the clinical range, meaning that medication-use did not diminish ADHD-symptoms sufficiently. Also, our sample size and hence the statistical power were relatively small. This prohibited analyses of neurocognitive subtypes as suggested in the literature (Nigg, 2005). To control the false alarm rate for the statistical inference, we a-priori chose a limited number of electrophysiological variables based on previous studies and our pilot-analysis. These choices restricted the analyses to one electrode, enlarging the potential influence of noise and disallowing topographical localization of the measures. The lack of a relationship between neurocognitive results and other measures questions whether causal claims can be made about different characteristics of ADHD; in particular the directionality and nature of relationship between core-symptoms, neurocognitive characteristics, and neurophysiology (Kendler & Neale, 2010). Simultaneous measurement of neurocognition and neurophysiology might give more insight as to whether these are part of a similar causal pathway; an important question that needs to be addressed in the future (Kendler & Neale, 2010). As a last remark, this study was performed under the assumption that findings can be captured within frequency-bands with independent functions. A more integrated analysis will contribute to a more full understanding of the underlying neurophysiology. In conclusion, this study confirmed the influence of IAPF on the conventional EEG measures in ADHD. Until now, resting-state EEG research in ADHD has been primarily focused on fixed theta- and beta-band; future research should expand to studying individualized frequency band patterns.

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Supplement

Independent pilot study

To make an informed choice of analysis parameters and to limit the number of EEG variables, i.e., minimize multiple comparisons for the subsequent analysis, we used literature and a pilot analysis on independent data. These data came from children participating in the selection procedure from the same clinical trial, that were a priori excluded from analysis due EEG-recording with a non-comparable EEG system (n = 5, all data available n = 4). In these subjects EEG was recorded from 32 scalp electrodes placed according to the 10-20 system using the Acticap and BrainAmp system (Brain Products GmbH, Munich). The left mastoid (earlobe) was used as online reference, offline the data were referenced to linked mastoids (earlobes). Electrode Fpz was used as ground. Electrode impedance was kept below 10 kOhm. The sampling rate was set to 256 Hz.

Regarding theta power, the pilot results showed – in line with the literature (Boutros, Fraenkel & Feingold, 2005) – that relative rather than absolute theta power was more predictive. Relative power is less sensitive to individual variation (accounting for the variation in thickness and resistance of the skull). The analyses suggested no relationship between the behavioral measures and absolute or relative beta power, consistent with the ambiguous findings in the literature (Arns et al., 2012), although possibly also due to the small pilot sample size. Alpha activity is generally observed strongest in the visual/occipital regions when closing the eyes. To verify whether individualized alpha frequencies (IAPFs) could also be derived from the vertex, the method to derive the IAPFs was applied to occipital and vertex electrodes. The pilot data showed that it was possible to identify the IAPF at the vertex.

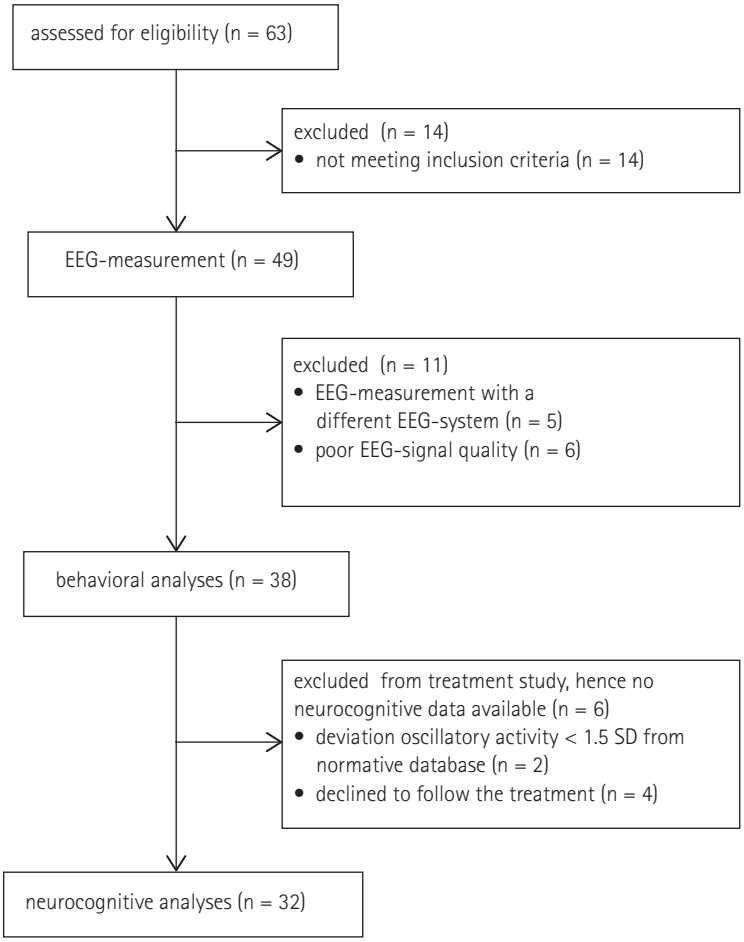

Figure 1 CONSORT flow diagram of study participants.

Abbreviations: CONSORT, Consolidated Standards of Reporting Trials, n, number; EEG, electroencephalographic; SD, standard deviation.

Table 1 Descriptive characteristics

descriptive characteristics	EEG analyses	
	core symptoms analyses (n = 38)	neurocognitive analyses (n = 32)
age, m (SD), y	10.5 ± 2.6	10.6 ± 2.2
gender, n (%)		
male	32 (84.2)	26 (81.3)
race, n (%)		
Caucasian	36 (94.7)	30 (93.8)
Black	2 (5.3)	2 (6.3)
handedness, n (%)		
right	34 (89.5)	29 (90.6)
left	4 (10.5)	3 (9.4)
full scale IQ, m (SD)	104.5 ± 17.1[x]	103.8 ± 15.9
medication for ADHD, n (%)		
psychostimulants	21 (55.3)	18 (56.3)
atomoxetine	1 (2.6)	1 (3.1)
no medication	16 (42.1)	13 (40.6)
melatonin, n (%)	8 (21.1)	7 (21.9)
ADHD subtype, n (%)		
combined	27 (71.1)	23 (71.9)
inattentive	10 (26.3)	8 (25.0)
hyperactive/impulsive	1 (2.6)	1 (3.1)
comorbidity, n (%)		
oppositional defiant disorder	5 (13.2)	5 (15.6)
anxiety disorders	4 (10.5)	3 (9.4)
dyslexia	5 (13.2)	2 (6.3)
ADHD-RS, m (SD)		
total score	32.2 ± 9.2	32.2 ± 8.8
inattentive symptom score	18.3 ± 4.1	18.3 ± 4.2
hyperactive/impulsive symptom score	13.8 ± 7.0	13.9 ± 6.9

Note: [x] indicates that the n is two points lower than the rest.
Abbreviations: EEG, electroencephalographic; n, number; m, mean; SD, standard deviation; y, years, IQ, Intelligent Quotient; ADHD-RS, ADHD Rating Scale IV.

Table 2 Partial correlations

test variables	no control IAPF		control IAPF	
	Θ/β	Θ	Θ/β	Θ
ADHD-RS				
total symptoms	.335*	.315	.392*	.427**
inattentive symptoms	.212	.112	.307	.272
hyperactive/impulsive symptoms	.312	.344*	.331*	.396*
SA-DOTS[x]				
mean response time	.046	-.007	.034	-.057
standard deviation of response time	-.105	-.060	-.126	-.133
number of hits	.121	-.010	.186	.165
number of correct rejections	.015	-.126	.052	-.009
VSS[x]				
number of correct trials	-.169	-.111	-.147	.003
number of identified targets	-.227	-.196	-.210	-.111
number of identified targets in correct order	-.121	-.051	-.095	.073
number of false alarms	.236	.210	.220	.125
Digit Span-WISC-III				
forward repetition of digits	-.085	-.075	-.052	.071
backward repetition of digits	-.027	.110	-.004	.212
RAVLT				
direct recalled words	.177	-.021	.171	-.052
delayed recalled words	-.065	-.162	-.057	-.141
Instrumental Learning task				
high reward % targets chosen in reward condition	.098	-.029	.116	.030
high reward % target chosen in neutral condition	.075	-.107	.088	-.067
reach learning criterion in reward condition	-.158	.105	-.154	.131
reach learning criterion in neutral condition	-.096	-.110	-.110	-.163
Time Production task				
mean deviation	.082	.019	.082	.020
standard deviation from mean deviation	-.002	-.075	.019	-.004
Time Reproduction task[x]				
mean deviation	.055	.111	.044	.039
standard deviation from mean deviation	.025	.110	.014	.049

* $p \leq .05$, ** $p \leq .01$.

Note: [x] indicates that the r is displayed for pooled results after imputation.

Abbreviations; IAPF, individual alpha peak frequency; Θ, relative theta power; Θ/β, theta/beta ratio; ADHD-RS, ADHD Rating Scale IV; SA-DOTS, Sustained Attention Dots task; VSS, Visuospatial Sequencing; Digit Span-WISC-III, Digit Span from the Wechsler Intelligence Scale for Children-III; RAVLT, Rey Auditory-Verbal Learning Test.

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NON-PHARMACOLOGICAL INTERVENTIONS IN CHILDREN WITH ADHD

Frequency neurofeedback

IV

A randomized placebo-controlled trial of electroencephalographic (EEG) neurofeedback in children with attention-deficit/hyperactivity disorder

Martine van Dongen-Boomsma, Madelon A. Vollebregt, Dorine Slaats-Willemse*
& Jan K. Buitelaar*

** joint last authors*

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Abstract

A double-blind, randomized, placebo-controlled study was designed to assess the efficacy and safety of electroencephalographic (EEG) neurofeedback in children with attention-deficit/hyperactivity disorder (ADHD). The study started in August 2008 and ended in July 2012 and was conducted at Karakter Child and Adolescent Psychiatry University Centre in Nijmegen, The Netherlands.

Forty-one children (8-15 years) with a *DSM-IV-TR* diagnosis of ADHD were randomly assigned to EEG-neurofeedback or placebo-neurofeedback treatment for 30 sessions, given as 2 sessions per week. The children were stratified by age, electrophysiological state of arousal, and medication use. Everyone involved in the study, except the neurofeedback therapist and the principal investigator, was blinded to treatment assignment. The primary outcome was the severity of ADHD symptoms on the ADHD Rating Scale IV, scored at baseline, during treatment, and at study end. Clinical improvement as measured by the Clinical Global Impressions-Improvement (CGI-I) scale was a secondary outcome.

While total ADHD symptoms improved over time in both groups ($p < .001$), there was no significant treatment effect, i.e., group x time interaction ($F_{(1,39)} = 0.36$, $p = .554$); the same was true for clinical improvement as measured by the CGI-I scale ($p = .092$). No clinically relevant side effects were observed. Among the children and their parents, guessing treatment assignment was not better than chance level ($p = .224$ for children, $p = .643$ for parents).

EEG-neurofeedback was not superior to placebo-neurofeedback in improving ADHD symptoms in children with ADHD.

Trial Registration: ClinicalTrials.gov identifier: NCT00723684.

Introduction

A substantial proportion of children with attention-deficit/hyperactivity disorder (ADHD) fails to respond favorably to the first-line treatment medication (Brown et al., 2005). Indications that long-term use of medication affects growth, neural functioning and the cardiovascular system (Graham et al., 2011) and the absence of evidence for long-term efficacy of medication for ADHD (Spencer, Biederman, Wilens & Faraone, 2002; van de Loo-Neus, Rommelse & Buitelaar, 2011) points to the need for non-pharmacological treatment options.

Electroencephalographic (EEG) neurofeedback is such an option. With EEG-neurofeedback, the hypothesis is that voluntary modulation of specific brain activity patterns can be learned by operant learning strategies via provision of continuous real-time feedback, i.e., positive reinforcement when changes are made in the desired direction, through visual and/or acoustic signals representing the brain activity (Gevensleben, Rothenberger, Moll & Heinrich, 2012). Most often, the aim of EEG-neurofeedback is to increase beta activity (or sensorimotor rhythm (SMR), 12-15 Hz over the motor cortex), while suppressing theta activity (Monastra et al., 2005). This goal is based on the observation that slow-wave activity (primarily theta [4-7 Hz]) is increased and fast-wave activity (beta [12-30 Hz]) is decreased in most patients with ADHD (see the review by Barry et al, 2003). Different EEG-neurofeedback treatment protocols are in use. For example, a predetermined protocol (mostly a theta/beta protocol) can be used that does not necessary require pre-treatment EEG analysis to assess the individual resting-state EEG. Alternatively, a pre-treatment quantitative electroencephalogram (qEEG) analysis is performed, and, after comparison of findings with those from a normative database, a personalized treatment protocol focusing on the resting-state EEG features of that individual is drawn up. The first method has the advantage that a standardized treatment protocol is used, and the second has the advantage that treatment is personalized and targeted to the specific EEG deviations of that individual.

Recent reviews are reserved about the efficacy of EEG-neurofeedback in children with ADHD, despite the finding of medium to large effect sizes (ESs), mainly because of methodological shortcomings of the studies (Gevensleben et al., 2012; Lofthouse, Arnold, Hersch, Hurt & DeBeus, 2012; Lofthouse, Arnold & Hurt, 2012; Moriyama et al., 2012). Although the most recent published studies have more robust methodological designs, only 3 of more than 20 published randomized controlled trials (RCTs) included a placebo condition (Perreau-Linck, Lessard, Levesque & Beauregard, 2010; Lansbergen, van Dongen-Boomsma, Buitelaar & Slaats-Willemse, 2011; Arnold et al., 2012). A systematic review and meta-analysis of RCTs of non-pharmacological interventions in children with ADHD reported non-significant results for the blinded rating of symptoms ($p = .07$) (Sonuga-Barke et al., 2013). Moreover, none of the three published placebo-controlled trials showed EEG-neurofeedback to be superior to placebo-neurofeedback. The question whether EEG-neurofeedback is a safe treatment has still to be addressed. As far as we know, our pilot study was the first to systematically monitor safety (Lansbergen et al., 2011).

At the time our study was designed and begun, EEG-neurofeedback was thought to be a promising treatment for ADHD. So, we expected significant improvement of ADHD symptoms after EEG-neurofeedback compared to placebo-neurofeedback.
This current study is a valuable addition to the existing literature because of a larger study sample, the use of qualified neurofeedback therapists, the double-blind design and the inclusion of only participants with a deviant pre-treatment EEG. The latter made it possible to apply personalized EEG-neurofeedback.
In sum, the present, double-blind, randomized, placebo-controlled trial was designed to critically evaluate the efficacy in reducing ADHD symptoms and the safety of EEG-neurofeedback in children with ADHD. The study was registered on ClinicalTrials.gov (identifier: NCT00723684).

Methods

Trial design

This study started as a triple-blind, placebo-controlled treatment trial, with stratified randomization for age (younger vs. older than 12 years), electrophysiological state of arousal (hyper-arousal vs. hypo-arousal), and use of medication (with vs. without medication). After our pilot study (Lansbergen et al., 2011), we made 2 changes: (1) Automatically adjusted reward thresholds in the EEG-neurofeedback condition were changed into manually adjusted reward thresholds, with the consequence that the neurofeedback therapist was no longer blinded to treatment assignment; note that the children, their parents and teachers, and the raters were still blinded to treatment assignment. (2) Active learning strategies were introduced, so that children could integrate the learned strategies into daily life.
Children with ADHD were stratified and then randomly assigned in a double-blind manner (1:1 assignment using random block sizes of two) to either EEG-neurofeedback or placebo-neurofeedback (treatments to be given twice per week for a total of 30 sessions). The assignment was done by the principal investigator, who was not involved in data collection. All people involved in the study were blinded to treatment assignment, with the exception of the neurofeedback therapist and the principal investigator, who were not involved in data collection, data entry, and data analysis. Since both participants and raters were still blinded to treatment assignment, this study was labeled as double-blind.

Participants

Children (aged 8-15 years) were included if 1) they had been clinically diagnosed with ADHD according to the *Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.; DSM-IV-TR*, American Psychiatric Association, 2000), 2) they had an (estimated) full-scale intelligence quotient (IQ) of at least 80, 3) their qEEG, a technique to produce a visual map of different frequencies and locations of a signal measured from the brain using EEG,

deviated at least 1.5 standard deviations (SDs) from normative data, 4) they did not use psychoactive drugs, or they used a stable dose of psychostimulants or atomoxetine, and 5) there was room for improvement, defined as a minimum score of 2 on a 4-point Likert scale for at least 6 items of the ADHD Rating Scale IV (ADHD-RS; Zhang, Faries, Vowles & Michelson, 2005). Children were excluded if they 1) were involved in individual or group psychotherapy, 2) used medication other than psychostimulants or atomoxetine, 3) had a comorbid disorder other than oppositional defiant disorder or any anxiety disorder, 4) had a neurological disorder and/or a cardiovascular disease, 5) participated in another clinical trial at the same time, 6) had received EEG-neurofeedback in the past, or 7) used alcohol or drugs.

Psychostimulants or atomoxetine were permitted because the majority of severely affected children with ADHD in The Netherlands uses medication. The discontinuation of medication would have been ethically questionable due to the consequence of withholding an evidence-based treatment; moreover, the exclusion of children on medication would have limited the generalizability of findings.

A psychologist or doctor screened potential participants for eligibility by asking their parents a number of questions over the telephone. Current ADHD symptoms and other psychiatric symptoms were checked. The Dutch version of the Autism Screening Questionnaire (ASQ; Berument, Rutter, Lord, Pickles & Bailey, 1999) was used to screen for autism spectrum disorders. Children who screened positive for ADHD symptoms underwent an extensive diagnostic procedure, including the ADHD-RS and a developmental and psychiatric interview with a child and adolescent psychiatrist, who confirmed the diagnosis on the basis of the findings. The presence of comorbid disorders was assessed with the Diagnostic Interview Schedule for Children (Shaffer, Fisher, Lucas, Dulcan & Schwab-Stone, 2000; Steenhuis, Serra, Minderaa & Hartman, 2009). General functioning was measured using the Children's Global Assessment Scale (CGAS; Shaffer et al., 1983), and the severity of ADHD was assessed with the Clinical Global Impressions-Severity Scale (Guy, 1976). If intelligence had not been assessed in the past 1.5 years, two subtests of the Wechsler Intelligence Scale for Children 3rd Edition (WISC-III) were administered (i.e., Vocabulary and Block Design) to estimate intelligence (Wechsler, 1949, 1989, 1991). Finally, a 20-minutes (min) EEG was recorded to assess whether the child's qEEG deviated from the NeuroGuide normative database (Thatcher, 1998).

As predetermined, recruitment started in August 2008 and ended in May 2012. Children were recruited from among referrals to Karakter Child and Adolescent Psychiatry University Centre in Nijmegen, The Netherlands, and from responders to advertisements in the magazine Balans (the Dutch association of parents with children with learning or behavioral disorders). The study was approved by the Dutch Central Medical Ethics Committee (www.ccmo.nl) and conducted in accordance with the Declaration of Helsinki. All parents and all children older than 12 years gave their written informed consent before participation; children younger than 12 year gave oral assent. Travel expenses were partially reimbursed.

All children received a gift certificate worth 10 euro and a small present during evaluation. Sample size was calculated for the primary outcome, on the basis of the following considerations. Double-blind, placebo-controlled trials have shown an ES of 0.6 or more for the first-line treatment of ADHD with medication (Michelson et al., 2002; Faraone & Buitelaar, 2010). Pilot open-label studies with EEG-neurofeedback also report an ES of about 0.6 (Fuchs, Birbaumer, Lutzenberger, Gruzelier & Kaiser, 2003). With an alpha error of .05, we calculated that a sample of 60 children in the EEG-neurofeedback arm and 60 in the placebo-neurofeedback arm would enable us to detect treatment effects with an ES of 0.5 and a power of 80.0%.

Interventions

The Neurofeedback Instituut Nederland provided the EEG-neurofeedback and placebo-neurofeedback training. Individualized EEG-neurofeedback protocols based on visual inspection of the raw EEG and qEEG were used for EEG-neurofeedback training.

To determine whether EEG data deviated from the NeuroGuide database, a minimum of 10 minutes of de-artifacted raw EEG per condition (i.e., eyes-open and eyes-closed) was acquired. The aim of the EEG-neurofeedback training was to normalize power within individually determined frequency bands and electrode sites by receiving feedback on their real-time EEG signal. During the 45-min sessions, after preparation, the children watched a film for 20 min while sitting quietly on a chair in an 'active focusing state' with eyes open. They were instructed to try to self-regulate their brain activity by receiving positive feedback. Positive feedback was provided by brightening the computer screen and by presenting auditory tones. Most children in the EEG-neurofeedback group were trained to increase the presence of SMR or low-beta activity while simultaneously suppressing the presence of theta activity, meaning that when the production of SMR remained above threshold and/or the theta/beta remained below threshold positive feedback was given. Reward threshold levels were manually adjusted so that the child was rewarded about 80% of the time (i.e., received positive feedback). Consequently, the amount of reward remained at about the same level across sessions and across groups. An identical procedure was provided in the placebo-neurofeedback group, except that children in the placebo-neurofeedback group received feedback on a simulated EEG signal, consisting of a random signal similar to real EEG. BrainMaster Atlantis hardware and software were used to provide both training modalities (BrainMaster Technologies; Bedford, Ohio). Feedback on real EEG and simulated EEG signals seemed similar, in experiences in an earlier study (Logemann, Lansbergen, van Os, Bocker & Kenemans, 2010) and in our pilot study (Lansbergen et al., 2011), such that participants did not know whether they had received real or placebo-neurofeedback.

At each session the child was given a sticker, and 30 stickers were rewarded, with a small present given at the last appointment.

Recruitment and assessments were performed at Karakter Child and Adolescent Psychiatry University Centre in Nijmegen, The Netherlands.

Outcomes

Efficacy measures

The primary endpoint was efficacy, measured as the difference before and after training of the total severity of inattentive and hyperactive/impulsive symptoms of ADHD according to the ADHD-RS, scored by the investigator in an interview with the parents at baseline; after 6, 10, and 20 sessions, and at study end, using a 4-point Likert scale (0 = never occurs, 1 = occurs sometimes, 2 = occurs often, 3 = occurs very often). Additional analyses were performed for teacher-reported symptoms conducted on the ADHD-RS at baseline, after 10 and 20 sessions, and at study end. The Clinical Global Impressions-Improvement scale (CGI-I) (Guy, 1976), a widely used scale to evaluate clinical effects in intervention studies, was administered in a final interview by the investigator and was used as an additional outcome measure. The CGI-I consists of a single item 7-point scale (1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse). Responders were defined as children who were rated as very much improved or much improved. Another outcome measurement was the global improvement in functioning, which was assessed as the difference between baseline and end-of-study scores on the CGAS (scale 0–100, with 0 = most affected global functioning and 100 = best global functioning).

Safety measures

Potential adverse effects of the intervention were measured with the Pittsburgh Side Effects Rating Scale (PSERS), a scale often used in drug treatment studies (Pelham et al., 1993; Sandler & Bodfish, 2008), using the total score for all items (4-point scale: 0 = not present, 1 = mild, 2 = moderate, 3 = severe) at baseline, in between, and at study end (Pelham et al., 1993; Sandler & Bodfish, 2008). For this study, three items were added to the original scale, i.e., epileptic seizures, nausea, and feeling agitated. Side effects on sleep quality were assessed by summing the scores of 14 insomnia items on the Dutch version of the Sleep Disorders Questionnaire (SDQ) (Sweere, 1998) (5-point scale: 0 = never, 1 = rarely, 2 = sometimes, 3 = usually, 4 = always) at baseline and at study end.

Feasibility outcome

Parents and children were asked about their experience with the training and whether they thought the child had received EEG-neurofeedback or placebo-neurofeedback training.

Statistical methods

Statistical analyses were performed with the IBM SPSS Statistics, version 20.0 (Armonk, New York; IBM Corp.). For each parameter, mean and SD were computed. The significance level was set at $p = .05$ (two-tailed). Repeated-measures analyses of variance, with time as within-subjects factor and group (EEG-neurofeedback vs. placebo-neurofeedback) as between-subjects factor were performed separately for the sum of inattentive symptoms,

the sum of hyperactive/impulsive symptoms, the sum of all symptoms on the ADHD-RS, the total sum of adverse events (PSERS), the total sum of sleep problems as rated by the SDQ, and the CGAS. For the analysis of the ADHD-RS scores, as rated by the investigator, the within-subjects factor time had five levels (i.e., baseline, after 6, 10, and 20 sessions, and at study end). For the analysis of the teacher-rated ADHD-RS, the PSERS, the SDQ, and the CGAS, the within-subjects factor time had two levels (i.e., baseline and study end). Differences between the groups on the CGI-I at study end were tested by a t-test. Post-hoc analysis of covariance was performed with the covariates gender, age, medication, and electrophysiological state of arousal.

In preliminary analyses, the efficacy and safety of the EEG-neurofeedback treatment of the first 8 patients (automatic thresholding, no implementation of active learning strategies) and of another 14 patients (manual thresholding and implementation of active learning strategies) were assessed. As there were no differences in efficacy and safety between these two groups, the data of the two series of EEG-neurofeedback were summed, and results for the whole sample are reported.

Results

Demographic and clinical characteristics

In total, 63 children and their parents were eligible for the study and were examined clinically (*Figure 1*). Twenty-two subjects were excluded. One child withdrew during selection. Four children were included but not enrolled; just before training started, the parents and/or child decided to withdraw because it was difficult fitting the sessions into their daily schedule. Seventeen children either did not meet the inclusion criteria or did meet exclusion criteria and were excluded for the following reasons: no room for improvement (n = 6), no deviant EEG (n = 3), epileptic activity on EEG (n = 1), comorbid Gilles de la Tourette (n = 1), no ADHD (but dysthymic disorder) (n = 1), too great a burden to participate (n = 1), unstable use of ADHD-medication (n = 1) and a combination of criteria (n = 3) (above the cut-off score on the SCQ, unstable use of ADHD-medication and too great a burden to participate [n = 2], above cut-off score on the SCQ and no room for improvement [n = 1]).

Thus, 41 children participated in the study. The mean (SD) age of the sample was 10.62 (2.25) and there were 34 boys; 22 children were allocated to the EEG-neurofeedback group (8 in the pilot study, 14 post-pilot study), and 19 were allocated to the placebo-neurofeedback group. As expected as a result of randomization, no significant differences were found between the two groups on baseline characteristics (*Table 1*). All 41 children completed training. Two children unintentionally changed the dosage of their medication during the treatment phase (one increased the dosage of the psychostimulant, and the other incidentally introduced drug-free weekends and holidays).

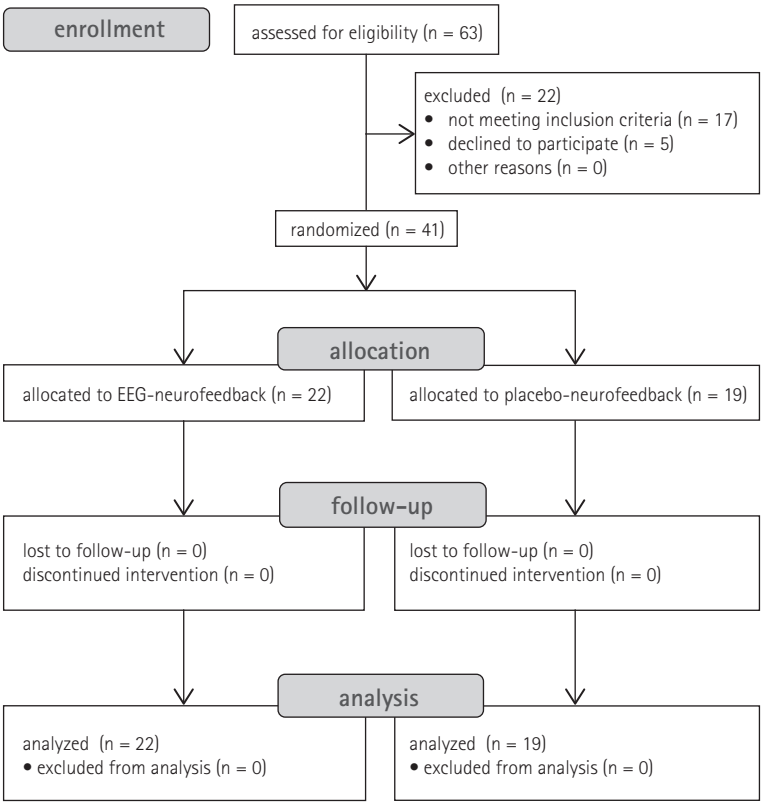

Figure 1 CONSORT flow diagram of study participants.

Abbreviations: CONSORT, Consolidated Standards of Reporting Trials, n, number; EEG, electroencephalographic.

Efficacy outcomes

Table 2 presents detailed statistical results for all study measures by treatment group.

ADHD-RS as rated by the investigator. ADHD symptoms decreased over time ($F_{(1,39)} = 26.56$, $p < .001$) to a similar extent in both groups and there was no group x time interaction effect ($F_{(1,39)} = 0.36$, $p = .554$) (*Figure 2*). Similar results were observed when the inattentive and hyperactive/impulsive scores were analyzed separately.

ADHD-RS as rated by the teacher. As nine teacher questionnaires were missing for the end-of-study assessment, last observation carrier forward (LOCF) data were used, except for two end-of-study measurements for which a baseline measurement was the only data

Table 1 Descriptive baseline demographic and clinical characteristics by treatment group (n = 41)

characteristics	EEG-neurofeedback (n = 22)	placebo-neurofeedback (n = 19)	analysis T, χ^2 *p*-value
age, m (SD), y	10.5 (2.2)	10.7 (2.3)	*p* = .734
gender, n (%)			*p* = 1.000
male	19 (86.4)	15 (78.9)	
female	3 (13.6)	4 (21.1)	
race, n (%)			*p* = 1.000
Caucasian	20 (91)	18 (95)	
Black	2 (9)	1 (5)	
full-scale IQ, m (SD)	108.8 (19.4)	102.1 (12.2)	*P* = .205
medication for ADHD, n (%)			*p* = .726
psychostimulants	11 (50)	14 (73.7)	
atomoxetine	1 (4.5)	0 (0)	
no medication	10 (45.5)	5 (26.3)	
EEG arousal, n (%)			*p* =.513
hypo-aroused	19 (86.4)	14 (73.7)	
hyper-aroused	3 (13.6)	5 (26.3)	
ADHD subtype, n (%)			*p* =.543
combined	17 (77.3)	13 (68.4)	
inattentive	4 (18.2)	5 (26.3)	
hyperactive/impulsive	1 (4.5)	1 (5.3)	
comorbidity, n (%)			
oppositional defiant disorder	5 (22.7)	1 (5.3)	*p* = .191
anxiety disorders	3 (13.6)	2 (10.5)	*p* = 1.000
dyslexia	2 (9)	3 (15.8)	*p* = .649
ADHD-RS-INV, m (SD)			
total symptoms	30.6 (7.5)	32.0 (9.6)	*p* = .601
inattentive symptoms	17.0 (5.1)	18.2 (3.4)	*p* = .369
hyperactive/impulsive symptoms	13.6 (5.5)	13.8 (7.9)	*p* = .942
ADHD-RS-Teacher, m (SD)			
total symptoms	23.6 (14.8)	25.7 (12.8)	*p* = .639
inattentive symptoms	13.1 (7.5)	13.9 (6.2)	*p* = .712
hyperactive/impulsive symptoms	10.6 (8.4)	11.8 (8.2)	*p* = .632
CGI-S, n (%)			*p* = .405
3- mildly ill	3 (13.6)	0 (0)	
4- moderately ill	12 (54.5)	11 (57.9)	
5- markedly ill	7 (31.8)	8 (42.1)	
CGAS, m (SD)	51.3 (6.6)	51.6 (5.6)	*p* = .703

Abbreviations: EEG, electroencephalographic; n, number; T, independent sample t-test; χ^2, chi-square test; *p*-value, probability value; m, mean; SD, standard deviation; y, years; IQ, Intelligence Quotient; ADHD, attention-deficit/hyperactivity disorder; ADHD-RS, ADHD Rating Scale IV; INV, Investigator; CGI-S scale, Clinical Global-Impressions Severity scale; CGAS, Children's Global Assessment Scale.

Table 2 Results for all study outcomes by treatment group (n = 41)

	EEG-neurofeedback[a]		placebo-neurofeedback[a]		analyses	
	baseline m (SD)	study end m (SD)	baseline m (SD)	study end m (SD)	time-effect F, *p*	group x time-effect F, *p*
ADHD-RS-INV					$F_{(1,39)}$	$F_{(1,39)}$
total symptoms	30.6 (7.5)	23.4 (9.5)	32.0 (9.6)	26.3 (7.2)	26.56, $p < .001$	0.36, $p = .554$
inattentive symptoms	17.0 (5.1)	13.2 (6.0)	18.2 (3.4)	13.8 (3.1)	27.17, $p < .001$	0.17, $p = .682$
hyperactive/impulsive symptoms	13.6 (5.5)	10.2 (5.3)	13.8 (7.9)	12.5 (6.3)	10.80, $p = .002$	2.26, $p = .141$
ADHD-RS-T					$F_{(1,37)}$	$F_{(1,37)}$
total symptoms	23.6 (14.8)	19.3 (11.4)	25.2 (12.5)	18.9 (10.2)	13.54, $p = .001$	0.45, $p = .509$
inattentive symptoms	13.1 (7.5)	11.3 (5.7)	13.4 (5.9)	11.0 (4.8)	7.63, $p = .009$	0.25, $p = .624$
hyperactive/impulsive symptoms	10.6 (8.4)	8.0 (7.0)	11.8 (8.3)	8.0 (6.6)	15.74, $p < .001$	0.53, $p = .473$
CGI-I[b]		3.2 (0.8)		3.6 (0.5)		$p = .092$
CGAS[b]	51.3(6.6)	58.1 (9.1)	51.6 (5.6)	54.8 (4.5)	$F_{(1,38)}$ 15.47, $p < .001$	$F_{(1,38)}$ 1,96, $p = .169$
SDQ	25.3 (8.3)	24.0 (7.0)	26.3 (6.3)	24.9 (9.2)	$F_{(1,37)}$ 5.42, $p = .025$	$F_{(1,37)}$ 0.05, $p = .818$
PSERS	5.5 (5.5)	4.1 (4.3)	5.6 (4.9)	3.9 (4.2)	$F_{(1,39)}$ 6.30, $p = .016$	$F_{(1,39)}$ 0.10, $p = .754$

Note: [a] Mean and standard deviation (in parentheses) are given for each parameter at baseline and study end. [b] Reduced scores reflect improvement, except for the CGI and CGAS. *Abbreviations:* m, mean; SD, standard deviation; *p*, probability value; ADHD-RS, ADHD Rating Scale IV; -INV, rated by the investigator; -T, rated by the teacher; CGI-I, Clinical Global Impressions-Improvement scale; CGAS, Children's Global Assessment Scale; SDQ, Sleep Disorders Questionnaire; PSERS, Pittsburgh Side Effects Rating Scale.

present. Teacher-rated ADHD symptoms decreased significantly over time ($F_{(1,37)}$ = 13.54, p = .001), without a difference between groups ($F_{(1,37)}$ = 0.45, p = .509). Similar results were obtained for the inattentive and hyperactive/impulsive scores.

CGI-I. On the CGI-I scale, 4 of 22 children (18%) in the EEG-neurofeedback group were rated as 'much improved', 9 of 22 (41%) in the EEG-neurofeedback group and 8 of 19 (42%) in the placebo-neurofeedback group were rated as 'minimally improved', and 9 of 22 (41%) in the EEG-neurofeedback group and 11 of 19 (58%) in the placebo-neurofeedback group were rated as unchanged at the end of the study. The differences between the groups were not significant (p = .092). None of the children deteriorated.

CGAS. One end-of-study value was missing in the EEG-neurofeedback group. The CGAS score increased significantly over time ($F_{(1,38)}$ = 15.47, p < .001), but increased similarly in the two groups ($F_{(1,38)}$ = 1.96, p = .169).

Safety outcomes

Adapted SDQ. Two end-of-study scores were missing in the placebo-neurofeedback group. Total sleep problems decreased significantly over time ($F_{(1,37)}$ = 5.42, p = .025), but similarly in the two groups ($F_{(1,37)}$ = 0.05, p = .818).

Adapted PSERS. Two values were missing in the EEG-neurofeedback group; the LOCF method was used for the missing data. The total number of adverse events decreased significantly over time ($F_{(1,39)}$ = 6.30, p = .016) and decreased similarly in the two groups ($F_{(1,39)}$ = 0.10, p = .754).

Post-hoc analyses

Post-hoc analyses with the covariates age, gender, medication use, and state of electrophysiological arousal did not reveal any significant treatment effect (i.e., group by time interaction) for any outcome. After correction, almost all significant results became non-significant, except for the effect of time on the CGAS, which changed to a marginally significant level ($F_{(1,34)}$ =3.48, p = .071).

Feasibility examination

Among the children, 10 of 41 (24%) correctly guessed which treatment they had received, 13 of 41 (32%) guessed incorrectly, and 10 of 41 (24%) did not know; data were missing for 8 of 41 (20%) children. Among the parents, 14 of 41 (34%) guessed the treatment assignment correctly, 19 of 41 guessed incorrectly (46%), and 6 of 41 did not know (15%); data were missing for 2 of 41 (5%) parents. Fisher exact tests showed that the children and their parents did not guess treatment assignment significantly better than chance level (p = .224 for children, p = .643 for parents).

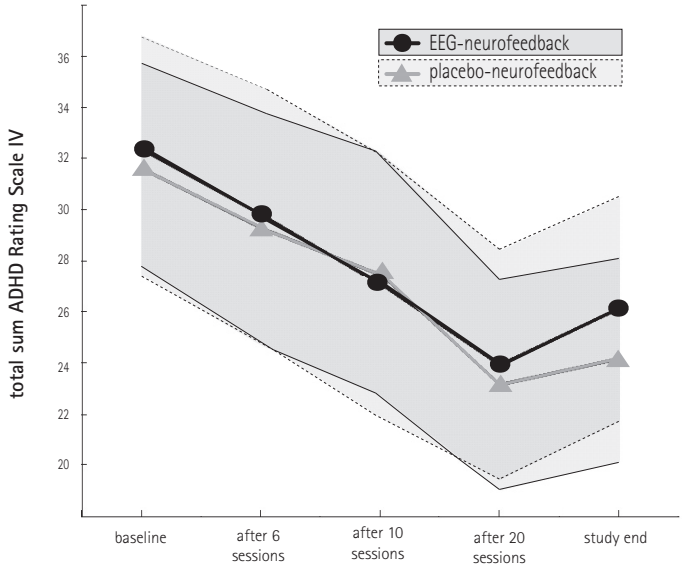

Figure 2 Mean total summed score and 95% confidence intervals for the ADHD Rating Scale IV over time as rated by the investigator and shown by treatment group.

Discussion

This study examined the safety and efficacy of EEG-neurofeedback treatment for core symptoms in children with ADHD, using a double-blind, randomized, placebo-controlled design with blinded participants and raters. Treatment assignment was not guessed better than chance level. EEG-neurofeedback was not superior to placebo-neurofeedback in affecting ADHD symptoms or other secondary efficacy outcomes. The intervention was safe as no adverse effects were reported. Post-hoc analyses with the covariates age, gender, medication, and electrophysiological state of arousal did not lead to any significant results compared to the main analyses. These findings are in line with those of our previous feasibility pilot study (Lansbergen et al., 2011) and two recently published placebo-controlled EEG-neurofeedback studies (Perreau-Linck et al., 2010; Arnold et al., 2012). Moreover, a recent systematic review and meta-analysis of randomized controlled trials of non-pharmacological interventions in children with ADHD concluded that the significant effect size of unblinded ratings could not have been replicated if blinded ratings were used (meta-analysis of seven open-label and one triple-blind EEG-neurofeedback studies) (Sonuga-Barke et al., 2013). Thus, it seems that methodologically sound studies do not confirm the efficacy of EEG-neurofeedback in children with ADHD.

Changing from automatic to manual thresholds did not result in larger effects for EEG-neurofeedback, nor did the addition of active learning strategies. Making passive learning active by adopting learning strategies is hypothesized to be an important aspect of the working mechanism of EEG-neurofeedback (Gevensleben et al., 2012). Our findings did not support this hypothesis.

Unfortunately, we were unable to recruit a sufficient number of participants to meet our planned sample size. Post-hoc, our sample had 80% power to detect a treatment effect of 0.90. However, since there was virtually no difference between the effect of EEG-neurofeedback and placebo-neurofeedback in the smaller sample, it is unlikely that our negative results were due to limited statistical power.

The study was carefully designed to tackle the methodological shortcomings of previous studies, resulting in a randomized placebo-controlled trial with blinded participants and raters, an extended selection procedure, and several behavior and safety evaluations of both interventions. Conducting such study has drawbacks. First, the 50% chance of receiving placebo-neurofeedback treatment probably adversely influenced recruitment. During our entire clinical trial, patients with ADHD had access to EEG-neurofeedback in the general clinical practice without the risk of being assigned to placebo-neurofeedback and treatment costs were fully reimbursed by health insurance companies. Another potential limitation is the change from a triple-blind to a double-blind design (which means that the neurofeedback therapist was no longer blinded); however, participants and raters were still blinded to treatment assignment. The use of medication by most participants may have influenced the ability to detect a significant effect of EEG-neurofeedback. At this time, follow-up data are not available yet; we plan to re-assess all participants after six months and will describe these findings in a separate report. Last, because most children were white, the generalizability of findings to other races cannot readily be assumed.

In conclusion, our results seriously question claims that EEG-neurofeedback is an effective treatment for children with ADHD. Further research with more participants is needed to determine whether this traditional form of neurofeedback is effective in particular patient subgroups.

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Clinical Points

- The findings are in line with a recent meta-analysis that concluded that EEG-neurofeedback does not have proven efficacy as a treatment for children with ADHD.
- Guidance regarding EEG-neurofeedback as a treatment for children with ADHD must be in line with these current findings.
- Further research on this topic is needed to determine whether EEG-neurofeedback is of clinical relevance in subgroups of children with ADHD.

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V

Does EEG-neurofeedback improve neurocognitive functioning in children with attention-deficit/hyperactivity disorder? A systematic review and a double-blind placebo-controlled study

Madelon A. Vollebregt*, Martine van Dongen-Boomsma*, Jan K. Buitelaar & Dorine Slaats-Willemse

** joint first authors*

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Abstract

The number of placebo-controlled randomized studies relating to EEG-neurofeedback and its effect on neurocognition in ADHD is limited. For this reason, a double-blind, randomized, placebo-controlled study was designed to assess the effects of EEG-neurofeedback on neurocognitive functioning in children with attention-deficit/hyperactivity disorder (ADHD), and a systematic review on this topic was performed.

Forty-one children (8-15 years) with a *DSM-IV-TR* diagnosis of ADHD were randomly allocated to EEG-neurofeedback or placebo-neurofeedback treatment for 30 sessions, twice a week. Children were stratified by age, electrophysiological state of arousal, and medication use. Neurocognitive tests measuring executive functioning, attention, reward-related processes, and timing were administered before and after treatment. Researchers, teachers, children, and their parents, with the exception of the neurofeedback-therapist, were all blinded to treatment assignment. Outcome measures were the changes in neurocognitive performance before and after treatment.

No significant treatment effect on any of the neurocognitive variables was found. A systematic review of the current literature also did not find any systematic beneficial effect of EEG-neurofeedback on neurocognitive functioning.

Overall, the existing literature and this study fail to support any benefit of neurofeedback on neurocognitive functioning in ADHD, possibly due to small sample sizes and other study limitations.

Trial Registration: ClinicalTrials.gov identifier: NCT00723684.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common childhood mental disorder, affecting about 5% of all children worldwide (Polanczyk, de Lima, Horta, Biederman & Rohde, 2007) with an increasing prevalence over the last decade (Getahun et al., 2013). ADHD affects children's personal development substantially and is associated with impairments in social and emotional development, and poor academic and vocational outcomes (Wehmeier, Schacht & Barkley, 2010). Consequently, the substantial burden on families and society in general is notable (Biederman, 2005; Biederman et al., 2012). Because of the severity and long-term nature of the impairments associated with ADHD, efforts have been made to understand the underlying deficits and identify effective treatments for ADHD.

ADHD & neurocognitive dysfunctions

Neurocognitive models of ADHD have attempted to explain the behavioral symptoms in underlying impairments in executive functions (EFs), attention regulation, reward-related processes, and timing. Associations between ADHD and EFs are found in domains of response inhibition, vigilance, working memory, and planning (Martinussen, Hayden, Hogg-Johnson & Tannock, 2005; Willcutt, Doyle, Nigg, Faraone & Pennington, 2005). ADHD-related attention problems are described as weak performances in selective and sustained attention, and attention shifting tasks (Weissman, Chu, Reddy & Mohlman, 2012). Studies on reward-related processes in ADHD indicate a preference for small immediate rewards over later larger rewards (for review see Sonuga-Barke, Sergeant, Nigg & Willcutt, 2008). Finally, timing deficits have consistently been found in subjects with ADHD in three major domains, i.e., motor timing, perceptual timing, and temporal foresight (for review see Noreika, Falter & Rubia, 2013). Differentiation could be made between timing deficits and delay deficits (Sonuga-Barke, Bitsakou & Thompson, 2010; de Zeeuw, Weusten, van Dijk, van Belle & Durston, 2012).

ADHD & EEG-neurofeedback

Concerns about the safety and long term efficacy of first-line treatment medication in ADHD have led to interest in developing alternative non-pharmacological treatment approaches. Electroencephalographic neurofeedback (EEG-NF) is based on the rationale that voluntary modulation of specific brain activity patterns can be learned by operant learning strategies. In other words, by providing continuous real time feedback, i.e., positive reinforcement when changes are made in the desired direction, the self-regulation of ongoing neuronal oscillations in one or more frequency-bands can be enhanced (Gevensleben, Rothenberger, Moll & Heinrich, 2012). Resting-state electroencephalogram (EEG) in the majority of children with ADHD is characterized by increased slow-wave activity and decreased fast-wave activity, primarily theta and beta activity respectively, and higher

theta/beta and theta/alpha ratios compared to controls (for review see Barry, Clarke & Johnstone, 2003), often referred to as an hypo-aroused physiological state. Therefore most neurofeedback protocols focus on these frequency-bands (Monastra et al., 2005). A minority of children with ADHD has shown increased power of beta activity (Clarke, Barry, McCarthy, Selikowitz & Brown, 2002), creating a subgroup with a hyper-aroused physiological state.

The placebo-controlled randomized trials published to date, have not found superior effects of EEG-NF compared to placebo-neurofeedback (PL-NF) (Perreau-Linck, Lessard, Levesque & Beauregard, 2010; Lansbergen, van Dongen-Boomsma, Buitelaar & Slaats-Willemse, 2011; Arnold et al., 2012; van Dongen-Boomsma, Vollebregt, Slaats-Willemse & Buitelaar, 2013). In addition, a systematic review and meta-analysis of randomized controlled trials (RCTs) of non-pharmacological interventions in children with ADHD including EEG-NF studies, reported non-significant results for the blinded rating of symptoms (p = .07) (Sonuga-Barke et al., 2013).

Most studies have focused on behavioral outcome measures. However, it is worthwhile to examine whether EEG-NF is able to improve neurocognitive functioning in ADHD because the persistence of neurocognitive deficits is strongly associated with occupational problems and morbidity (Barkley & Murphy, 2010; Biederman et al., 2012).

The objectives of this paper were two-fold: (1) to systematically review the existing literature on the effects of two modalities of EEG-NF, namely frequency NF (F-NF) and Slow Cortical Potential (SCP)-NF on neurocognitive functioning and (2) to assess the effect of F-NF on neurocognitive functioning in a double-blind, placebo-controlled trial in children with ADHD.

Review on neurocognitive outcome measures after EEG–NF in children with ADHD

A literature research was carried out in PubMed for the period between 1994 and May 2012 by combining the following MeSH terms; ('Attention Deficit Disorder with Hyperactivity'[MeSH]) AND ('Biofeedback, Psychology'[MeSH] OR 'Neurofeedback'[MeSH]). A final search was conducted to check for the most recent published trials (February 2013). The database search outlined above was supplemented by manual searches. The inclusion criteria that were applied to the publications retrieved were a) study was peer reviewed, b) diagnosis of ADHD was classified by the *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed.; *DSM-III*; American Psychiatric Association, 1980), *DSM-III-R* (American Psychiatric Association, 1987), *DSM-IV*(American Psychiatric Association, 1994), *DSM-IV-TR* (American Psychiatric Association, 2000), or the *ICD-10* (World Health Organization, 1992), c) age was in the range from 0-18 years, d) the study was an RCT, e) F-NF and/or SCP-NF was used as treatment modality, f) neurocognitive data were reported in the publication. In total, 10 randomized controlled trials met these inclusion criteria (Linden, Habib & Radojevic, 1996; Heinrich, Gevensleben, Freisleder, Moll & Rothenberger, 2004; Levesque, Beauregard & Mensour, 2006; Leins et al., 2007; Holtmann et al., 2009; Perreau-Linck et al., 2010;

Bakhshayesh, Hansch, Wyschkon, Rezai & Esser, 2011; Steiner, Sheldrick, Gotthelf & Perrin, 2011; Wangler et al., 2011; Arnold et al., 2012). See *Table 1* of the *supplement*.

The 10 selected EEG-NF studies were quite heterogeneous in their design and methodology. The studies included a range of different sample sizes and control conditions (e.g., passive control conditions vs. active control conditions). Investigators were blinded to treatment assignment in some studies while in others they were not. The NF-protocol as well as the duration, frequency, and number of sessions varied between studies. Significant differences between the studies were also noted in terms of the participants' characteristics (especially the use of medication), the statistical methods used, and the choice of neurocognitive tasks. The differences in neurocognitive tasks employed also render a meta-analysis impossible. However, areas in which the studies overlapped included the use of predominantly male participants in the same age range (mean round 10 years) as well as a common inclusion criterion that subjects must have a full-scale intelligence quotient (FSIQ) of more than 80 points.

Three of the 10 studies reported significant improvement on at least one neurocognitive variable for the NF condition superior to the control condition (Heinrich et al., 2004; Holtmann et al., 2009; Bakhshayesh et al., 2011). More specifically, treatment (i.e., time x group interaction) effects were seen for the variable representing impulsivity on the stop-signal task (Holtmann et al., 2009) and for all variables representing attention on the paper-and-pencil attention test (Bakhshayesh et al., 2011). However, in the paper-and-pencil attention test, the number of errors also increased significantly more in the F-NF condition than in the control condition, suggesting that improved speed came at the expense of accuracy. Note that speed-accuracy trade-off calculation was not reported. One study appeared to show a time x group effect on the composite variable of the Kaufman-BRIEF Intelligence Test, a German intelligence scale. However, this was not explicitly reported (Linden et al., 1996). The study investigating the efficacy of SCP-NF showed a time x group effect for the variable representing impulsivity on a Continuous Performance Task (Heinrich et al., 2004).

Overall, these studies had many methodological limitations (including small sample sizes, increasing the chance for type II errors), and the majority failed to show positive neurocognitive effects of F-NF or SCP-NF. Taken together, these studies suggest that there is no systematic beneficial effect of these two types of NF on neurocognitive functioning.

Methods

Trial design

This study was designed as a triple-blind, placebo-controlled treatment trial, with stratified randomization for age (younger vs. older than 12 years), electrophysiological state of arousal (hyper-arousal vs. hypo-arousal), and use of medication (with vs. without

medication). After a pilot study (Lansbergen et al., 2011), two adaptations were made: 1) In the F-NF condition, reward thresholds were changed from automatic into manual adjustment, resulting in the unblinding of the neurofeedback-therapist (NF-therapist). Participants and raters remained blinded, creating a double-blind study. 2) Active learning strategies were implemented, so that children could apply the learned strategies into daily life.

Participants

Children (8-15 years) were included if 1) they had been clinically diagnosed with ADHD according to the criteria of the *DSM-IV-TR* (American Psychiatric Association, 2000), 2) they had an FSIQ of at least 80, 3) their quantitative EEG (qEEG) deviated at least 1.5 standard deviations (SD) from normative data, 4) they did not use psychopharmaca or used a stable dose of ADHD medication, and 5) there was room for improvement, defined as a minimum score of 2 on a 4-point Likert scale (0-3) for at least 6 items of the ADHD Rating Scale IV (ADHD-RS; Zhang, Faries, Vowles & Michelson, 2005). Children were excluded if they 1) were involved in psychotherapy, 2) used medication other than ADHD medication, 3) had a comorbid disorder other than oppositional defiant disorder or any anxiety disorder, 4) had a neurological disorder and/or a cardiovascular disease, 5) participated in another clinical trial simultaneously, 6) had received NF in the past, or 7) used alcohol or drugs.

A doctor or psychologist screened potential children via a telephone interview with their parents in which ADHD symptoms and other psychiatric symptoms were checked. The Dutch version of the Social Communication Questionnaire (SCQ; Berument, Rutter, Lord, Pickles & Bailey, 1999) was used to screen for autism spectrum disorders. The presence of other comorbid disorders was assessed with the Diagnostic Interview Schedule for Children (Shaffer, Fisher, Lucas, Dulcan & Schwab-Stone, 2000; Steenhuis, Serra, Minderaa & Hartman, 2009). A positive screening-outcome was followed by a diagnostic procedure, including the ADHD-RS and a developmental and psychiatric interview with a child and adolescent psychiatrist. General functioning was measured by the Children's Global Assessment Scale (CGAS; Shaffer et al., 1983) and the severity of ADHD was assessed with the Clinical Global Impressions-Severity scale (CGI-S; Guy, 1976). If an intelligence test had not taken place over the past 1.5 years, two subtests of the Wechsler Intelligence Scale for Children (WISC-III) were administered (i.e., Vocabulary and Block Design) to estimate intelligence (Wechsler, 1991). Finally, 20 minutes (min) of de-artifacted raw EEG in an eyes-open and eyes-closed condition was acquired to determine deviation from the NeuroGuide database (Thatcher, Walker, Biver, North & Curtin, 2003).

Recruitment started in August 2008 and ended in May 2012. Children were recruited from referrals to Karakter Child and Adolescent Psychiatry University Centre in Nijmegen, and from responders to advertisements in the journal of the Dutch Parents Association for Children with Developmental Disorders. The study was approved by the Dutch Central Medical Ethics Committee (www.ccmo.nl) and conducted in accordance with the declaration of Helsinki. All parents and children older than 12 years gave their written informed consent

before participation; children younger than 12 year gave oral assent. Travel costs were partially reimbursed. All children received a 10-euro gift certificate and a small present after collecting 30 stickers, given after each session.
The study was registered in the Clinical trial register under 'Project ADHD and EEG-Neurofeedback THERapy'; www.clinicaltrials.gov; NCT00723684.

Interventions

The Neurofeedback Instituut Nederland B.V. provided both the F-NF and the PL-NF training. Individualized F-NF protocols based on visual inspection of the raw EEG and qEEG were used for F-NF training.
The F-NF training was intended to normalize power within individually determined frequency-bands and electrode sites by receiving feedback on their real-time EEG-signal. In this study, personalized protocols were used to address different EEG abnormalities, i.e., hypo-arousal vs. hyper-arousal, in children with ADHD, consisting of a protocol focusing on the EEG abnormality in that child.
Children watched a film for 20 min in an 'active focusing state' with eyes open. They were instructed to attempt to self-regulate their brain activity. Positive feedback was provided by brightening the computer screen and presentation of auditory tones. Most children in the F-NF group were trained to increase the presence of the sensory motor rhythm (SMR) or low-beta activity while simultaneously suppressing the presence of theta activity, meaning that when the production of SMR remained above threshold, and/or the theta/beta remained below threshold, positive feedback was given. Reward threshold levels were manually adjusted to 80% for each training target (i.e., frequency- band and/or location). Therefore, the actual percentage reinforcement depended on the amount of co-occurrence of desirable activity towards training targets (e.g., theta power going downwards at P3 while simultaneously going downwards at P4). Reinforcement was 80% when all training targets were achieved simultaneously only. When assuming no correlation in activity between the different training targets, the reinforcement was 0.8 to the power of the number of training targets (e.g., training theta power downwards and beta power upwards resulted in a rewarding percentage of 64%). In practice, the reinforcement lay between 0.8 and 0.8 to the power of the number of training targets. Thresholds were manually adjusted according to the expertise of the NF-therapist. No specific guideline or protocol was followed. This method was in line with the objective of this study to investigate the efficacy of NF as delivered in 'care as usual', in which decisions about adjustments of the threshold are determined by the involved clinical NF-therapist. All of the NF-therapists were BCIA certified (Biofeedback Certification International Alliance, 10200 W 44th Ave, Suite 310, Wheat Ridge CO 80033-2840). An identical procedure was provided in the PL-NF group, except that children in the PL-NF group received feedback on a simulated EEG signal, consisting of a random signal similar to real EEG, in accordance with the procedure of an earlier study (Logemann, Lansbergen, van Os, Bocker & Kenemans, 2010). BrainMaster

Atlantis hardware and software provided both training modalities (BrainMaster Technologies; Bedford, Ohio). Feedback on real EEG and simulated EEG signals seemed similar in experience in an earlier study and in our pilot study (Logemann et al., 2010; Lansbergen et al., 2011). The behavioral effects of this study have been published elsewhere (van Dongen-Boomsma et al., 2013).

Neurocognitive outcomes

All children included in the study underwent a neurocognitive assessment of 90 min before and after treatment. Two versions of the neurocognitive battery controlled for a possible task-order effect. If available, different versions of the tasks were administered before and after the treatment to control for a potential learning effect. Complete task descriptions can be found in the *supplement* (subsection; 'neurocognitive task descriptions'). Below, the neurocognitive tasks are briefly described.

Sustained Attention Dots task (SA-DOTS). The Continuous Performance Task from the computerized neurocognitive test-battery of the Amsterdamse Neuropsychologische Taken (ANT; de Sonneville, Schmidt, Michel & Batzler, 1990; de Sonneville, 1999) was used to measure sustained attention. Variables of interest were the number of correct responses, the mean reaction time (RT) in milliseconds (ms) on correct responses and its standard deviation, and the number of premature responses (RT < 150 ms). Note there was a trade-off to be made between RT and accuracy. Therefore, the expected (negative) relationship between RT and number of correct trials was addressed by performing similar analyses while controlling for each other.

Visuospatial Sequencing (VSS). To measure visuospatial memory, the VSS subtest from the ANT (de Sonneville, 1999) was used. The number of correct trials and the number of targets identified in the correct order were determined and used for analyses.

Digit Span from the Wechsler Intelligence Scale for Children-III (DS-WISC-III). To measure verbal working memory, the DS (forward and backward) from the WISC-III (Wechsler, 1991; de Kort et al., 2002) was used. The total number of correctly recalled forward digit-sequences and backward digit-sequences compared to an age-norm was the variable of interest.

The Rey Auditory-Verbal Learning Test (RAVLT). Verbal working memory and long term verbal memory was assessed using the Dutch adaptation of the RAVLT. In the Dutch version Rey's procedure (Rey, 1964) is applied without an interference trial (van den Burg & Kingma, 1999). In this form, the AVLT was administered in the present study. The total number of immediately recalled words over all five presentations and the amount of words recalled 20 min after the last presentation were chosen as the variables of interest.

Instrumental Learning task. Instrumental learning tasks are widely used instruments that have their origin in the instrumental/operant learning principle (Thorndike, 1898). A version of this task appropriate for children was created derived from two example instrumental learning paradigms (O'Doherty et al., 2004; Pessiglione, Seymour, Flandin, Dolan & Frith, 2006). The variables of interest were the total number of choices of high versus low

probability actions in reward trials and the trial at which the learning criterion was reached. The learning criterion was defined as 8 consecutive high probability actions.

Time Production task. To measure precision of time perception, a time production task was constructed based on the task description of van Meel, Oosterlaan, Heslenfeld & Sergeant (2005). The mean absolute discrepancy and its standard deviation between stimulus length and response length were measured.

Time Reproduction task. To measure precision of time reproduction, a task was constructed based on the task description of Rommelse, Oosterlaan, Buitelaar, Faraone & Sergeant (2007). The mean absolute discrepancy and its standard deviation between stimulus length and response length were measured.

Sample size

Sample size was calculated for the primary outcome and was based on the following considerations. Double-blind, placebo-controlled trials have shown an effect size (ES) of 0.6 or more for the first-line treatment of ADHD with medication (Michelson et al., 2002; Faraone & Buitelaar, 2010). Pilot open-label studies with EEG-neurofeedback also report an ES around 0.6 (Fuchs, Birbaumer, Lutzenberger, Gruzelier & Kaiser, 2003). With an alpha error of .05, a sample of 60 children in the EEG- neurofeedback arm and 60 in the placebo-neurofeedback group and a power of 80.0% would enable treatment effects to be detected with an ES of 0.5.

Randomization

Participating children were stratified and subsequently randomly assigned (1:1 assignment using random block sizes of two), double-blindly, to either F-NF or PL-NF. The principal investigator who was not involved in data collection performed this. Randomization by means of minimization was applied, including EEG profile, age, and medication use as factors (Han, Enas & McEntegart, 2009). The treatment group that most strongly would minimize the imbalance was chosen to allocate the participant.

Blinding

All people involved in the study were blinded to treatment assignment, except the NF-therapist and the principal investigator, who were not involved in data collection, data entry, and data analysis.

Statistical methods

As first step, we analyzed all neurocognitive variables at group level. Variables of the Instrumental Learning task, Time Reproduction task, and the Time Production task were created using MATLAB R2009a (The Math-Works, Inc., Natrick, MA). All statistical analyses were conducted employing the IBM SPSS Statistics, version 20.0 (Armonk, New York; IBM Corp.). The significance level was set at $p = .05$. Imputation of missing data was used to

obtain the most accurate data set (Donders, van der Heijden, Stijnen & Moons, 2006).
To optimize control for the variance at baseline, baseline was used as a covariate in analyses of the covariance (ANCOVA). For each neurocognitive parameter the endpoint measurement was the dependent variable while the baseline measurement was a covariate, and group (F-NF vs. PL-NF) was the fixed factor.
To reduce within-group error variance and to eliminate confounding, additional ANCOVAs were performed (Field, 2009). For all main analyses, we also conducted ANCOVAs with age, gender, FSIQ, medication use, and electrophysiological arousal as covariates to control for their possible influence.
To confirm the reliable use of ANCOVA, all required assumptions were tested per variable, except the assumption for independence of the sample, which was not expected to be present in this experimental design and the independence of the covariate and treatment effect, which was covered, by randomization and stratification. B-weights, the unstandardized regression coefficients, represent the relationship between the groups and the outcome variable included in the analysis. In this study, a positive value indicates an effect for the F-NF group, a negative value an effect for the PL-NF group. The significance on the t-tests tells whether this relationship is significant.
The next step was to examine whether participants might show significant and reliable individual changes on neurocognitive variables that might be overlooked at group level. The Reliable Change Index (RCI) was used to address this issue. The RCI-method, described by Jacobson & Truax (1991) was subsequently applied to a placebo-controlled medication study in children with ADHD (Buitelaar, van der Gaag, Swaab-Barneveld & Kuiper, 1995). This method was also used by another NF study (Perreau-Linck et al., 2010). The RCI was calculated for each individual, *i*, using the following formula:

$$RCI = \frac{D_i - P_i}{SE}$$

In which D_i is the observed change between pre- and post- measurement, P_i the mean change score of the placebo group, and *SE* the corresponding standard error. If a child exceeded the critical value of (-)1.96 (equaling our significance value set at $p = .05$), it was said to reliably change on this measure.

Results

The demographic and clinical characteristics are summarized in *Table 1*. In sum, 41 children (mean age 10.6 ± 2.3 83.0 % boys, and estimated FSIQ of 105.7 ± 16.7) were included. Of these, 22 children were assigned to the F-NF group (8 of the pilot-study, 14 post pilot-study) and 19 children to the PL-NF group (no differences made after pilot). Analyses with respect to the neurocognitive results performed on the sample without the pilot NF sample (n = 33)

Table 1 Demographic characteristics

characteristics	frequency neurofeedback (n = 22)	placebo-neurofeedback (n = 19)	analysis T, χ^2 *p*-value
age, m (SD), y	10.5 (2.2)	10.7 (2.3)	$p = .734$
gender (%)			$p = 1.000$
male	86.4	78.9	
female	13.6	21.1	
race (%)			$p = 1.000$
Caucasian	91	95	
Black	9	5	
full scale IQ, m (SD)	108.8 (19.4)	102.1 (12.2)	$p = .205$
medication for ADHD (%)			$p = .726$
psychostimulants	50	73.7	
atomoxetine	4.5	0	
no medication	45.5	26.3	
EEG arousal (%)			$p = .513$
hypo-aroused	86.4	73.7	
hyper-aroused	13.6	26.3	
ADHD subtype (%)			$p = .543$
combined	77.3	68.4	
inattentive	18.2	26.3	
hyperactive/impulsive	4.5	5.3	
comorbidity (%)			
oppositional defiant disorder	22.7	5.3	$p = .191$
anxiety disorders	13.6	10.5	$p = 1.000$
dyslexia	9	15.8	$p = .649$

Abbreviations: n, number; T, independent sample t-test; χ^2, chi-square test; *p*, probability; m, mean; SD, standard deviation; y, years; IQ, Intelligent Quotient; ADHD, attention-deficit/hyperactivity disorder; EEG, electro-encephalographic.

and the total sample (n = 41), did not yield different results, and therefore data of the total sample will be presented. Further, we did test for blinding of the participants. This test revealed that guessing treatment assignment was not better than at chance level ($p = .224$ for children, $p = .643$ for parents). For a complete overview of the clinically examination procedure and the administered NF, see *Figure 1* and *Table 2*, both in the *supplement*.

Neurocognitive characteristics

All variables were distributed normally within groups, unless specifically stated and dealt with accordingly (e.g., by removing outliers, defined as 25% of the size of the largest leaf entry in the clustering feature tree, based on the default definition used by SPSS 20.0). All

Table 2 Baseline and endpoint scores on all neurocognitive parameters. Also depicted are the change scores between baseline and endpoint and the mean individual interaction effect size

neurocognitive parameter (m and SD)	baseline[a]	
	F-NF (n ≤ 22)	PL-NF (n ≤ 19)
Sustained Attention Dots		
correct trials	551.9 (31.5)	556.6 (29.6)
response time correct trials	3417.2 (873.6)	3434.9 (824.5)
SD response time correct trials	1533.8 (736.8)	1649.6 (674.5)
Visuospatial Sequencing		
correct trials	19.6 (2.5)	18.3 (2.9)
identified in correct order	90.9 (9.7)	86.7 (10.8)
Digit Span-WISC-III		
z-score forward and backward	10.6 (3.2)	10.0 (2.7)
RAVLT		
direct recall	46.6 (8.4)	44.2 (6.7)
delayed recall	9.7 (2.6)	9.6 (2.5)
Instrumental Learning task		
high probability action	44.8 (3.9)	44.9 (4.1)
reach learning criterion	17.3 (2.7)	16.8 (2.0)
Time Production task		
MAD from 1 sec (ms)	205.5 (80.4)	224.9 (74.0)
SD from MAD (ms)	182.5 (76.2)	208.2 (84.4)
Time Reproduction task		
MAD from trial (ms)	2043.2 (1254.0)	2694.4 (1740.2)
SD from MAD (ms)	2178.1 (1584.8)	2947.5 (1644.2)

* $p < .01$.

Note: Data were used without using imputed data or outliers. [a] Independent sample t-tests between groups for which $p > .20$. [b] Time x group interactions of repeated measures ANOVAs for which $p > .10$.

Abbreviations: m, mean; SD, standard deviation; F-NF, frequency neurofeedback; n, number; PL-NF, placebo-neurofeedback; Cohen's *d*, the difference between groups (PL-NF subtracted from F-NF) for the change scores between endpoint and baseline divided by the pooled standard deviation of the change scores taking into account the sample size; ↓, direction of the change score in opposite direction than direction hypothesized to be improvement; Digit Span-WISC-III, Digit Span from the Wechsler Intelligence Scale for Children-III; RAVLT, Rey Auditory Verbal Learning Test; MAD, mean absolute deviation.

endpoint		change score		effect size[b]
F-NF (n ≤ 22)	PL-NF (n ≤ 19)	F-NF (n ≤ 22)	PL-NF (n ≤ 19)	Cohen's *d*
549.2 (29.7)	555.5 (32.2)	-0.9 (14.9) ↓	-0.8 (25.1) ↓	-0.01
3146.7 (1058.1)	2981.5 (653.5)	-354.5 (571.9)	-511.7 (342.4)	0.34
1464.9 (891.8)	1504.3 (777.2)	-155.5 (551.9)	-212.5 (336.8)	0.13
19.1 (3.8)	19.4 (3.3)	0.0 (3.7)	1.1 (3.0)	-0.34
87.6 (16.0)	90.3 (12.0)	-1.5 (15.3) ↓	3.8 (11.2)	-0.42
11.5 (3.4)	11.5 (2.4)	0.9 (2.8)	1.5 (2.2)	-0.24
45.5 (9.0)	45.1 (7.0)	-1.1 (7.5) ↓	0.9 (6.0)	-0.30
9.7 (2.5)	9.8 (2.5)	0.0 (2.5)	0.2 (2.2)	0.15
42.5 (7.3)	40.2 (7.2)	-2.3 (8.2) ↓	4.8 (7.9)	-0.90
17.9 (4.6)	18.0 (4.5)	0.6 (5.8) ↓	1.2 (4.4) ↓	-0.12
228.2 (113.7)	230.4 (83.8)	22.7 (83.8) ↓	5.5 (65.0) ↓	0.23
338.1 (473.0)	209.7 (102.8)	155.5 (429.5) ↓	1.5 (97.2) ↓	0.50
2672.4 (1604.7)	2388.5 (1556.2)	473.9 (949.3) ↓	310.3 (1258.5) ↓	0.15
3089.6 (1597.1)	2317.6 (1281.6)	734.1 (1453.1) ↓	619.6 (1412.3) ↓	0.08*

assumptions confirmed permission for using ANCOVA as statistical test method. However, for some variables removing outliers was needed to meet these assumptions. A maximum of 4.9% was removed in favor of creating a normal distribution. Imputation of missing data was used for the SA-DOTS, the VSS, the Instrumental Learning task, and the Time Reproduction task with an average of 4.9% and a maximal imputation of 14.6%. *Table 2*, among others, gives an overview of baseline values and shows that there was no difference between groups at baseline.

Neurocognitive outcomes

All main outcomes are depicted in *Table 2* and *Figure 1*.

SA-DOTS. Two outliers were detected in the F-NF group and three in the PL-NF group. No treatment effect was found on any of the variables (correct: $t(33) = -0.090$, $p = .928$; RT: $t(33) = 0.868$, $p = .385$; SD of RT: $t(33) = 0.109$, $p = .913$). When additionally controlling for the number of correct trials, RT still did not reveal a treatment effect ($t(32) = 0.864$, $p = .387$). Likewise, the number of correct trials did not reveal a treatment effect after additionally controlling for RT ($t(32) = -0.075$, $p = .940$). Making more than eight premature responses was defined as an outlier. After treatment no difference in premature responses between groups was found (Fisher's Exact Test: $p = 1.000$).

VSS. Two outliers were detected in the F-NF group and excluded from the dataset. The number of correct trials after controlling for baseline score did not show a treatment effect ($t(36) = -0.672$, $p = .502$), neither did the number of targets identified in correct order ($t(36) = -0.810$, $p = .418$).

DS-WISC-III. No significant treatment effect was found on the norm-score of forward and backward DS after controlling for the baseline-score ($t(38) = 0.586$, $p = .561$).

RAVLT. No significant treatment effect was found on direct- and delayed recall after controlling for the baseline-score (direct: $t(38) = 0.591$, $p = .558$; delayed: $t(38) = -0.290$, $p = .773$).

Instrumental Learning task. Two outliers were detected in the PL-NF group when exploring the data and were excluded from the dataset. No treatment effect was observed on the number of high probability actions ($t(36) = 1.003$, $p = .316$) or on the moment at which the learning criterion of 8 consecutive high probability actions was reached ($t(36) = -0.028$, $p = .978$).

Time Production task. Two outliers were detected in the F-NF group and excluded from the dataset. No significant treatment effect was found on the mean absolute deviation (MAD; in ms) from 1 second after controlling for baseline-score ($t(36) = 0.599$, $p = .553$). A trend towards more variance in response length (standard deviation of MAD) in the F-NF than PL-NF group was observed ($t(36) = 1.833$, $p = .075$).

Time Reproduction task. No significant treatment effect was found on the MAD from the trial ($t(38) = 1.771$, $p = .077$). A significant treatment effect, the F-NF fluctuating more in response length than the PL-NF, was observed on the SD of MAD ($t(38) = 2.674$, $p = .008$).

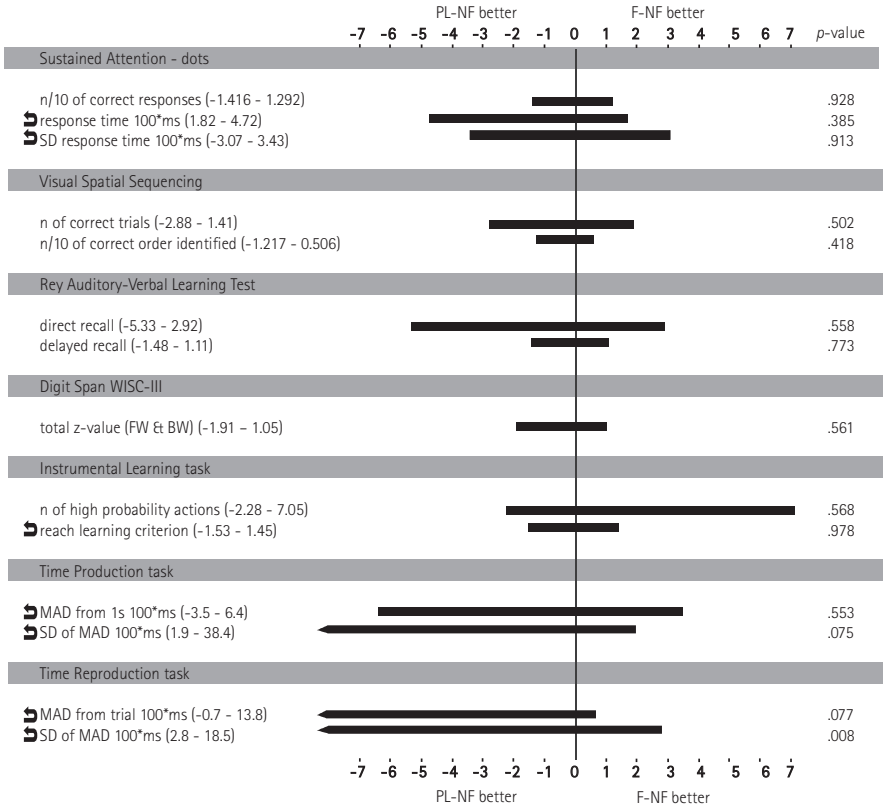

Figure 1 95% confidence intervals for each neurocognitive parameter
Based on B-weights, this figure shows that despite a relatively small sample size and thus limited statistical power, there is no reason to reject the null-hypothesis. A positive value indicates an effect for the EEG-neurofeedback group; a negative value indicates an effect for the placebo-neurofeedback group.

Note: Values of which lowering is hypothesized to be an improvement are indicated with a preceding arrow (⮌) and scales are inverted.
Abbreviations: PL-NF, placebo-neurofeedback group; F-NF, frequency neurofeedback group; *p*-value, probability-value; n, number; ms, milliseconds; SD, standard deviation; Digit Span-WISC-III, Digit Span from the Wechsler Intelligence Scale for Children-III; FW, forward; BW, backward; MAD, mean absolute deviation; s, seconds.

Covariates analyses

To control for the influence of age, gender, FSIQ, medication, and electrophysiological arousal, these variables were added as covariates to the main ANCOVA with the neurocognitive parameter as dependent variable, and group as fixed variable. These analyses

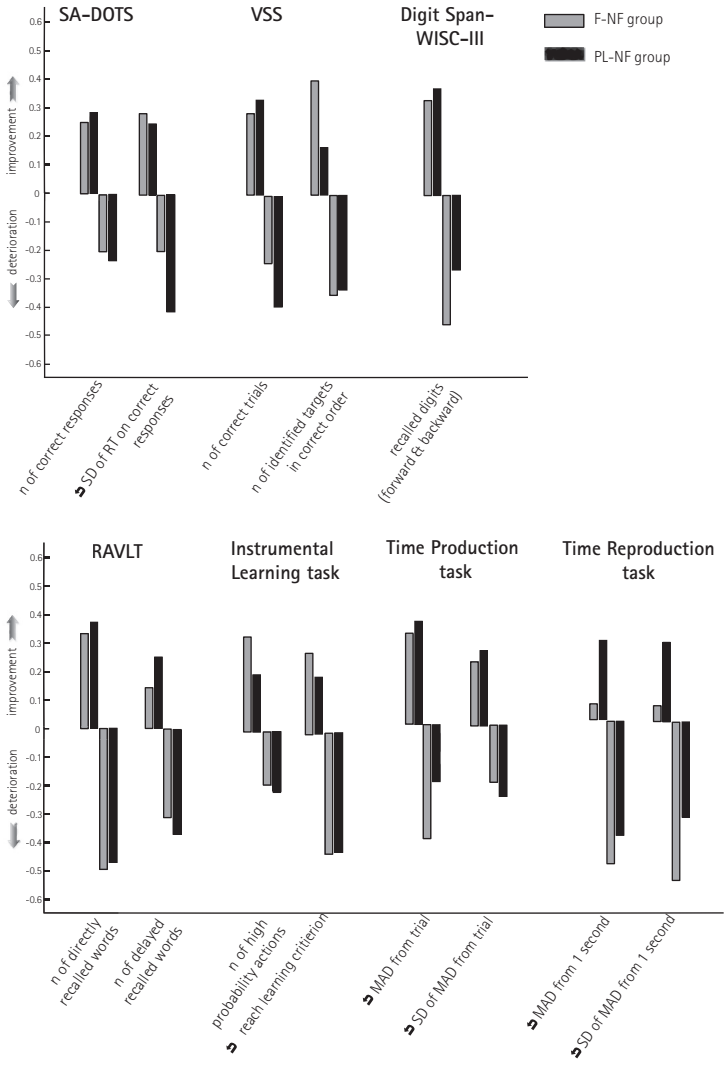

Figure 2 Proportion of children that shows improvement or deterioration on the Reliable Change Index per group for each variable.

Note: The preceding arrow (⮌) indicates an inverted scale; values of which lowering is hypothesized to be an improvement.

Abbreviations: SA-DOTS, Sustained Attention Dots; VSS, Visuospatial Sequencing; Digit Span-WISC-III, Digit Span from the Wechsler Intelligence Scale for Children-III; F-NF, frequency neurofeedback; PL-NF, placebo-neurofeedback; n, number; SD, standard deviation; RT, reaction time; RAVLT, Rey Auditory Verbal Learning Test; MAD, mean absolute deviation.

did not reveal any significant treatment effects and also abolished the previous ANCOVA-results that suggested a potential treatment effect.

Reliable Change Index

Similar to results of Perreau-Linck and colleagues (2010), each participant improved on at least one measure, however, each participant also deteriorated on at least one measure. *Figure 2* displays the percentage children that showed improvement and deterioration per group for each variable. These results did not yield a different conclusion than group analyses did; i.e., F-NF was not superior to PL-NF in improvement on the neurocognitive measures. When focusing on the few children that showed a significant behavioral improvement (i.e., a clinical response), see van Dongen-Boomsma and colleagues (2013), each of these children showed improvement on some neurocognitive measures but deterioration on others.

Post-hoc analyses of the F–NF training

EEG-data during the sessions were available for 10 children (14 children were part of the pilot group in which EEG recordings were not saved and for 4 additional children, data were missing). Mean power was calculated per trained frequency-band and electrode for the first, 10th, 20th, and last session. Seven children showed a change in power towards one of the training targets. However, the variability between sessions was great and no children showed such a desired change in more than one frequency-band. Moreover, all children additionally showed a change in power away from a training target. Clinical responders showed an EEG change in the desired as well as non-desired direction also.

Discussion

This study evaluated whether or not F-NF had beneficial effects on neurocognitive functioning in children with ADHD, based on the results of our placebo-controlled double-blind design, and on a review of the existing literature.

No significant improvement of neurocognitive functioning after F-NF compared to PL-NF was found, which is in line with previous analyses of behavioral effects on the same dataset (van Dongen-Boomsma et al., 2013). Participants who showed positive behavioral responses to F-NF did not show any sign of neurocognitive improvement. In addition, RCIs assessing individual changes in neurocognitive measures for each participant yielded essentially the same results. Furthermore, the only significant interaction effect found was in favor of the PL-NF.

The systematic review suggests that neurocognitive improvements occur over time, but when compared with the control conditions, only two out of the nine RCTs reported a treatment effect of F-NF on some neurocognitive variables (i.e., impulsivity and attention).

The findings of these two RCTs are likely based on chance since the family-wise error rate is large when conducting such a high number of statistical tests. Also, the few papers that report neurocognitive improvements had significant methodological limitations.

The most likely explanation why we did not find improvement of neurocognitive functioning after F-NF is that F-NF is not an effective treatment in ADHD. This conclusion is in line with three recently published placebo-controlled F-NF studies reporting no superior effect on the core behavior symptoms of ADHD (Perreau-Linck et al., 2010; Lansbergen et al., 2011; Arnold et al., 2012; van Dongen-Boomsma et al., 2013). Yet another explanation is that neurocognitive improvement takes longer to manifest and may only be detectable at later time periods after end of the study. Furthermore, the results are based on a selected battery of neurocognitive tests, reflecting neurocognitive functions hypothesized to be impaired in ADHD (Nigg, 2005). The battery focussed more on attentional processes, since these have been shown to be most sensitive to EEG-NF on behavioral level (Arns, de Ridder, Strehl, Breteler & Coenen, 2009). However, not all hypothesized impaired neurocognitive functions were (fully) represented by the chosen test-battery, as is the case for conflict resolution and inhibition. The current study was conducted with care, especially with respect to study design and implementation of a comprehensive neurocognitive test-battery. Due to the requirement of a deviant pre-treatment EEG, this study enabled the child to train specific EEG deviations, in line with the hypothesis that EEG-NF improves or even normalizes deviant pre-treatment brain activity. This requirement did not lead to generalizability problems, because 95% of the participating children did have a deviant pre-treatment EEG.

Nevertheless, this study has some limitations. First, children with all subtypes of ADHD and with an FSIQ of at least 80 points were included in this study. Thus, clear findings of improvements in subgroups of ADHD or children with a significant lower IQ cannot be made. Second, the current cohort is smaller in size than planned, due to recruitment difficulties. Especially the F-NF pilot group, which could have shown improvement driven by implemented learning strategies, was small (n = 14). However, all 95%-CIs of the B-weights, the unstandardized regression coefficients (*Figure 1*) are centered around zero, which suggests that the significant and marginal effects that were found for three parameters were possibly based on chance. Type II errors due to a lack of power are therefore less likely than if the 95%-CIs had not been centered around zero. The RCI analyses also suggest that power was not the most likely explanation of the failure to find an effect. Third, the NF-therapist was not blinded, allowing for the possibility of a different attitude or bias towards the child, depending on group assignment. Fourth, to arrive at a normal distribution, up to 4.9% of the data was removed and to deal with missing data, imputation was used for an average of 4.9%, up to 14.6% of the data. Although these procedures were necessary to perform analyses in the most valid way, these procedures are still regarded as limitations of the study. It should also be noted that the current findings are based on a Caucasian sample and thus should not be presumed to be applicable to other races. Finally, this study aimed to

investigate neurofeedback training delivered in 'care as usual'. Applying 80% positive feedback per condition leaded to a relatively low amount of reward in the more complex protocols. This decision was made in congruency with 'care as usual', but adds a limitation to this study-design. Furthermore, EEG-data from children in the F-NF group (after the two protocol adaptations) recorded during the sessions, showed that not all desired training directions were met. Significant improvement on group level can only solidly be interpreted if all training conditions hypothesized to improve ADHD (on either behavioral or neurocognitive level) are actually improved in the desired direction. In 'care as usual', decisions about adjustments of the threshold were determined by the involved clinical NF-therapist. Future research should focus on different ways to deliver neurofeedback. In addition, the influence of F-NF on neurocognitive domains not covered by the current study therapy should be investigated.

This study was unable to establish positive treatment effects on neurocognitive functioning after F-NF compared to PL-NF. This finding is in line with a systematic review of the current literature, but maybe influenced by the existing study limitations.

Key Points

- This double-blind, randomized, placebo-controlled study could not demonstrate superior effects of F-NF on neurocognitive functioning.
- A systematic review of the existing literature on this topic was also unable to find a firm indication of superior neurocognitive improvement after EEG-NF compared to control conditions.
- The systematic review as well as this small study does not support significant benefits of EEG-NF in its current form on neurocognitive functioning of children with ADHD, however this finding is probably influenced by methodological limitations.

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Supplement

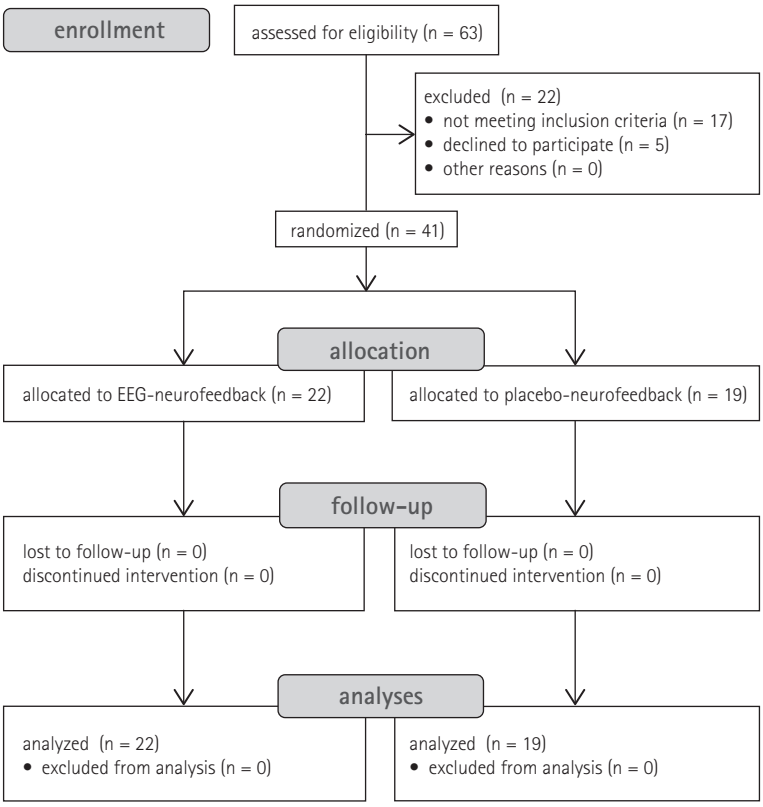

Figure 1 CONSORT flow diagram of study participants.

Abbreviations: CONSORT, Consolidated Standards of Reporting Trials; n, number; EEG, electroencephalographic.

Table 1 Overview studies

Study	**age (years)**[1] **(m, SD)**	**n (total)** *n (F-NF)* *n (controls)*	**duration** **frequency** **n sessions**	**blinding** **P** **R** **NFT**
Linden et al., 1996	5-15	18 *9 (F-NF)* *9 (WL)*	45 minutes 2/week 40 sessions	P: no R: yes NFT: NAP
Heinrich et al., 2004	10.8 (1.8)	22 *13 (SCP-NF)* *9 (WL)*	50 minutes 5/week 25 sessions	P: no R: no NFT: no
Lévesque et al., 2006	10.2 (0.9)	20 *15 (F-NF)* *5 (no F-NF)*	60 minutes 3/week 40 sessions	No blinding
Leins et al., 2007	9.2 (1.5)	38 *19 (F-NF)* *19 (SCP-NF)*	60 minutes 5/week[3] 3x10 sessions	P: yes R: NA NFT: no
Holtmann et al., 2009	10.3 (1.2)	34 *20 (F-NF)* *14 (CAST)*	30 minutes 2/week 20 sessions	P: no R: NA NFT: no
Perreau-Linck et al., 2010	10.4 (1.7)	9 *5 (F-NF)* *4 (PL)*	60 minutes 2/day[5] 40 sessions	P: yes R: no NFT: yes
Wangler et al., 2011	9.6 (1.2)	94 *59 (F-NF/SCP-NF)* *35 (AST)*	50 minutes 2/day[6] 36 sessions	P: no R: yes NFT: no
Bakhshayesh et al., 2011	9.3 (1.9)	35 *18 (F-NF)* *17 (EMG-F)*	30 minutes 2-3/week 30 sessions	P: no R: NA NFT: no
Steiner et al., 2011	12.4 (0.9)	36 *10 (F-NF)* *11 (SCF-AT)* *15 (WL)*	30 minutes 2/week 32 sessions	No blinding

NC- tests	**results**[2]	**results**[2] **Cohen's *d***
K-BIT	*K-BIT**	1.26
CPT	*CPT Impulsivity errors**	-0.39
IVA-CPT	IVA-CPT ***	0.34
Digit Span	Digit Span*	0.17
c- Stroop	c- Stroop*	0.94-1.18
TAP-7	TAP-7 for theta/beta*[4]	0.66, -[4]
HAWIK-II	HAWIK-II for theta/beta****	0.82
	TAP-7 for SCP***-****	0.92-1.09, 0.77
	HAWIK-II for SCP***	0.54
Stop signal-t	*Stop signal-t impulsivity****	-1.03
CPT Digit Span Spatial span VF/CWI-t Key search Zoo map Six part test Beels/Mesula's-ct Child CAT TEA-ch D2	All participants showed significant change in the desired direction on at least one measure with equivalent change occurring in both groups.	-
ANT	ANT** - ****	-0.345-0.171
CPT[7]		
p-p attention-t	*p-p attention-t* *-****[8]	0.68-0.99
CPT	CPT**	-0.70
IVA-CPT	No significant effects at all	-

Table 1 Overview studies

Study	**age (years)**[1] **(m, SD)**	**n (total)** *n (F-NF)* *n (controls)*	**duration** **frequency** **n sessions**	**blinding** **P** **R** **NFT**
Arnold et al., 2012	8.9 (1.7)	39 *26 (F-NF)* *13 (PL)*	45 minutes 2-3/week Max. 40 sessions	P: yes R: NA NFT: NAP

Note: [1] If mean and standard deviation were not available, the inclusion criterion was given. [2] Results are represented by Cohen's *d* interaction when there were significant time effects. Time effects are depicted in standard black and time x group effects in italic and bold in favor of the frequency neurofeedback group. If there are no time effects and/or time x group effects in favor of the frequency neurofeedback group, these are not mentioned. [3] 3 phases of 10 sessions in two weeks, breaks of 4-6 weeks in between, transfer trials between phases. [4] Since this study contained active treatment groups only, time effect rather than treatment effects are given. Time effects consisted of either baseline-endpoint or baseline-follow-up measurements. Analyses were performed for 'below and above average achievers' and are reported as such respectively, separated by a comma. [5] spread over 7-9 weeks. [6] 2-3 times a week with a break of 2-3 weeks between the two blocks. [7] Due to adaptation of the CPT during the study, the authors decided not to publish the results (personal communication with one of the authors). [8] On the paper-and-pencil attention test, there are time-effects for the variables speed and total concentration score, but also for the variable error. So the effects on variable error are in the opposite direction. Time x group effects are seen for these variables too, and also for the variable reaction time. For the CPT there was a time effect for commissions only.

* $p < .05$, ** $p < .01$, *** $p < .005$, **** $p \leq .001$. When different *p*-values are within one test, the minimum and maximum *p*-values are presented. When there is also a time x group interaction, only this *p*-value is reported.

Abbreviations: m, mean; SD, standard deviation; n, number; F-NF, frequency neurofeedback; P, participants; R, rater; NFT, neurofeedback-therapist; NC-tests, neurocognitive tests; Cohen's *d*, effect size of interaction; et al., et alii, meaning 'and others'; WL, waiting list; NAP, not applicable; K-BIT, Kaufman-BRIEF Intelligence Test; SCP-NF, Slow Cortical Potential-neurofeedback; CPT, continuous performance task; IVA-CPT, Integrated Visual and Auditory Continuous Performance Task; c-Stroop, counting Stroop; NA, not available; TAP-7, Testbatterie zur Aufmerksamkeits-prufung; HAWIK-II, Hamburger-Wechsler-Intelligentenztest fur Kinder; CAST, Computerized Attention Skills Training; -t, test; PL, placebo; VF/CWI-t, Verbal Fluency Color Word Interference test; Beels/Mesula's-ct, Beels and Mesula's cancellation task; Child CAT, Children's Apperception Test; TEA-ch, Test of Everyd; d2, d2 Test of Attention; AST, Attention Skills Training; ANT, Attentional Network Test; EMG-F, electromyograph-feedback; p-p attention-t, paper-and-pencil attention test; SCF-AT, Standard Computer Format-Attention Training; tx, tests; W-abbr.-IQ, Wechsler Abbreviated Scale of Intelligence; BRC-tx, 7 Brain Resource Center computer-based normed neuropsychological tests.

NC- tests	results[2]	results[2] Cohen's *d*
Achievement-tx Timed math-t W-abbr-IQ BRC-tx	"No apparent advantage of active treatment over placebo" (no quantitative data reported)	-

Table 2 Characteristics of the administered EEG-neurofeedback for the EEG-neurofeedback group

participant	electrode position	low frequencies (Hz) train downwards	beta, low range (Hz) train upwards	beta, high range (Hz) train downwards
1	F3, F4	4-7	12-15	20-30
2	F3, F4	4-7	12-15	20-30
3	C3, C4	4-7	12-15	
4	P3, C4	4-6	12-15	
5	P3, P4	4-7	12-15	
6	Fz	4-7	12-15	
7	C3, C4	4-7	12-15	
8	C3, C4		12-15	15-20 + 20-25
9	P3, P4	4-5	12-15	24-27
10	F3, F4	4-7	12-14	20-30
11	F3, F4		11-13	18-23 +24-28
12	CZ	4-7	15-20	
13	CZ	4-7	12-16	
14	P3, P4		11-13 +12-15	20-25
15	Fz	3-5	12-15	15-18
16	F3, F4	3-5	12-15	
17	C3, C4	5-7	12-15	
18	CZ	3-4	15-18	
19	F3, F4			15-18 +18-20
20	P3, P4	3-6	12-15	
21	CZ	3-7	12-15	
22	CZ	4-7	15-18	

Note: Electrode positions are according to the international 10-20 system. The trained frequencies deviated 1.5 SD or more from the normative NeuroGuide database and were trained in the opposite direction.
Abbreviations: SD, standard deviation; EEG-neurofeedback, electroencephalographic neurofeedback; Hz, Hertz.

Neurocognitive task descriptions

Sustained Attention Dots task. Dot patterns of random asymmetric 10 x 10 centimeter configurations were randomly presented. Children covered the buttons of a mouse with both hands using their index fingers and had to response 'yes' with their dominant hand if a four-dots pattern was presented, and 'no' with their non-dominant hand if a three- or five-dots pattern was presented. In case of an opposite response an audible error-signal was presented. The interval between a response and the next stimulus was fixed at 250

milliseconds (ms). Reaction times were allowed to vary between 150 and 1000 ms. Responses outside these bounds were labeled as non-valid trials and therefore automatically replaced by a new trial. After 12 practice trials, a total of 600 valid trials were presented in 20-30 minutes (min).

Visuospatial Sequencing. In a 3 x 3 matrix of nine circles, several circles were pointed at with a computer-driven hand. Children had to point at the same circles in correct order with a self-driven hand without having any time constraints. Difficulty level increased after every correct trial by an increase in number of circles or by an increase in complication of the spatial pattern, hence the distance between circles pointed at. One practice trial and a fixed amount of 24 experimental trials were presented in 5-10 min.

Digit Span from the Wechsler Intelligence Scale for Children-III. In the first block, sequences of digits were verbally presented, which the child had to repeat in forward order in the first block and in backward order in the second block. The maximum sequence-length depended on the number of correctly repeated sequences. For each block, 2 trials of each sequence-length (two-eight digits) were presented until two repeatedly incorrect sequences of the same length occurred, at the most 14 presented trials.

The Rey Auditory-Verbal Learning Test. Fifteen unrelated concrete nouns were read aloud in five learning trials with an interval of 2 seconds (sec) between words. This series of words was presented five times. After each presentation immediate recall was tested. Twenty min after the fifth presentation, the number of words correctly recalled indexed long-term memory.

Instrumental Learning Task. In this modified version, each trial involves the simultaneous presentation of a pair of cartoon-pictures. Children were required to choose between one of two stimuli: one associated with a high probability of obtaining feedback (70%) and the other with a low probability of obtaining feedback (30%). The task consists of two different pairs of pictures, each alone signifies the onset of one of 2 distinct trial types: reward or neutral. In the reward trials, positive feedback involved the presentation of a smiley and a point, whereas neutral feedback involved the presentation of a smiley alone. After 14 practice trials, two blocks, each containing 40 trials and two different sets of cartoon-pairs, were performed in a total duration of about 12 min. Children were encouraged to 'break the record' which was fictively set at 25 points (62.5% rewarded responses).

Time Reproduction task. In this task, two light bulbs were presented on the lateral sides of a computer screen. A trial started with the word 'kijk' ('look' in Dutch) displayed above the left light bulb for 3000 ms. Then the left light bulb turned yellow for different durations (4, 8, 12, 16, or 20 sec) in random order. As soon as the light bulb turned back to white, 'jouw beurt' ('your turn' in Dutch) were displayed above the right light bulb. This indicated that the duration of the stimulus had to be reproduced as accurately as possible by pressing a button for the same amount of time as the stimulus presentation, turning the right light bulb yellow. After release of the button, both light bulbs remained white for 1500 ms. After three practice trials, 20 experimental stimuli were presented in around 20 min. Children were not

informed about the length of the intervals and did not receive feedback concerning their performance.

Time Production task. In this task, one-sec intervals had to be produced. After presentation of a fixation cross for 200 ms, an auditory tone of 800 Hz was presented for 50 ms. The end of the tone announced the start of the interval. Children were instructed to produce as accurately as possible the one-sec interval by pressing a button at the end of the one-sec interval. 1500 ms after the subject's response, visual feedback (1000 ms) was given, indicating whether the response was correct, too short, or too long. A response was correct, if it fell between the lower and upper boundary set by a dynamic tracking algorithm. Boundaries were set at 500 to 1500 ms at the beginning of the task. If the response fell within or outside these boundaries, the boundaries of the subsequent trial were respectively narrowed or widened by 100 ms. The task consisted of 10 practice trials and 80 experimental trials are administered. Before the task started a picture of a cartoon-cow was presented for one sec 10 times. Children were instructed to develop a strategy to 'get a feeling' of how long a sec is. These variables were created using MATLAB 7.5.0.

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NON-PHARMACOLOGICAL INTERVENTIONS IN CHILDREN WITH ADHD

Cogmed working memory training

VI

Working memory training in young children with ADHD: A randomized placebo-controlled trial

Martine van Dongen-Boomsma*, Madelon A. Vollebregt*, Jan K. Buitelaar**
& Dorine Slaats-Willemse**

** joint first authors, ** joint last authors*

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Abstract

Until now, working memory training (WMT) has not reached sufficient evidence as effective treatment for attention-deficit/hyperactivity disorder (ADHD) core behavioral symptoms in children with ADHD; for young children with ADHD, no studies are available. To this end, a triple-blind, randomized, placebo-controlled study was designed to assess the efficacy of Cogmed WMT (CWMT) in young children with ADHD.

Fifty-one children (5-7 years) with a *DSM-IV-TR* diagnosis of ADHD (without current psychotropic medication) were randomly assigned to the active (adaptive) or placebo (non-adaptive) training condition for 25 sessions during five weeks. The compliance criterion (≥ 20 sessions) was met for 47 children. The primary outcome measure concerned the core behavioral symptoms of ADHD, measured with the ADHD Rating Scale IV (ADHD-RS). Secondary outcome measures were neurocognitive functioning, daily executive functioning, and global clinical functioning. The influence of the increase in difficulty level (index-improvement) for the treatment group was also analyzed.

A significant improvement in favor of the active condition was found on a verbal working memory task (p = .041; adapted Digit Span of the Wechsler Intelligence Scale for Children-III, backward condition). However, it did not survive correction for multiple testing. No significant treatment effect on any of the primary or other secondary outcome measurements was found. The index-improvement significantly contributed to ADHD-RS and the Behavior Rating Inventory of Executive Function, both rated by the teacher, but revealed no significant group difference.

This study failed to find robust evidence for benefits of CWMT over the placebo training on behavioral symptoms, neurocognitive, daily executive, and global clinical functioning in young children with ADHD.

Trial Registration: ClinicalTrials.gov identifier: NCT00819611.

Introduction

Persistence of neurocognitive deficits in attention-deficit/hyperactivity disorder (ADHD) is strongly associated with occupational problems and morbidity (Barkley & Murphy, 2010; Biederman et al., 2012). Medication is currently the most effective treatment for ADHD (Faraone & Buitelaar, 2010). However, insufficient knowledge about long-term safety (Berger, Dor, Nevo & Goldzweig, 2008) and efficacy (van de Loo-Neus, Rommelse & Buitelaar, 2011), as well as the continuous need for treatment (Jensen et al., 2007; Murray et al., 2008) call for non-pharmacological alternatives. Treatment alternatives have been developed, focusing on improvement of behavioral symptoms by training of ADHD-related neurocognitive functions. One of these cognitive training possibilities is Cogmed working memory training (CWMT). CWMT is based on the rationale that working memory (WM) (i.e., the ability to temporarily hold information while simultaneously manipulating the information [Baddeley, 1986]) is regarded as a fundamental higher-order function, underlying other executive functions (EFs) (Klingberg et al., 2005), and essential for goal-directed behavior (Molfese & Molfese, 2002). Training of WM might improve WM capacity, other neurocognitive functions, and core behavioral symptoms of ADHD.

So far, six studies examined the efficacy of the original version of CWMT in children with ADHD (Klingberg, Forssberg & Westerberg, 2002; Klingberg et al., 2005; Holmes, Gathercole & Dunning, 2009; Beck, Hanson, Puffenberger, Benninger & Benninger, 2010; Gray et al., 2012; Green et al., 2012); all but one (Holmes et al., 2009) used a randomized controlled trial design. Three out of four studies that investigated the efficacy on the core behavioral symptoms of ADHD showed significant treatment effects (Klingberg et al., 2005; Beck et al., 2010; Green et al., 2012). Five studies reported on neurocognitive data and found improvement on at least one trained WM task (Klingberg et al., 2002; Klingberg et al., 2005; Holmes et al., 2009; Gray et al., 2012; Green et al., 2012). Four of these studies reported non-trained neurocognitive outcome measures, with two showing significant improvement (i.e., on WM, response inhibition, and attention) (Klingberg et al., 2002; Klingberg et al., 2005).

Recently, two meta-analyses on non-pharmacological treatment studies in children with ADHD were unable to derive an overall significant ES for the core symptoms of ADHD for cognitive training (Hodgson, Hutchinson & Denson, 2012; Sonuga-Barke et al., 2013) as well as for several neurocognitive functions (Hodgson et al., 2012). In two meta-analytic reviews (Melby-Lervag & Hulme, 2013; Rapport, Orban, Kofler & Friedman, 2013) and two reviews (Shipstead, Redick & Engle, 2012; Chacko et al., 2013) further concerns were expressed about the efficacy of WM training (WMT). Inconsistent findings within and between studies, yielded doubt about the generalization of the trained task effect in this training (Chacko et al., 2013).

In sum, WMT is not yet a well-established treatment in school-aged children with ADHD. Data on the efficacy of WMT in a younger target group are not available yet. A relationship

between ADHD symptoms and WM deficits has already been observed at preschool age (Kalff et al., 2002; Thorell & Wåhlstedt, 2006; Skogan et al., 2013). Whereas medication has been found to be less effective in younger children with ADHD (Riddle et al., 2013), WM shows a rapid development throughout preschool and early school-age (Carlson, 2005). Training children at this young age, before larger demands from school exist, could be beneficial by increasing WM capacity and thereby *preventing* development of cognitive and/or behavioral problems (Rueda, Posner & Rothbart, 2005; Thorell, Lindqvist, Bergman Nutley, Bohlin & Klingberg, 2009). Therefore, investigating the efficacy of WMT in younger children in ADHD is worthwhile.

The present study investigates the efficacy of CWMT in young children (age 5-7 years) with ADHD on behavioral, neurocognitive, and global clinical functioning. To this end, a triple-blind, randomized, placebo-controlled design was used, including an extensive diagnostic procedure and neurocognitive battery assessing different EFs and attention in ADHD.

Methods

Trial design

The Cogmed JM training program designed for the age 4-7 years (developed by Cogmed Cognitive Medical Systems AB, Stockholm, Sweden) was used for the active condition and its (non-adaptive) placebo version. Children with ADHD were randomly and triple-blindly assigned to the active condition (the working memory group [WMG]) or the placebo condition (placebo group, [PLG]) with stratification for age and gender. A research team member, not involved in data collection, assigned the children (in predetermined random order and 1:1 allocation). The study was triple-blind since the participants (the children, their parents, and teachers), the training coaches, and the investigators were blinded to treatment assignment. Endpoint of the study was defined as the date of the assessment after the training, within two weeks after the last training session.

Participants

To be included in the study, children had to meet the following criteria 1) age between 5.5-7.3 years, 2) a diagnosis of ADHD classified according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.; DSM-IV-TR;* American Psychiatric Association, 2000), 3) a full scale intelligence quotient (FSIQ) of at least 80, 4) without current psychotropic medication, and 5) access to a computer with Windows Vista/XP/7 and speakers, and access to internet. Children were excluded in case of 1) current intensive (i.e., weekly) psychotherapy, 2) another comorbid psychiatric diagnosis except for pervasive developmental disorder not otherwise specified or oppositional defiant disorder, 3) any neurological and/or cardiovascular disease, currently or in the past, 4) a serious motor or perceptual handicap, and 5) participation in another clinical trial.

A trained psychologist screened potential participants in a telephone interview with the parents. For children with a positive screening for ADHD symptoms, eligibility was assessed and a diagnostic procedure scheduled that included a developmental and psychiatric assessment with a board certified child and adolescent psychiatrist or a certified child mental health psychologist. This assessment also included the ADHD Rating Scale IV (ADHD-RS; Zhang, Faries, Vowles & Michelson, 2005). Autism spectrum disorders were screened with the Social Communication Questionnaire (Berument, Rutter, Lord, Pickles & Bailey, 1999) and the presence of other psychiatric disorders was screened with the Diagnostic Schedule for Children (Shaffer, Fisher, Lucas, Dulcan & Schwab-Stone, 2000; Steenhuis, Serra, Minderaa & Hartman, 2009). All were subsequently examined in a clinical assessment. If intelligence had not been assessed in the past 1.5 years, the subtests picture completion, vocabulary, block design, and similarities from the Wechsler Preschool and Primary Scale of Intelligence Revised (Wechsler, 1989), translated in Dutch (WPPSI-R NL; van der Steene, 1997) were administered.

Recruitment (May 2009-March 2013, predetermined) and assessments were performed at Karakter Child and Adolescent Psychiatry University Centre in Nijmegen, The Netherlands. Children were recruited among referrals to the centre and from responders to advertisements on the website and magazine of the Dutch Parents Association of Children with ADHD, and advertisements in two Dutch local newspapers. The training took place at home, except for one child who trained at school due to the lack of computer-facilities at home.

The study was approved by the local Dutch Medical Ethics Committee and conducted in accordance with the declaration of Helsinki. All parents gave their written informed consent before participation; their children gave their oral assent. Travel expenses were partially reimbursed. All children received a gift certificate of 10 euro.

At the start of the study, the only published randomized controlled trial on CWMT reported an effect size (ES) of 0.6 for their primary outcome (Klingberg et al., 2005). Given an alpha error of .05 and an estimated dropout of 10%, a sample of 50 children per group gives a power of 81.2% to detect treatment effects of 0.6 ES.

Interventions

Both conditions were translated in Dutch by Cogmed qualified practice BeterBrein (Groningen, The Netherlands). The training consisted of 25 sessions of 15 minutes, five days a week. Both conditions included seven visuospatial WM tasks. For all tasks, a number of visual stimuli were presented sequentially on the computer screen and the child had to remember both their location and order to subsequently respond by mouse clicking the targets in correct order. In the active condition, the software adjusted task difficulty based on the child's performance. The placebo condition was identical to the active condition, except that the items to be remembered did not exceed the starting level of two items. Training data were uploaded to a server after each training session. The parents were instructed to encourage the child during the training course, and gave small rewards every five sessions and after training completion. A certified Cogmed coach contacted the parents

every week to evaluate the performance and motivation of the child with a standardized questionnaire. A complier was defined by fulfilment of at least 20 sessions as defined in the study by Klingberg (2005).

Behavioral outcomes

The primary outcome measure was the difference between baseline and endpoint on the total symptom-score of the ADHD-RS rated by the investigator (ADHD-RS-INV), using a 4-point Likert scale (0 = never occurs, 1 = occurs sometimes, 2 = occurs often, 3 = occurs very often). The teacher also rated the ADHD-RS at baseline and endpoint (ADHD-RS-T).
Another outcome measurement was the change between baseline and endpoint on the Dutch version of the Behavior Rating Inventory of Executive Function (BRIEF), filled out by parents (BRIEF-P) and teacher (BRIEF-T) (see *appendix* for detailed information) (Gioia, Isquith, Guy & Kenworthy, 2000; Smidts & Huizinga, 2009). The BRIEF-P was additionally used to determine WM deviance at baseline by using the test-scores of the WM subscale. The amount of children that scored above clinical threshold ($t \geq 6.5$) was determined.

Neurocognitive outcomes

A neurocognitive assessment of approximately 60 minutes included the adapted Digit Span from the Wechsler Intelligence Scale for Children-III (DS-WISC-III) to measure verbal WM (Wechsler, 1949; Smidts, 2003; Raaijmakers et al., 2008), the Knox Cubes Leidse Diagnostische test (LDT) to measure short term memory for spatial sequences (Schroots & van Alphen de Veer, 1976), the Sentences of the WPPSI-R NL (Sentences) to assess memory for sentences (Wechsler, 1991), the Shortened Raven Coloured Progressive Matrices (RAVEN) for non-verbal reasoning ability (Raven, 1998), the Day-Night Stroop Task (DNST) to measure motor inhibition (Gerstadt, Hong & Diamond, 1994), the Sustained Attention Dots task, version 02K (SA-DOTS-02K) to measure visual sustained attention (de Sonneville, Schmidt, Michel & Batzler, 1990; de Sonneville, 1999) and the Shape School to assess inhibition and switching processes (Espy, 1997; Smidts & Groot, 2005). The *appendix* contains the neurocognitive task descriptions.

Global clinical functioning outcomes

Global clinical functioning served as a secondary outcome measure. The Clinical Global Impressions-Improvement scale (CGI-I) was administered after the training to measure training effect. The CGI-I consists of a single item 7-point scale (1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse) (Guy, 1976). Responders were defined as children that were rated 'much improved' or 'very much improved'.
Global improvement was assessed as the difference between baseline and endpoint on the Children's Global Assessment Scale (CGAS) (scale 0–100, with 0 = most affected global functioning and 100 = best global functioning) (Shaffer et al., 1983).

Index-improvement

Trained task effects were assessed through a task improvement index (index-improvement) provided by Cogmed, calculated by subtracting the 'start index' (average performance on day 2 and 3 from four of the tasks in the program) from the 'max index' (average of the best two trials over the course of the training).

Statistical methods

Statistical analyses were performed with IBM SPSS Statistics, version 20.0 (Armonk, New York; IBM Corp.). For each parameter, mean (M) and standard deviation (SD) were computed. The significance level was set at $p = .05$ (two-tailed). To evaluate the impact of multiple comparisons, a Bonferroni correction was performed, in which the amount of dependent variables corrected for was defined per level (the initial *p*-value of the matching level was divided by 6 behavioral, 18 neurocognitive, and 2 global clinical variables, resulting in a significance level of $p = .008$, $p = .002$, and $p = .025$ respectively). Missing data were imputed, using multiple imputation with 20 iterations (Donders, van der Heijden, Stijnen & Moons, 2006). Outliers (defined as 25% of the size of the largest leaf entry in the clustering feature tree, based on the default definition used by SPSS 20.0) were removed. When all assumptions were valid, analysis of the covariance (ANCOVA) was applied to optimize control for the variance at baseline. For each parameter the endpoint measurement was the dependent variable, the baseline measurement a covariate, and group the independent variable. For the tasks containing a RT-accuracy trade-off (DNST, SA-DOTS-02K, and the Shape School), accuracy was an additional covariate. To inspect the overall pattern of the results, the 95% confidence intervals (95%-CIs) of the b-values were calculated. When the parametric assumptions were not valid, non-parametric testing on the change score (baseline subtracted from endpoint score) was performed on non-imputed data, or the Reliable Change Index (RCI) (Jacobson & Truax, 1991) was measured in case of a very small remaining sample. Difference between the groups on the CGI-I was tested by a chi-square test. ESs (Cohen's *d;* the difference between the change scores [endpoint-baseline] of each group divided by the pooled standard deviations of both groups at baseline) were calculated on the non-imputed data.

Post-hoc, the difference between the start index and max index in the WMG was analyzed using a paired samples t-test. The difference between groups regarding the start index was calculated using a Mann-Whitney-Wilcoxon test, since it was a priory known that per definition the variance of distributions would be different between groups. The influence of the index-improvement in the WMG was evaluated for the DS-WISC-III, the total scores on the BRIEF-P, BRIEF-T, ADHD-RS-INV, and ADHD-RS-T, and the CGI-I. These scales were thought to reflect near to far transfer, respectively. If ANCOVAs were performed in the main analyses, they were repeated post-hoc with the index-improvement as additional covariate. If non-parametric tests were performed in the main analyses, a Pearson correlation between the change scores and index-improvement was determined. The CGI-I was tested using an

analysis of the variance (ANOVA) with the CGI-I as fixed factor and the index-improvement as dependent variable. We calculated the correlation between the WM deviance measured with the BRIEF-P at baseline and the index-improvement to determine the importance of baseline deficits to the ability to improve on the training. Finally, in addition to the analysis of all compliers describe above, an intention-to-treat (ITT) analysis was performed on all randomized children (independent of treatment completion) using the ADHD-RS-INV.

Results

All variables were distributed normally within groups and variances were homogeneous among groups, unless explicitly stated and dealt with accordingly. See *Table 2* for all statistical results. See the *appendix* for detailed results and an overview of the 95%-CIs of the group difference b-values. Note that time differences, i.e., improvement independent of the groups, were often present.

Demographic and clinical characteristics

In total, 53 children were eligible for the study and were clinically examined (*Figure 1*). Two children were excluded; one due to technical problems and one due to a FSIQ<80. Twenty-seven children were allocated to the WMG and 24 to the PLG. Four children finished less than 20 sessions and were defined as decliners. Forty-three children completed all training-sessions; two children completed 21 and two 22 training-sessions. Complier analyses thus were conducted for 47 children. Expected as a result of randomization, no differences were found on baseline characteristics (see *Table 1*). All children were psychotropic medication-naïve, except for one child that quit medication (pipamperon and methylphenidate) more than two months before the start of the study.

WM deficits at baseline

For six children, the WM subscale of the BRIEF-P was missing. A clinical threshold ($t \geq 6.5$) was reached by 29.3% of the children (12/41). Another 31.7% (13/41) scored subthreshold (under clinical threshold but $t \geq 6$).

Behavioral functioning outcomes

There were no treatment effects of the primary outcome measurement, i.e., any of the ADHD-RS-INV subscales (total: $t(41) = -0.237$, $p = .813$; inattentive: $p = .380$; hyperactive/impulsive: $t(41) = -0.655$, $p = .512$). Neither were treatment effects observed on the ADHD-RS-T or the BRIEF-P and BRIEF-T composite scores.

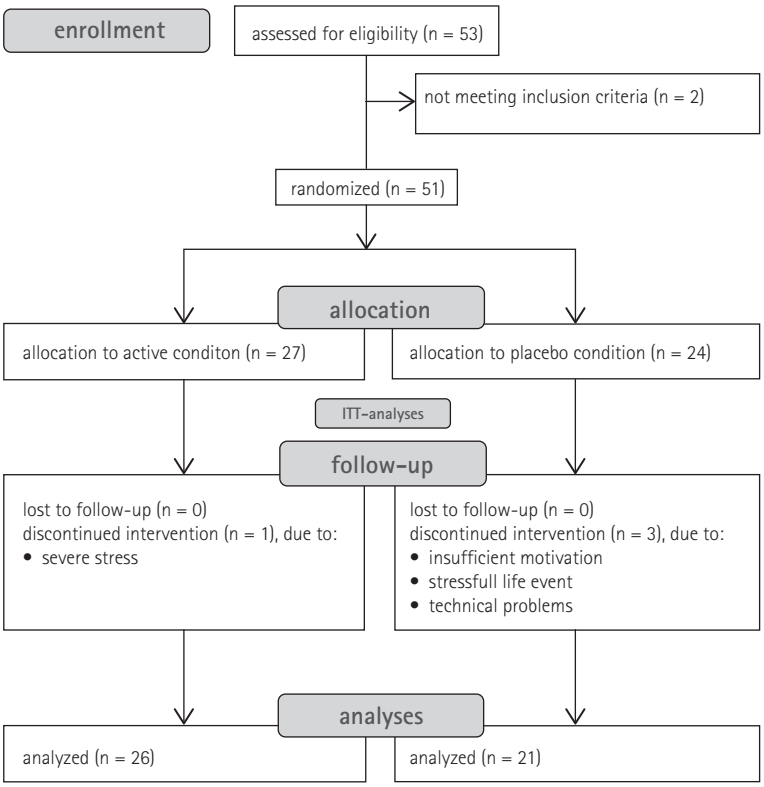

Figure 1 CONSORT flow diagram of study participants.

Abbreviations: CONSORT, Consolidated Standards of Reporting Trials, n, number; ITT, intention-to-treat.

Neurocognitive functioning outcomes

A significant difference in favor of the WMG was found on the backward (BW) condition of the DS-WISC-III ($p = .041$), which did not survive the Bonferroni corrected significance level of $p = .002$. No treatment effect was found on the forward condition ($p = .980$), or any of the other neurocognitive functioning outcomes.

Global clinical functioning outcomes

There were no significant differences on the global clinical functioning outcomes (CGI-I: χ^2-test, $p = .124$; CGAS: $t(44) = -0.658$, $p = .514$).

Table 1 Descriptive characteristics

characteristics	WMG (n = 26)	PLG (n = 21)	analysis (T, χ^2)
age, m (SD), y	6.5 ± 0.6	6.6 ± 0.7	*p* = .536
gender, n (%)			
male	18 (69.2)	16 (76.2)	*p* = .596
race, n (%)			
Caucasian	26 (100)	21 (100)	*p* = 1.00
full-scale IQ, m (SD)	99.9 ± 10.2	96.8 ± 10.7	*p* = .325
BRIEF WM t-score (m ± SD)[x]	60.3 ± 7.4	61.1 ± 7.2	*p* = .749
ADHD subtype, n (%)			*p* = .168
combined	21 (80.8)	12 (57.1)	
inattentive	2 (7.7)	2 (9.5)	
hyperactive/impulsive	3 (11.5)	7 (33.3)	
comorbidity, n (%)			*p* = 1.00
pervasive developmental disorder NOS	0 (0)	1 (4.8)	
oppositional defiant disorder	1 (3.8)	2 (9.5)	
developmental coordination disorder	0 (0)	2 (9.5)	
disruptive behavior NOS	0 (0)	1 (4.8)	
nocturnal enuresis	1 (3.8)	0 (0)	
parent-child relational problem	0 (0)	1 (4.8)	
no comorbidity	24 (92.3)	14 (66.7)	

[x] WMG n = 22, PLG n = 19.

Abbreviations: WMG, working memory group; n, number; PLG, placebo group; T, independent sample t-test; χ^2, chi-square test; m, mean; SD, standard deviation; y, years; *p*, probability; IQ, Intelligence Quotient; BRIEF, Behavior Rating Inventory of Executive Function; WM, working memory; ADHD, attention-deficit/hyperactivity disorder; NOS, not otherwise specified.

The relation between index-improvement and outcome measures

There was a significant difference between groups ($p < .001$) on the start index. Nevertheless, the WMG significantly improved on the task, as illustrated by a significant difference between the start index and the max index ($t(25) = 15.59$, $p < .001$). The mean index-improvement of all Cogmed JM users in 2012 (18.44 ± 6.17; S. Söderqvist, Cogmed employee, personal communication, October, 17, 2013) did not significantly differ from the mean index-improvement of the WMG in the current sample (16.60 ± 5.170; $t(26) = -1.818$, $p = .081$). A correlation analysis (chosen because of violation of normality) showed no relationship between index-improvement and the DS-WISC-III-BW ($r = 0.129$, $p = .568$). Also, the BRIEF-P and the ADHD-RS-INV were not influenced by the index-improvement as covariate. The outcome of the BRIEF-T and ADHD-RS-T however, were significantly influenced by the index-improvement, even though no group difference was revealed

(Global Executive Composition BRIEF-T: index-improvement: t(42) = 2.401, p = .016; treatment-effect: t(42) = 1.623, p = .105; ADHD-RS-T: index-improvement: t(42) = 2.073, p = .038; treatment-effect: t(42) = 1.267, p = .205). Lastly, an ANOVA between the improvement CGI-I categories as fixed factor and the index-improvement from the WMG as dependent variable, did not show an effect (F(20) = 0.145, p = .866). We were also unable to establish a significant correlation between the baseline WM t-score on the BRIEF-P and the index-improvement (r = -.268, p = .228).

Compliance to the training

Data on the ADHD-RS-INV were available for two non-compliers that finished 16 and 17 sessions, but not for those that finished 6 and 13 sessions. In addition, data were available for four children (three for the primary outcome) that were defined as compliers, but did not finish all 25 sessions. Since an ITT-analysis would only expand the data with two children, children who completed all sessions were compared to children who completed fewer sessions instead. Of eight children that did not complete all sessions of training, only one was from the WMG. Assumptions to perform ANCOVA were valid after removal of outliers. An ANCOVA controlling for baseline showed significant group differences between children that did and did not complete the entire training, independent of treatment assignment (total: t(40) = -3.172, p = .003; inattentive: t(40) = -2.858, p = .007; hyperactive/impulsive: t(4) = -2.901, p = .006). Note however, that group sizes were very unequal (completers n = 38, non-completers n = 5).

Discussion

This study was designed to investigate the efficacy of CWMT in young children with ADHD. A triple-blind, randomized, placebo-controlled design was used with outcome measures concerning behavioral, neurocognitive, and global clinical functioning.

The results showed a significant improvement in favor of the active condition on a verbal WM task, but this effect did not survive correction for multiple testing. Further, both the active and the placebo condition improved on many outcome measures over time. However, no additional effect in favor of the active condition was found on any of the primary or other secondary outcome measurements. The task improvement index influenced the BRIEF and ADHD-RS outcome, both evaluated by teacher, but correction for this variable did not yield significant group differences.

The hypothesis underlying WMT is that WM performance principally reflects the effects of a general-purpose attentional system and that effective WM training should 1) lead to a growth in a domain-general attentional capacity, and 2) show transfer effects to untrained tasks (Barnett & Ceci, 2002; Shipstead et al., 2012). Near-transfer effects are effects on tasks closely related to trained tasks, whereas far-transfer effects are effects on tasks not

Table 1 Results on behavioral, neurocognitive, and global clinical functioning

	WMG–baseline	WMG–endpoint	PLG–baseline
ADHD-RS–INV, m (SD)			
total Sx	35.9 ± 6.1	32.4 ± 5.7	32.3 ± 4.1
inattentive Sx	16.8 ± 3.8	15.0 ± 4.7	15.4 ± 2.4
hyperact./imp. Sx	19.0 ± 4.1	17.4 ± 3.2	16.9 ± 3.6
ADHD-RS-T, m (SD)			
total Sx	31.2 ± 7.2	27.5 ± 10.1	29.3 ± 6.7
inattentive Sx	13.5 ± 5.7	12.6 ± 6.5	14.9 ± 4.9
hyperact./imp. Sx	17.7 ± 4.7	15.0 ± 5.3	14.3 ± 5.3
BRIEF-P, m (SD)			
BRI	60.4 ± 12.8	58.4 ± 11.4	56.8 ± 10.0
MI	91.4 ± 11.8	94.4 ± 10.2	92.6 ± 11.2
GEC	151.8 ± 20.7	152.8 ± 13.9	149.4 ± 17.1
BRIEF-T, m (SD)			
BRI	50.3 ± 14.6	57.4 ± 12.9	54.7 ± 13.4
MI	88.8 ± 21.4	93.1 ± 20.2	92.7 ± 14.5
GEC	149.2 ± 31.7	150.4 ± 28.2	147.4 ± 22.5
DS-WISC-III, m (SD)			
FW	5.7 ± 0.9	5.9 ± 1.3	5.4 ± 1.0
BW	2.6 ± 0.7	2.9 ± 0.9	2.8 ± 0.8
LDT, m (SD)			
FW	7.4 ± 2.9	8.7 ± 2.1	5.8 ± 2.4
BW	4.0 ± 1.6	4.9 ± 2.2	3.4 ± 1.6
Sentences, m (SD)	21.0 ± 5.9	21.4 ± 6.0	20.1 ± 4.5
RAVEN, m (SD)	22.0 ± 5.9	24.7 ± 4.8	20.5 ± 5.7
DNST, m (SD)			
control time	35.0 ± 11.0	28.4 ± 4.2	35.7 ± 11.4
switch time	35.6 ± 7.5	33.9 ± 7.1	39.4 ± 8.7
difference	0.6 ± 11.3	5.5 ± 5.7	4.9 ± 9.7
SA-DOTS-02K, m (SD)			
RT	1315.0 ± 247.2	1255.5 ± 249.6	1370.6 ± 317.5
SD-RT	231.8 ± 79.2	278.0 ± 97.4	289.2 ± 83.0
Shape School, m (SD)			
Control			
red RT	1780.1 ± 449.8	1630.9 ± 632.7	1778.4 ± 790.8
red SD-RT	587.2 ± 454.1	455.0 ± 434.5	560.1 ± 326.5
yellow RT	1635.7 ± 426.0	1603.7 ± 478.6	1626.8 ± 422.7
yellow SD-RT	511.9 ± 536.7	503.7 ± 354.1	302.3 ± 251.0
Switch			
red RT	1992.1 ± 481.2	1945.4 ± 712.7	2102.2 ± 552.8
red SD-RT	502.2 ± 351.1	302.9 ± 345.0	353.1 ± 278.0
yellow RT	2133.4 ± 554.5	2079.8 ± 949.9	2221.0 ± 791.0
yellow SD-RT	516.4 ± 333.2	552.9 ± 1035.4	545.8 ± 348.4

PLG-endpoint	n	time effect	group effect	test	Cohen's *d*
	22-19				
30.3 ± 7.4		t(41) = 2.719**	t(41) = -0.237	ANCOVA	0.28
14.9 ± 4.1		NAP	-	MWW	0.40
15.4 ± 5.0		t(41) = 3.789***	t(41) = -0.655	ANCOVA	0.03
	18-14			ANCOVA	
25.5 ± 7.7		t(42) = 2.103*	t(42) = -0.398		-0.01
14.0 ± 4.7		t(42) = 2.732**	t(42) = 0.318		0.00
11.5 ± 4.9		t(42) = 2.320*	t(42) = -1.175		-0.02
	15-16			ANCOVA	
57.2 ± 10.0		t(43) = 6.740***	t(43) = 0.553		0.21
92.7 ± 13.3		t(43) = 2.654**	t(43) = -0.617		-0.25
149.9 ± 20.7		t(43) = 4.110***	t(43) = -0.307		-0.03
	14-14				
53.1 ± 10.8		t(43) = 4.017***	t(43) = -0.095	ANCOVA	-0.62
96.3 ± 15.5		NAP	-	MWW	-0.04
149.4 ± 22.6		t(43) = 2.593**	t(43) = -0.109	ANCOVA	0.03
	22-21	NAP		MWW	
5.4 ± 0.9			-		0.21
2.4 ± 1.0			*		0.93
	26-19	NAP		MWW	
7.0 ± 2.7			-		0.04
4.1 ± 2.3			-		0.13
21.2 ± 5.1	25-21	t(44) = 8.973***	t(44) = 0.800	ANCOVA	-0.13
23.7 ± 5.0	26-21	t(44) = 6.174***	t(44) = -0.106	ANCOVA	-0.09
	20-20				
34.6 ± 10.0		NA	NA	NA	NA
37.9 ± 6.9		NA	NA	NA	NA
3.2 ± 8.2		t(39) = 1.782	t(39) = 1.399	ANCOVA+	0.63
	23-20			ANCOVA+	
1231.0 ± 410.7		t(40) = 2.104*	t(40) = -0.288		0.28
311.6 ± 93.0		t(40) = 2.863**	t(40) = 0.136		0.29
				ANCOVA+	
1474.7 ± 714.9	24-15	t(35) = 1.428	t(35) = 0.018		-0.26
387.0 ± 416.5	23-12	t(31) = -0.113	t(31) = -0.976		-0.10
1566.3 ± 669.1	24-13	t(33) = 0.966	t(33) = 0.203		-0.07
255.2 ± 275.6	18-10	t(24) = 0.395	t(24) = -0.738		-0.08
1743.3 ± 590.6	22-11	t(29) = 2.924**	t(29) = -0.679		-0.62
325.3 ± 301.2	17-8	t(21) = 0.346	t(21) = 1.581		0.52
1728.3 ± 718.0	21-13	t(30) = 1.032	t(30) = -1.179		-0.67
185.6 ± 168.0	18-10	t(24) = 1.995	t(24) = -1.803		-1.17

Table 1 Continued

	WMG-baseline	WMG-endpoint	PLG-baseline
CGI-S, n (%)		NAP	
3-mildly ill	1 (4.2)		1 (5)
4-moderately ill	17 (70.8)		17 (85)
5-markedly ill	6 (25)		2 (10)
CGI-I, n (%)	NAP		NAP
2-much improved		1 (4)	
3-minimally improved		11 (44)	
4-no change		12 (48)	
5-minimally worse		1 (4)	
CGAS, m (SD)	51.2 ± 6.8	53.8 ± 6.7	52.3 ± 7.0

* $p < .05$, ** $p < .01$, *** $p < .001$.
Note: '-' indicates a non-significant ($p < .05$) result after non-parametric testing.
Abbreviations: WMG, working memory group; PLG, placebo group; n, number of children for which both a baseline and endpoint measurement were available; Cohen's *d* of interaction, the difference in change scores (endpoint-baseline) between groups (WMG-PLG) divided by the pooled baseline standard deviation based on the standard deviation while taking into account the overlapping non-imputed n per group; ADHD-RS-IV, attention-deficit/hyperactivity disorder Rating Scale IV; -INV, rated by the investigator; SD, standard deviation; Sx, symptoms; hyperact./imp., hyperactive/impulsive; NAP, not applicable; ANCOVA, analysis of covariance with the measurement at baseline as covariate; MWW, Mann–Whitney–Wilcoxon; -T, rated by the teacher; m, mean; BRIEF, Behavior Rating Inventory of Executive Function; -P, rated by parent; BRI, Behavioral Regulation Index; MI, Metacognition Index; GEC, Global Executive Composition; DS-WISC-III, adapted Digit Span of the Wechsler Intelligence Scale for Children-III; FW, forward condition; BW condition, backward; LDT, Knox Cubes Leidse Diagnostische Test; Sentences, Sentences of the Wechsler Preschool and Primary Scale of Intelligence revised, translated in Dutch; RAVEN, Shortened Raven Coloured Progressive Matrices; DNST, Day-Night Stroop Task; NA, not analysed; +, additionally controlling for correct responses; SA-DOTS-02K, Sustained Attention Dots task, version 02K; RT, response time; SD-RT, standard deviation response time; CGI-S, Clinical Global-Impressions Severity scale; CGI-I; Clinical Global Impressions-Improvement scale; χ^2; chi-square test; CGAS, Children's Global Assessment Scale.

closely related to trained tasks (Melby-Lervag & Hulme, 2013). This study suggested improvement on the trained visuospatial WM represented by a significant improvement on the training in the active condition. A near-transfer effect was not maintained after correcting for multiple testing. Far-transfer effects were absent. These results were in line with recent meta-analyses and reviews (Shipstead et al., 2012; Chacko et al., 2013; Melby-Lervag & Hulme, 2013; Rapport et al., 2013), which questioned if WMT could enable transfer effects. Rapport and colleagues explicitly targeted near vs. far transfer effects in their meta-analysis and concluded that CWMT was associated with moderate near transfer effects only ($d = 0.63$). Cognitive and behavioral far transfer effects were lacking. Moreover, higher ESs were found for unblinded raters than for blinded raters (Rapport et al., 2013;

PLG-endpoint	n	time effect	group effect	test	Cohen's *d*
NAP	24-20	NAP	NAP	NAP	NAP
2 (9.5) 3(14.3) 15 (71.4) 1 (4.8)	25 -21	NAP	-	χ^2 test	NAP
53.2 ± 9.3	26-21	t(44) = 4.593***	t(44) = -0.658	ANCOVA	0.38

Sonuga-Barke et al., 2013). Our study showed an ES of 0.28 for the total score on the ADHD-RS-investigator, which is in accordance with the mean ES of 0.24 for cognitive training as reported by probably blinded raters in a meta-analysis on non-pharmacological treatment studies in children with ADHD (Sonuga-Barke et al., 2013).

Despite the robust trial design, this study had some limitations. First, the CWMT placebo condition has been criticized in that it does not match with the intensity of parents' support of the active condition. Although the placebo condition is designed to be as long and intense as the active condition, due to a stable difficulty level along with improvement in training skills, training is less challenging and training time per session is shorter in the placebo condition than in the active condition. This possibly influenced the quality of

interaction with the parent and involvement of the coach during training negatively (Chacko et al., 2013). In line with the concern by Chacko and colleagues, compliance in the current study was found to be different between groups, since 87.5% of the children who did not complete the training were in the PLG. Comparison between children who did and did not complete the training showed a group difference in favor of the completers' group. The impact of these findings would be more relevant if treatment effects had been found in this study. Second, although the coach was able to encourage parents and child, motivation and support of parents and child in this study - in contrast to CWMT in clinical practice – could not be based on individual training results because the coach was blinded to group assignment (due to the triple-blind design). Furthermore, treatment outcome studies in youth with ADHD have shown that support and motivation may improve parent reports of ADHD symptoms (Sonuga-Barke, Daley, Thompson, Laver-Bradbury & Weeks, 2001), suggesting a need to work in partnership with the family. Third, since our study showed time effects independent of group assignment, inclusion of a passive control condition (i.e., a waiting list group) might have differentiated between non-specific training effects and learning effects. Fourth, the sample was smaller in size than planned, due to recruitment difficulties, leading to an elevated chance for making a type-II error. The fact that the 95%-CIs of the b-values were centred around zero (*see Figure 1, appendix*), supported an actual lack of difference between groups rather than a type-II error. Furthermore, imputation was necessary to deal with missing data. Due to the sample characteristics, current findings should not be presumed to be applicable to races other than Caucasian, other age-ranges than 5-7 years, or children with IQs lower than 80.

There are several possible explanations for the lack of transfer effects of CWMT to ADHD symptoms and global functioning. First, weekly call-contact between therapist and parents in CWMT may be insufficient to keep parents active and involved. Second, coaching based on training results -equal to coaching in clinical practice- might already enlarge the possible efficacy. Third, CWMT training can be seen as an intensive but rather short intervention. A much longer training period may be more effective. This may however have other trade-off effects, such as lower feasibility, less compliance, and larger drop-out percentage, and may induce side-effects as well, such as fatigue. Fourth, an active transfer component might be further created if WM and EF exercises are implemented in daily life. Practising in real life situations during meal times, leisure activities, etc. might be a decisive factor regarding efficacy. Another explanation is that an intervention that improves a single EF component such as WM may be too limited to lead to meaningful reductions of behavioral symptoms. In this way, CWMT is possibly too much a stand-alone intervention. Probably a broader set of EFs, such as inhibition, set shifting, and WM, should be addressed. Yet another possibility is that WM deficits are not part of the causal pathway to ADHD symptoms. Rather, WM deficits may be associated with ADHD as a form of 'cognitive comorbidity'. Moreover, it has been suggested that CWMT would be more accurately classified as a short-term memory training (Gibson et al., 2011; Shipstead et al., 2012; Rapport et al., 2013) than a WMT. The

claim of CMWT is that improving the targeted memory functioning would lead to improvement regarding the academic, behavioral, and cognitive benefits. However, the specific targeted memory is not clear-cut the most impaired executive function in ADHD (Rapport et al., 2013).

This study provides clinical implications by casting doubts on claims that CWMT is an effective treatment in young children with ADHD. We were able to provide support for the hypothesis that changes can be brought in aspects of WM in children as young as 5-7 year old, but unable to support the hypothesis that changes in trained measures can affect untrained measures. Future studies might consider a more specific (i.e., coaching based on training results) and active role for the coach (e.g. weekly face-to-face contacts), with the consequence that the coach should be unblinded and should focus on better understanding of affected components and the neural bases of WM to optimize the possible effects of this training. This recommendation is based on the general concerns about enabling transfer effects in cognitive training programs (Shipstead et al., 2012; Chacko et al., 2013; Melby-Lervag & Hulme, 2013), and although some studies showed neural indices for WMT (Olesen, Westerberg & Klingberg, 2004; McNab et al., 2009; Takeuchi et al., 2011), a specific neural mechanism underlying WMT and transfer effects has not yet been indicated (Buschkuehl, Jaeggi & Jonides, 2012).

Key Points

- So far, reviews and meta-analyses did not prove WMT to be a well-established treatment for children with ADHD.
- The present study failed to support robust benefit of CWMT on behavioral, neurocognitive, and global clinical functioning in young children with ADHD, i.e., no transfer effect was found.
- Guidance regarding CWMT as a treatment for children with ADHD must be in line with these findings.
- Future research might focus on discovering a specific neural mechanism underlying WMT and transfer effects.

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Appendix

Methods

Behavior Rating Inventory of Executive Function (BRIEF)

The Dutch BRIEF consists of 75 items. Each item pertains to specific everyday behavior, relevant to executive functioning of which 72 comprise the eight clinical scales. The remaining items comprise (among others) two validity scales 'Negativity' (the extent to which the respondent answers selected BRIEF items in an unusually negative manner relative to clinical samples) and 'Inconsistency' (the extent to which the respondent answers similar BRIEF items in an inconsistent manner relative to the clinical samples, a measure of validity). The items of the BRIEF are categorized into eight clinical scales: 'Inhibit', 'Shift', 'Emotional Control', 'Initiate', 'Working Memory', 'Plan/Organize', 'Organization of Materials', and 'Monitor'. Two composite scores can be obtained based on these eight scales: Behavior Regulation Index (BRI) based on the first three and the Metacognition Index (MI) based on the latter four scales. BRI and MI form the summary score Global Executive Composite (GEC). In case the inconsistency score was acceptable, the BRI, MI, and GEC scales were the variables of interest.

Adapted Digit Span from the Wechsler Intelligence Scale for Children-III (DS-WISC-III)

This task required the child to repeat strings of words, i.e., concrete unrelated nouns, which were read aloud. In the forward condition (FW), this repetition should be in similar order, in the backward condition (BW) in reversed order. The maximum presented sequence-length depended on the number of correctly repeated sequences. For each block, 2 trials of each sequence-length (two-six words) were presented until two repeatedly incorrect sequences of the same length occurred, with a maximum of 10 presented trials per condition. The total number of correctly recalled words the child repeated in FW and BW order were the variables of interest.

Knox Cubes Leidse Diagnostische Test (LDT)

In this task the child had to repeat a series of ticking blocks in FW and BW order. First, after having watched the instructor ticking series of blocks, series should be repeated in FW order. The second part of the task required BW repeating. Preceding the task, two 2-series practice trials were offered on which the child was not scored. The actual task started with one 2-series trial, followed by four 3-series, four 4-series, and three 5-series. The task finished when the child repeated three sequences erroneously or after the last presented trial. The total number of correctly FW and BW repeated taps were the variables of interest.

Sentences from the WPPSI-R NL (Sentences)

Sentences with variable length of 2-19 words were read aloud by the instructor and had to be repeated by the child. Maximum possible score varied with length from one to five points per sentence. Individual score was acquired by subtracting the number of errors (i.e., omission of a word, interchange of words, substitution by a new word, addition of a new word) from the maximum score. The sum score of all sentences was the variable of interest.

Shortened Raven Coloured Progressive Matrices (RAVEN)

Thirty-six items of the RAVEN were presented in three sets (A, Ab, B); 12 items per set. Each of the set of items started with a problem and ascended in order of the difficulty by building on the argument of what was done before. This ascending order of the difficulty approach provided the respondent with five opportunities to become familiar with the frame and method of thought required to solve the problems. The variable of interest was the total number of problems solved.

Day-Night Stroop task (DNST)

This task was programmed and presented using Presentation software (Neurobehavioral Systems, Inc). DNST was administered in two blocks of trials; a control and conflict block. Each block contained 16 randomly ordered and even pictures of a sun and a moon. In the first block, congruent responses were required; hence the child had to say day when a sun was depicted and night when a moon was depicted. In the second block, incongruent responses were required, saying night to the sun-picture and day to the moon-picture. Instructions were given while the appropriate pictures were presented on the screen. Understanding of the instructions was monitored by asking the child to correctly respond to the two possible pictures. It was explicitly mentioned that the word should be pronounced correctly to avoid a mixture of the answers. If such a mixture did occur, it was counted incorrect. If an immediate self-correction was made after an error, the picture response was counted correct, but also as a self-correction. The variable of interest was completion time of the congruent condition minus that of the incongruent condition, while controlling for the amount of correct responses on the incongruent condition.

Sustained Attention Dots task (SA-DOTS, version 02K)

This task consists of a series of 240 valid trials. On the computer screen a house with three windows was continuously presented. On each trial a yellow bee, blue bird, or purple butterfly was presented in one of windows in a random order. The child had to respond yes if a bee picture was presented, and no if a bird or butterfly picture was presented. Because of balanced presentations of the animal presentations, a 'no'-response (bird or butterfly picture) was required twice as often as a 'yes'-response (bee picture). The child was told to press the 'yes'-button when a bee was displayed in one of the windows and the 'no'-button when he or she saw another animal. In case of an error, the computer generated a beep

signal. Because of the variable response latencies, the task was self-paced. The variables of interest were the mean and fluctuation of reaction time (RT and SD-RT, respectively) on hits while controlling for the amount of hits.

Shape School

The Shape School was modified into a computerized version. This task was programmed and presented using Presentation software (Neurobehavioral Systems, Inc). It consists of four blocks; the first block is a control condition in which the child had to push the button (a red right button or yellow left button) of the color of the figure (red or yellow) that appeared on the screen. Second, in the inhibition condition; the child had to respond by pushing the button of the correct color only when the figure looked happy, and had to suppress this response when the figure looked sad. Third, in the switch condition; the child had to respond to the color of the figure, but when the figure wears a hat, the child had to push the button of the contrasting color. In the last condition, both inhibiting and switching had to be applied. Only this 'both' condition was used for analyses. Variables were derived from the output log-files by using Matlab 2012a (The MathWorks, Inc., Natrick, MA). The variables of interest were the mean RT and SD-RT on correct trials while controlling for the number of correct responses, the total number of correct inhibitions, and the total amount of omissions in both the control and switch condition.

Results

Behavioral functioning outcomes

Despite randomization, the WMG was significantly more affected on two variables of interest at baseline (i.e., ADHD-RS-INV total score [p = .037] and ADHD-RS-T subscale hyperactive/impulsive [p = .049]).

ADHD-RS-INV. Three outliers were removed to reach a normal distribution. Homogeneity of variance was violated in the inattention subscale (p = .026). Therefore, this subscale was tested non-parametrically. For the other subscales, ANCOVAs were performed. 4.6% of the data were imputed at baseline and at endpoint. There were no treatment effects (i.e., differences between groups) for any of the ADHD-RS-INV subscales (total: t(41) = -0.237, p = .813; inattentive: p = .380; hyperactive/impulsive: t(41) = -0.655, p = .512)

ADHD-RS-T. Two outliers were removed to reach normality. ANCOVAs were performed on all subscales after imputation of 15.6% of the data at baseline and 20.0% at endpoint. No treatment effects on any of the ADHD-RS-T subscales were found (total: t(45) = -0.398, p = .691; inattentive: t(42) = 0.318, p = .750; hyperactive/impulsive: t(42) = -1.175, p = .240).

BRIEF-P. No outliers were removed. Data from one child were removed due to an unacceptable inconsistency scale. Data from four children at baseline and five at endpoint contained high negativity scores. At endpoint, ANCOVAs were performed on all subscales

after imputation of 13.0% of the data at baseline and 26.1% at endpoint. No differences between groups for any of the BRIEF-P composite scores or total score were found (BRI: t(43) = 0.553, p = .581; MI: t(43) = -0.617, p = .537; GEC: t(43) = -0.307, p = .759).

BRIEF-T. No outliers were removed. Data from 3 children were removed due to an unacceptable inconsistency scale. Data from 1 child at baseline contained high negativity scores. At endpoint, ANCOVAs were performed on all subscales after imputation of 17.4% of the data at baseline and 32.6% at endpoint. No treatment effects on any of the BRIEF-T composite scores or total score were found (BRI: t(43) = -0.095, p = .924; MI: p = .613; GEC: t(43) = 0.256, p = .798).

Neurocognitive functioning outcomes

Despite randomization, two significant differences between groups were found on the variables of interest at baseline (i.e., LDT-FW (p = .027), SA-DOTS-O2K SD-RT (p = .024).

DS-WISC-III. After removal of four outliers, data remained skewed. No data were missing. Differences between groups were analyzed non-parametrically. A significant difference in favor of the WMG was found on the BW condition (p = .041), which did not remain significant after multiple comparisons correction. No significant differences were found between the groups on the FW condition (p = .980).

LDT. Normality was still violated after removal of two outliers. Therefore, non-parametric tests were performed, without the two outliers. There were no data missing. For both conditions, no differences between groups were detected in the amount of correctly repeated tapping of the blocks (FW: p = .898; BW: p = 1.00).

Sentences. There were no outliers and 2.1% of the data were imputed at baseline. ANCOVAs were performed. The groups did not differ from each other on the correctly repeated sentences score (t(44) = 0.800, p = .424)

RAVEN. No outliers were removed and no data were missing. An ANCOVA showed no difference between the two groups on the total score (t(44) = -0.106, p = .916)

DNST. Four outliers were removed to reach normality. 4.7% of the data at baseline and 2.3% at endpoint were imputed. Afterwards, an ANCOVA was performed. The difference in RT between the switch and control condition while controlling for the amount of correct answers did not differ between groups (t(39) = 1.399, p = .162)

SA-DOTS-O2K. Three outliers were removed. Data were imputed for 2.3% at endpoint. ANCOVAs were performed while controlling for hits and showed no differences between groups (RT: t(40) = -0.288, p = .773; SD-RT: t(40) = 0.136, p = .892)

Shape School. One outlier was removed to reach normality. Data from four children at baseline and five children at endpoint were missing. Imputation was not possible due to non-random missing values of children with no correct responses (RT's and SD-RT's missing) or one correct response (SD-RT's missing) to all 3 stimuli of a certain trial-type (24 stimuli, 8 trial-types). ANCOVAs were performed despite the small variable sample size. There were no differences between groups (Control condition –red– RT: t(35) = 0.018,

p = .986; SD-RT: t(31)= -0.976, p = .337; –yellow– RT: t(33) = 0.203, p = .840; SD-RT: t(24) = -0.738, p = .468. Switch condition –red– RT: t(29) = -0.679, p = .502; –yellow– RT: t(21) = 1.581, p = .129) barring two marginal significant differences in the switch condition; one in favor of WMG (red SD-RT: t(30) = -1.179, p = .248) and one in favor of PLG (yellow SD-RT: t(24) = -1.803, p = .084).

Due to a leftward skewed distribution and the small remaining sample, the Reliable Change Index was calculated (including the outliers) for the number of omissions and correct inhibitions. The change in amount of control and switch stimuli that was omitted and correctly inhibited before and after training was not clearly different between groups. See, table 1 of this *appendix* for statistical details.

Table 1 Amount and percentage reliable improvement and deterioration per group on the Shape School task, according to the Reliable Change Index

	improvement, n (%)		deterioration, n (%)	
	WMG	**PLG**	**WMG**	**PLG**
inhibition				
control red	3/23 (13.0)	1/17 (5.9)	4/23 (17.4)	0/17 (0)
control yellow	5/23 (21.7)	3/17 (17.6)	3/23 (13.0)	3/17 (17.6)
switch red	1/24 (4.2)	2/17 (11.8)	5/24 (20.8)	2/17 (11.8)
switch yellow	1/24 (4.2)	3/17 (17.6)	4/24 (16.7)	4/17 (23.5)
omission				
control red	1/24 (4.2)	2/17 (11.8)	0 (0)	2/17 (11.8)
control yellow	3/24 (12.5)	3/17 (17.6)	0 (0)	1/17 (5.9)
switch red	6/24 (25)	4/17 (23.5)	1/24 (4.2)	2/17 (11.8)
switch yellow	2/24 (8.3)	3/17 (17.6)	1/24 (4.2)	1/17 (5.9)

Abbreviations: n, number; WMG, working memory group; PLG, placebo group.

Global clinical functioning outcomes

As expected due to randomization, no significant differences between groups were found on the variables of interest at baseline.

CGI-I. Four percent from the WMG and 9.5% from the PLG were rated as 'much improved'; 44.0% in the WMG and 14.3% in the PLG were rated as 'minimally improved', and 48.0% in the WMG and 71.4% in the PLG were rated as 'unchanged' at endpoint. 4.0% from the WMG and 4.8% from the PLG was rated as 'minimally worse'. The difference between the groups was not significant (χ^2-test, p = .124). None of the children showed clear deterioration.

CGAS. No outliers were removed and no data were missing. An ANCOVA was performed. The score on the CGAS did not significantly differ between the two groups (t(44) = -0.658, p = .514).

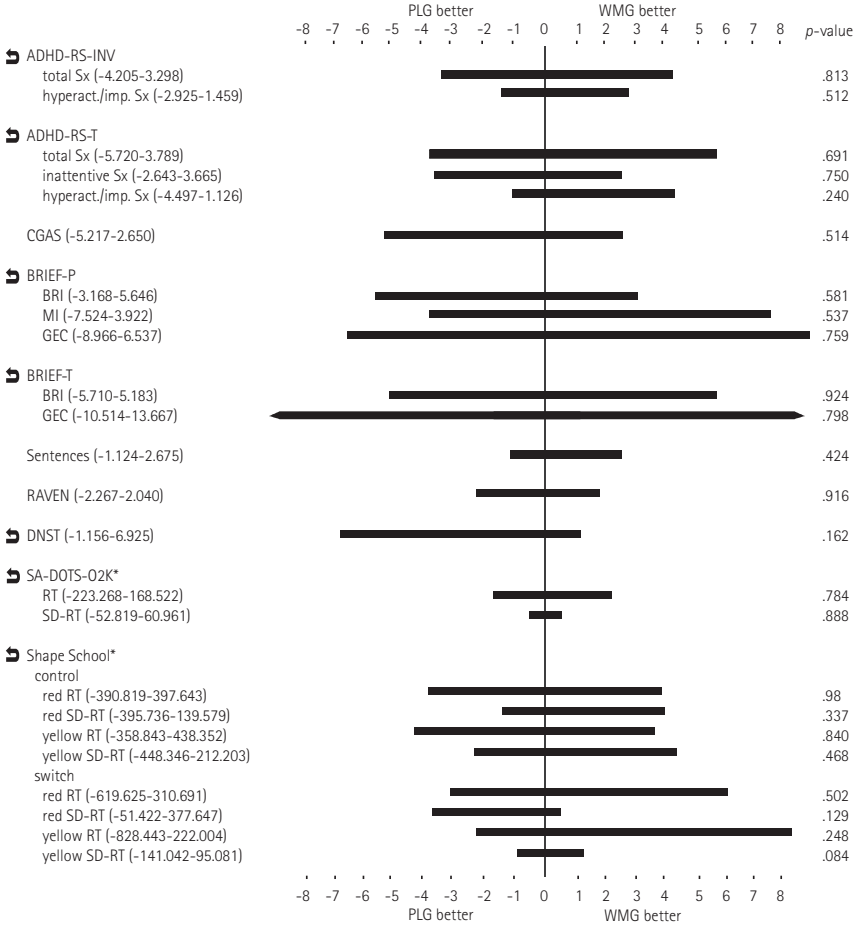

Figure 1 95% confidence intervals of the b-values for each parameter for which an ANCOVA could be performed; i.e., parametric assumptions were valid. A positive value indicates an effect for the working memory group, a negative value an effect for the placebo group. Note that values of which lowering is hypothesized to be an improvement are indicated with an arrow (⮌).

* additionally controlling for correct responses.

Abbreviations: ANCOVA, analysis of the covariance; PLG, placebo group; WMG, working memory group; ADHD-RS, attention-deficit/hyperactivity disorder Rating Scale IV; -INV, rated by the investigator; -T, rated by the teacher; Sx, symptoms; hyperact./imp., hyperactive/impulsive; CGAS, Children's Global Assessment Scale; BRIEF, Behavior Rating Inventory of Executive Function; -P, rated by parents; BRI, Behavioral Regulation Index; MI, Metacognition Index; GEC, Global Executive Composition; Sentences, Sentences of the Wechsler Preschool and Primary Scale of Intelligence revised, translated in Dutch; RAVEN, Shortened Raven Coloured Progressive Matrices; DNST, Day-Night Stroop Task, SA-DOTS-02K, Sustained Attention Dots task, version 02K; RT, response time; SD-RT, standard deviation response time.

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VII

SUMMARY

Attention-deficit/hyperactivity disorder (ADHD) affects about 5% of the children worldwide (Polanczyk, de Lima, Horta, Biederman & Rohde, 2007) and is associated with a high risk for adverse psychiatric outcomes in adult life (Biederman et al., 2006), poorer educational and vocational outcomes (Kuriyan et al., 2013), parental strain (Hinojosa, Hinojosa, Fernandez-Baca, Knapp & Thompson, 2012), and elevated financial costs by burden on health, social care, and justice systems in society (Pelham, Foster & Robb, 2007).

The essential feature of children with ADHD, defined by the *Diagnostic and Statistical Manual of Mental Disorders (fifth ed.; DSM5*; American Psychiatric Association, 2013) is a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with adaptive functioning or development. Children presenting with these symptoms have been described since almost three centuries, but the nomenclature of the clustered symptoms has been changed over time, due to variable opinions and increased knowledge.

Despite a remarkable effort to investigate the clinical concept and to discover etiological factors, the underlying pathophysiology, and potential effective treatment modalities, there are still gaps in our knowledge about ADHD.

To contribute to the knowledge about ADHD, this thesis addressed two important topics, i.e., **resting-state oscillations** and **non-pharmacological interventions**. The first part of this thesis (**Chapter II and III**) explored resting-state oscillations in ADHD and the relationship between resting-state oscillations on one side and neurocognitive and behavioral functioning on the other side in adults and children with ADHD. The second part of this thesis (**Chapter IV, V, and VI**) comprised two RCTs in children with ADHD, investigating the efficacy of frequency neurofeedback (F-NF) and Cogmed working memory training (CWMT).

NF is a form of biofeedback targeting brain oscillations, including conventional F-NF and slow cortical potential-NF, and is defined as a process, in which sensors are placed on the scalp and devices are used to monitor and provide moment-to-moment information about the physiological brain activity, that is fed back to the individual to improve brain functioning (Hammond et al., 2011). NF is hypothesized to work via operant learning, in which simultaneous and contingent feedback is given by positive reinforcement through visual and/or acoustic signals when changes in the brain oscillations are made in the desired direction, leading to voluntary modulation of these oscillations and controlling their underlying processes, thereby enhancing the self-regulation (Gevensleben, Rothenberger, Moll & Heinrich, 2012).

CWMT is based on the idea that intensive training of working memory (WM) may improve WM, other neurocognitive functions, and ultimately diminish the core behavioral symptoms of ADHD. WM is the ability to temporarily hold information while simultaneously manipulating the information (Baddeley, 1986) and is often regarded as a fundamental neurocognitive function underlying other executive functions (Klingberg et al., 2005).

Resting-state oscillations in ADHD

Chapter II

The case-control study described in this chapter was conducted 1) to investigate resting-state oscillations in adults with ADHD compared to healthy controls in an eyes-closed and eyes-open condition, and 2) to investigate the correlations between resting-state oscillations and performance on a neurocognitive task (a stop-signal task, measuring response inhibition) in both groups and the correlations between resting-state oscillations and the core behavioral symptoms in ADHD. The latter goal was of particularly interest because it was the first study investigating neurocognitive correlations in adults. To address both goals, for 24 adults with the combined subtype of ADHD and 24 healthy adults the resting-state electroencephalogram (EEG) in both eyes-open and eyes-closed condition was analyzed. Subsequently, the correlation analyses were performed. Adults with ADHD showed a greater reduction in alpha power from eyes-closed to eyes-open (i.e., alpha attenuation) compared to healthy controls. Regarding the correlation with neurocognitive functioning, theta/beta power ratio was negatively correlated to the speed of responding to choice stimuli; for the ADHD group this was probably at the expense of accuracy. No significant relation was found between resting-state oscillations and the core behavioral symptoms in adults with ADHD.

Chapter III

The study in this chapter focused on exploring whether the relationship between the theta/beta power ratio and/or relative theta power on one hand and neurocognitive functioning and behavioral symptoms on the other hand is confounded by a low alpha peak frequency (APF). This focus was based on earlier work in which a lower APF was actually responsible for the finding of an elevated theta/beta power ratio in a subgroup of children with ADHD. This led to the suggestion that the most robust finding of elevated theta power in ADHD (incorporated in the elevated ratio) is sometimes misinterpreted because of alpha peaking at a lower frequency thereby leaking into the theta-band power estimation. To investigate the influence of the APF on correlations between theta/beta power ratio and relative theta power on one hand and neurocognitive and behavioral functioning on the other hand, resting-state EEG, neurocognitive data, and ADHD symptom scores were analyzed. For 38 children (age between 8-15 years), resting-state oscillations data and ADHD symptom scores were available. Additional neurocognitive data were available for 32 children. The individual APF was measured by using both the eyes-open and eyes-closed resting-state recordings. The frequency-bands were analyzed using the eyes-open condition. A significant positive relationship was found between the theta/beta power ratio and the overall ADHD symptom score and the hyperactive/impulsive symptom sub-score. Further, a significant positive relationship between relative theta power and the hyperactive/impulsive symptom sub-score was found. Both relationships became stronger when controlling for the

individual APF. Eight out of 38 (21%) children showed a low APF (i.e., an APF of 9 Hz or lower), creating a supposed overlap between their individually determined alpha-band and the theta-band. Neurocognitive functioning did not show any relationship with the theta/beta power ratio or relative theta power. The results of this study confirmed that the theta/beta power ratio and relative theta power indeed correlated with behavioral symptoms in children with ADHD and stressed the important role for individual APF in studies concerning electrophysiological underpinnings in ADHD.

Non-pharmacological interventions in children with ADHD

Frequency neurofeedback

Chapter IV described a study investigating the efficacy and safety of daily practice F-NF in children with ADHD by a double-blind, semi-randomized, and placebo-controlled study. For this purpose, 41 children (8-15 years) with ADHD were semi-randomly allocated to F-NF or placebo-NF treatment for 30 sessions, twice a week. Children were stratified by age, electrophysiological state of arousal, and medication use. Everyone involved in the study, except the NF-therapist, was blinded to treatment assignment. Although both groups improved over time, this study did not find any benefit of F-NF compared to placebo-NF on the core behavioral symptoms in ADHD. In addition, no superior effect of F-NF was found on global clinical functioning. In both groups no relevant side effects were observed. The feasibility of this study-design by implementing a placebo-NF, in which the feedback signal was based on a simulated EEG signal, was satisfied by the finding that guessing treatment assignment was not better than chance level. **Chapter V** contained a second study in the same population, with the aim to detect possible efficacy of F-NF on neurocognitive functioning and included a systematic review on this topic. In this study, a wide range of neurocognitive tests was administered before and after treatment, chosen to reflect hypothesized impaired neurocognitive functioning in ADHD (i.e., attention, executive functioning, reward-related processes and timing). Nor significant effects in favor of F-NF on any of the neurocognitive variables was found by analyzing differences on group level, neither by analyzing individual changes. The included systematic review of the current literature also did not indicate any systematic beneficial effect of F-NF on neurocognitive functioning. In addition, based on analyzing neurophysiological measures (i.e., trained EEG targets), no support for improved core behavioral symptoms based on improved neural regulation was found.

In sum, F-NF was not found to be superior to placebo-NF in improving the core behavioral symptoms of ADHD, global clinical functioning, and neurocognitive functioning in children with ADHD. No support was found for the neurophysiological hypothesis.

Cogmed working memory training

Chapter VI consisted of a study investigating the efficacy of CWMT on the core behavioral symptoms, neurocognitive, daily executive, and global clinical functioning in children with ADHD. A triple-blind, semi-randomized, and placebo-controlled study was conducted. For this purpose, 51 children (5-7 years) with ADHD were semi-randomly assigned to the active or placebo condition of the Cogmed JM training program for 25 sessions, five times a week. Children were stratified by age and gender. Everyone involved in the study was blinded to treatment assignment. Although children improved over time (independent on groups assignment), this study did not find any benefit of CWMT compared to the placebo condition on the core behavioral symptoms of ADHD. In addition, no superior effect was found on neurocognitive functioning (based on a wide battery of neurocognitive tasks), daily executive, and global clinical functioning. Although children in the active condition improved on the trained WM task, no superior effects were found on the non-trained measures (the so-called transfer effects). In sum, this study failed to find evidence for benefits of CWMT training compared to the placebo condition on the core behavioral symptoms of ADHD, neurocognitive, daily executive and global clinical functioning in young children with ADHD. In other words, no evidence for transfer effects was found.

In the discussion (**Chapter VIII**) the findings of the five studies are discussed and clinical implications are given. These three points are regarded as the most relevant lessons from this thesis;

1) Resting-state oscillations may offer a great value to the knowledge about ADHD. However, currently, unraveling their role has not yet been finished. Alpha power and alpha peak frequency do merit a more prominent role in detecting the electrophysiological underpinnings of ADHD. Furthermore, correlations between resting-state oscillations on one hand and core behavioral symptoms of ADHD and neurocognitive functioning on the other hand have been found; however the inconsistency of these findings makes firm conclusions not yet possible.
2) The studies described in this thesis regarding F-NF and CWMT in children with ADHD could not prove superior benefit compared to the placebo condition. It is possible that methodological and other limitations of these studies have prevented us from finding specific treatment effects with large ESs comparable to those of ADHD-medication. However, since specific treatment effects were consistently lacking at all levels rather than found to be inconsistent, it is less likely that the negative findings are only due to limitations of the studies. Of course, future research should address these limitations to justify more firm conclusions about the efficacy of F-NF and CWMT.
3) Regarding F-NF and CWMT, guidance to parents and their children with ADHD must be in line with the actual findings of current research.

Further, directions for future research are given. Suggestions for improvement of the present studies are discussed. The most relevant recommendation for future research is to optimize earlier study designs to enlarge the chance to detect potential specific and unique effects of F-NF and CWMT to justify more definitive conclusions about the true impact of these interventions in the treatment of children with ADHD.

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VIII

GENERAL DISCUSSION, CONCLUSIONS, CLINICAL IMPLICATIONS & DIRECTIONS FOR FUTURE RESEARCH

The aim of the present thesis was two-fold. The first aim was to investigate resting-state oscillations and to examine the correlations between these oscillations on one hand, and neurocognitive functioning and the core behavioral symptoms in attention-deficit/hyperactivity disorder (ADHD) on the other hand. The second aim was to investigate the efficacy of two non-pharmacological interventions in children with ADHD, i.e., frequency neurofeedback (F-NF) and Cogmed working memory training (CWMT). Here, the findings of the studies will be discussed, followed by the clinical implications and directions for future research.

Resting-state oscillations in ADHD

Despite the bulk of research on resting-state oscillations in ADHD, the inconsistency of the findings complicates their interpretation. This inconsistency of resting-state findings may have different causes; differences between studies regarding methodological aspects, such as different sample characteristics (e.g., age, gender, and subtypes of ADHD) and technical aspects of the EEG recordings (e.g., differences in EEG registration and analysis and measurement, like relative and absolute power, and difference in the use of an eyes-closed and/or eyes-open condition). Furthermore, in studies on the correlation of resting-state oscillations on one hand and neurocognitive functioning and core behavioral symptoms in ADHD on the other hand, also the different ways of dealing with multiple testing can explain inconsistency. In addition, differences in neurocognitive tasks and behavioral rating scales may contribute to the inconsistency of the findings. Furthermore, inconsistency can also be based on the heterogeneity of ADHD itself. Besides, measurement over a short time interval, like recording resting-state oscillations, has been supposed to be more vulnerable to transient state effects, compared to behavioral measurements, which are based on a significantly longer time period (Kendler & Neale, 2010). Another possible explanation is based on the idea that these oscillations may reflect too complicated, too basic and/or too far away processes, to give a clear-cut electrophysiological fingerprint of the clinical and neurocognitive aspects of ADHD. Finally, of course a combination of these hypothesized causes may play a role in clarifying the inconsistency.

The first study in this thesis (**Chapter II**) was designed 1) to investigate resting-state oscillations in adults with ADHD, compared to healthy controls, and 2) to investigate correlations between resting-state oscillations on one hand and performance on a stop-signal task (measuring response inhibition) in both groups and core behavioral symptoms in the ADHD group on the other hand. Given the idea that the inconsistency of the resting-state oscillations findings may be partially based on the different use regarding the eyes-open and/or an eyes-closed condition, this study analyzed the results under both conditions. To address the possibly influence on findings based on difference in dealing with

multiple testing, the alpha level of significance was set at $p = .01$, two-tailed. Analyses of the mean absolute theta, alpha, beta power, the theta/beta power, and theta/alpha power ratios did not yield any significant difference between adults with ADHD and healthy controls for both conditions. So, in contrast to previous findings, this study did not replicate the most consistent finding of elevated theta power. The finding of a large variability in the theta power across participants may have prevented to find a significant result. Further analyses showed a greater reduction in alpha power from eyes-closed to eyes-open (i.e., alpha attenuation) in ADHD compared to the healthy controls. This finding is in line with a recent study in children with ADHD (Fonseca, Tedrus, Bianchini & Silva, 2013) and may reflect a hypo-arousal state (in the eyes-closed condition), based on the hypothesis that alpha activity is associated with arousal (Barry, Clarke, Johnstone, Magee & Rushby, 2007). Further exploration revealed no significant correlations between resting-state oscillations and the core behavioral symptoms of ADHD. However, positive significant correlations were found between the theta/beta power and theta/alpha ratios on one hand and the speed of responding on the stop-signal task on the other hand for both groups. These correlations were attributed to increased impulsivity, because not only the speed, but also the error rate was increased in the ADHD group; a so-called speed-accuracy trade-off effect was hypothesized in this group. However, for the control group, a speed-accuracy trade-off was probably not the case (no higher error rate was found), and so for this group these findings could not reflect impulsivity. Neglecting the latter remark, the findings for the ADHD group together were seen as supportive to the biophysical model presented by Rowe and colleagues (2005), in which hypo-arousal of the cortex is caused by a tonic overdrive of the locus coeruleus. This leads to an increase in inhibitory activity of the thalamic reticular nucleus, which in turn results in increased EEG slow waves.

Altogether, although the intention to diminish noise by analyzing both conditions and to deal with multiple testing, these results still indicate inconsistency of resting-state oscillations findings in ADHD, especially regarding the resting-state theta activity. Of course these findings may have been influenced by study limitations, such as a small sample, only reporting the absolute power, and the use of only one neurocognitive task. Correlations, however, between resting-state oscillations on one hand and neurocognitive functioning and core behavioral symptoms in ADHD on the other hand can be regarded as weak.

The design of the second study (**Chapter III**) was driven by the hypothesis that a low alpha peak frequency (APF) may influence the estimation of the most robust finding of an elevated theta power (incorporated in the theta/beta power ratio) in ADHD (Arns, Conners & Kraemer, 2012), thereby influencing the relationship between this finding and neurocognitive functioning and the core behavioral symptoms. The hypothesis that a low APF can lead to misinterpretation of theta power was proposed in earlier work; the study by Lansbergen and colleagues (2011a) showed a difference in the theta/beta power ratio between children with ADHD and healthy controls when using fixed frequency-bands, while this difference was

absent when the APF was used to determine individual frequency-bands, due to a lower individual APF in a subgroup of the sample. Our hypotheses were 1) theta and the theta/beta power ratio are positively related to impaired neurocognitive functioning and the core behavioral symptoms of ADHD, and 2) a low APF influences these relationships by showing an overlap between alpha-band based on APF and the fixed theta-band, thereby falsely overestimating theta. As expected, a positive relationship was found between the theta/beta power ratio and the total symptom score and hyperactive/impulsive symptom sub-score. In addition, also expected, a positive relationship was found between relative theta and hyperactive/impulsive symptoms. Twenty-one percent of the children in our study showed an overlap between the alpha-band based on APF and the fixed theta-band. All relationships between theta and the theta/beta power ratio, and core symptoms of ADHD became stronger when controlling for APF. In addition, the relationship between theta and total symptom score after controlling for APF changed from non-significant to a strong significant correlation. Based on the study by Lansbergen and colleagues (2011a), the direction of the influence of the individual APF in this study was not expected. Lansbergen and colleagues (2011a) found that a dichotomous difference between ADHD and controls was absent regarding the theta/beta power ratio when taking into account the individual APF. To come to this conclusion, the theta frequency-band in that study was determined using APF as anchor point. A shift of individual APF, however, does not necessarily imply a proportional shift of the other frequency-bands, among them the theta-band. Application of this method may have resulted in an underestimation of theta power since not the entire theta-band would be covered by this new determined band. Although those results illustrated that the individual APFs differ enough from 10 Hertz (Hz) to shift the bands away from the dichotomous difference, the results did not necessarily imply an actual lack of the dichotomous difference from the 'true' theta- and beta-band. The current study aimed at unraveling the influence of the APF-based alpha-band on the fixed theta-band of 4-8 Hz. By using a fixed theta-band comparable to the majority of previous studies (Arns et al., 2012), and an alpha-band based on APF comparable to Lansbergen and colleagues (2011a), we were able to show that the relationship between the conventional theta and the theta/beta power ratio, and core symptoms of ADHD became stronger when controlling for APF rather than eliminated. In contrast to our hypothesis, neurocognitive performance did not show any relationship with theta and the theta/beta power ratio. The fact that this study could not confirm the hypothesis for neurocognitive functioning may have different causes. One cause may be the neurocognitive heterogeneity found in ADHD (Nigg, 2005). Another is the vulnerability of both the neurocognitive as well as the EEG measurements for transient state effects due to the short duration of the measurements, compared to the behavioral measurement, which is based on a significantly longer time period (Kendler & Neale, 2010). Finally, interpretation of the findings should take into account the study limitations. First, the sample size and so the statistical power was small, and also made analyses of neurocognitive subtypes as suggested in the literature

not feasible. Second, the majority of the children in our sample used medication also during the assessment; yet, all children displayed symptoms in the clinical range, meaning that medication-use did not diminish ADHD-symptoms sufficiently. Third, the a-priori and conscious choice (based on previous studies as well as on our pilot-analysis) to include a limited number of electrophysiological variables, restricted the analyses to one electrode, enlarging the potential influence of noise and not allowing for topographical localization of the measures. Despite these limitations, this study supported the hypothesized influence of APF in ADHD.

Non-pharmacological interventions in children with ADHD

Most child and adolescent mental health specialists agree that new evidence-based non-pharmacological treatment modalities are needed for children with ADHD. This agreement may be based on different arguments, related to limitations of the first-line treatment medication, and/or to the need to provide an alternative treatment. For parents and the older child, the same arguments may be true. However, until now, not one non-pharmacological treatment modality has proven to be sufficient efficacious to claim an important role in the treatment of ADHD. Even, the benefit of behavioral therapy as an add-on modality above medication is only proven (MTA Cooperative Group, 1999b, 1999a) and advised in a minority of children with ADHD (Taylor et al., 2004; Landelijke Stuurgroep Multidisciplinaire Richtlijnontwikkeling in de GGZ, 2005; National Institute of Mental Health [NIMH], 2009). Nevertheless, the rise of non-pharmacological interventions is significant and often so the claim for their efficacy (distributed by social media, newspapers and magazines), causing parents, children, and often even health insurance companies to believe in these treatments, although they have not yet been proven to be effective and safe. Based on the grounded general agreement about the need for new evidence-based interventions and the potential harmfulness and unnecessary costs of widely administered non-evidence based treatments for children with ADHD, we felt encouraged to investigate the efficacy and the safety of two non-pharmacological treatments options, i.e., F-NF and CWMT.

Frequency neurofeedback

By now, quite many randomized controlled trials, reviews, and two meta-analyses concerning the efficacy of NF in children, have been published. However, the question about its efficacy has still been unanswered; the three randomized placebo controlled trials did not find a superior effect of F-NF over placebo-NF on the core behavioral symptoms of ADHD (Perreau-Linck, Lessard, Levesque & Beauregard, 2010; Lansbergen, van Dongen-Boomsma, Buitelaar & Slaats-Willemse, 2011b; Arnold et al., 2012). This conclusion was in line with the most recent systematic review/meta-analysis on randomised controlled trials

of non-pharmacological interventions in children with ADHD. Analyses of probably unblinded ratings for NF in children with ADHD showed an effect size (ES) of 0.29 ($p = .07$) (Sonuga-Barke et al., 2013). Furthermore, neurophysiological evidence that NF improves neural regulation and subsequently significantly affects behavioral outcome, has sparsely been investigated. The study in this thesis (described in **Chapter IV and V**) could not prove superior efficacy compared to the placebo condition on core behavioral symptoms, neurocognitive, and global clinical functioning in children with ADHD by using a double-blind, semi-randomized, placebo-controlled treatment design investigating daily practice personalized F-NF. In addition, analyses on the trained EEG-targets for children in the NF group across the sessions, did not find support for increased neural regulation after F-NF. Furthermore, analyzing these targets for the clinical responders only, no support for improved core behavioral symptoms due to improved neural regulation was found. No adverse side effects were found, indicating F-NF to be at least a safe intervention. A major limitation of this study was the small sample size. Furthermore, the implementation of mental learning strategies and the change from automatically into manually thresholds after the pilot period could only be of benefit for an even smaller sample. Taking into account these study limitations, a firm conclusion that daily clinical practice F-NF as performed widely in The Netherlands does not bring any benefit to children with ADHD is not appropriate. Nevertheless, this study adds serious doubts about the efficacy of F-NF, strengthened by similar negative findings (meaning no specific treatment effects were found) of the three other published placebo-controlled studies and the most recent systematic review/meta-analysis (including F-NF as well as SCP-neurofeedback) (Perreau-Linck et al., 2010; Lansbergen et al., 2011b; Arnold et al., 2012; Sonuga-Barke et al., 2013). Interestingly, although no superior effects of F-NF were found compared to the placebo condition, all placebo-controlled studies (including our studies) did find improvement over time on the core behavioral symptoms of ADHD in the active as well as the placebo condition.

There are two possible explanations for the negative findings on efficacy of F-NF;

1) There is in reality no effect, so the null-hypothesis is correctly conserved. This would implicate that the originally idea that regulating, whether it is improving, normalizing or rather controlling resting-state oscillations can lead to improvement on behavioral and/or neurocognitive level in children with ADHD has proven to be incorrectly. The time effects found are then purely based on non-specific treatment and/or placebo effects.
2) Actually there is an effect, so the null-hypothesis is incorrectly conserved. In this case, methodological (e.g., too small sample) and/or other shortcomings create a type-II error. This suggests that characteristics of the performed studies have prevented to find an effect that in reality did exist.

In my opinion, to come to more definitive conclusions about whether or not F-NF is an efficacious treatment modality in children with ADHD, future studies should address *all* the

following aspects. First, a larger sample is necessary to overcome the power-discussion. Second, the operant learning principles may be expanded by the development of a paradigm in which instructions are clearly goal-directed and in which the child is encouraged to actively attempt to reach a certain 'brain-state'. Third, more and better attempts to facilitate potential transfer effects are necessary. Furthermore, future studies should answer the key question whether there is supporting evidence, i.e., neurophysiological background, for a specific effect of F-NF. This can be reached by a similar method used in our study on a larger sample (i.e., analyzing EEG-targets during the sessions and correlations between these neurophysiological measures and behavioral outcome measures). Knowledge derived by neurofeedback studies with a more experimental set-up, such as tomographic NF (tNF) (Liechti et al., 2012), magnetoencephalographic NF (MEG-NF) (Foldes, Vinjamuri, Wang, Weber & Collinger, 2011), and real-time functional magnetic resonance imaging NF (fMRI-NF) (Weiskopf, 2012; Sulzer et al., 2013) may help to further unravel the neurophysiological background.

If these improved future studies don't bear specific treatment effects on a proven neurophysiological background, other effects must be ascribed to non-specific treatment and/or placebo effects. It would then be of valuable interest to know the background of these potential non-specific treatment effects. Implementing a third (next to an active and placebo condition), passive control condition would enable to further unravel the potential non-specific treatment effects like learning and expectancy effects. If a learning effect, like enhanced self-control clarifies (partially) the found time effects, it would offer great opportunities to develop new treatment modalities without the intermediate role of an EEG.

Cogmed working memory training

In recent years the amount of studies investigating the efficacy of cognitive training programs with among them WMT has been rising. In addition, a number of valuable reviews and meta-analyses have now been published. Focusing on cognitive training literature in ADHD children, including WMT, one systematic review/meta-analysis reported an ES of 0.24 (p = .34) for studies using probably blinded assessments, leading to the conclusion that efficacy of cognitive training cannot be stated until blinded studies will demonstrate efficacy (Sonuga-Barke et al., 2013). In addition, another meta-analytic review on non-pharmacological interventions concerning children with ADHD concluded that WMT did not result in greater improvement compared to the control condition (Hodgson, Hutchinson & Denson, 2012). Furthermore, a meta-analytic review and a review on WM programs seriously question the efficacy of WMT mainly due to insufficient evidence about generalization to non-trained skills, i.e., evidence for transfer effects (Shipstead, Redick & Engle, 2012; Melby-Lervag & Hulme, 2013). Transfer effects refer to improvements on trained WM-tasks leading to improvement on non-trained WM tasks (near-transfer effects), other neurocognitive functioning, and behavioral functioning (far transfer effects). Concerns about transfer effects were further expressed by a recent meta-analysis on training-modalities targeting neurocognitive functioning in children with ADHD because

CWMT was associated with moderate near transfer effects only ($d = 0.63$), so no far transfer effects were found (Rapport, Orban, Kofler & Friedman, 2013). The review by Chacko and colleagues (2013) focused exclusively on CWMT in children with ADHD and children with an elevated ADHD symptom-score. In this review, reasonable critical concerns are outlined, like the inconsistent findings within and between studies, the weak evidence for the hypothesized underlying working mechanism, the questionable quality of the placebo condition and the differences between the sample characteristics. Future directions were mainly based on these concerns, and consisted of the recommendations to investigate CWMT in a more heterogeneous and so more clinical sample, with a smaller and lower age range with broadening outcome measures referring functional impairment.

The study in this thesis (**Chapter VI**) addressed all the directions, discussed by Chacko and colleagues (2013). This study found improvement on the trained visuospatial WM represented by a significant improvement on the training in the active condition, however a near-transfer effect was not maintained after correcting for multiple testing and far-transfer effects were absent at all. No side effects were found (measured, but not reported). So, the hypothesis that changes in the adaptability of (some aspects of) WM may already be able in the pre-school developmental period (Carlson, 2005) was supported by improvement on the trained tasks, however, it was not supported by transfer to non-trained WM measures. Although addressing the earlier mentioned directions, this study also had some limitations. First of all, the sample size was smaller than planned. However, taking into account that the 95%-CIs of the b-values were all centered around zero, an actual lack of efficacy in favor of the active condition is more likely than a type-II error. The second limitation is the absence of feedback on the individual training performance of the child. In order to maintain triple-blindness, but in contrast to training applied in clinical setting, the therapist was blinded to the training progress of the child. Therefore, coaching based on personal training results was lacking. Personal feedback may be a prerequisite to challenge past performances and keep the child motivated to improve WM capacity. Therefore, this study might leave out an important aspect of the training efficacy.

Several factors may contribute to the lack of transfer effects in CWMT. First, CWMT training can be seen as an intensive but rather short intervention. A longer training period may be more effective. This may however have other undesirable effects, such as lower feasibility, less compliance, and a larger drop-out percentage and may induce side effects as well, such as fatigue (in case the frequency is kept the same) or loss of motivation. Second, the weekly call between therapist and parents may be insufficient to keep parents and child motivated. Third, implementation of WM exercises in daily life might be crucial to facilitate potential transfer effects. Fourth, it might be insufficient to train a single executive function (EF) component, i.e., WM, to diminish behavioral symptoms. Probably a broader set of executive functions EFs should be addressed. Yet another possibility is that WM deficits are not part of the causal pathway to ADHD symptoms. Rather, WM deficits may be associated with ADHD as a form of 'cognitive comorbidity'.

So, the conclusion, based on this study, is that the results suggest no benefit of CWMT on behavioral, neurocognitive, and global clinical functioning in young children with ADHD. Furthermore, this study supports earlier concerns about the efficacy of CWMT by not finding any transfer effects.

Future research needs a larger study sample. Another issue that needs to be addressed in future research is investigating the efficacy of CWMT with a more prominent, guiding role for the therapist. In addition, like for EEG-NF, studies should optimize the facilities to create potential transfer effects. Furthermore, similar to my recommendations regarding F-NF, further unraveling non-specific effects is necessary. This can be investigated by expanding our study design by implementing a third (next to an active and placebo condition) passive control condition. In case of a significant learning effect, aspects of the offered training do improve core behavioral symptoms, neurocognitive, daily executive, and/or global clinical functioning. This can guide future research to develop new treatment modalities.

Another concern is the actual lack of a specific neural mechanism underlying WMT and transfer effects that would fit within one single framework (Buschkuehl, Jaeggi & Jonides, 2012). Further research should focus on the potential neural correlates of WMT.

Conclusions

1) Resting-state oscillations may offer a great value to the knowledge about ADHD. However, currently, unraveling their role in ADHD has not yet been finished. Alpha power and alpha peak frequency do merit a more prominent role in detecting the electrophysiological underpinnings of ADHD. Correlations between resting-state oscillations on one hand and core behavioral symptoms of ADHD and neurocognitive functioning on the other hand have been found, however the inconsistency of the findings makes firm conclusions prematurely.
2) The studies described in this thesis regarding F-NF and CWMT in children with ADHD could not prove superior benefit compared to the placebo condition. It is possible that methodological and other limitations of these studies have prevented us from finding specific treatment effects with large ESs comparable to those of ADHD-medication. However, since specific treatment effects were consistently lacking at all levels rather than found to be inconsistent, it is less likely that the negative findings are only due to limitations of the studies. Of course, future research should address these limitations to justify more firm conclusions about the efficacy of F-NF and CWMT.

Clinical Implications

Guidance to parents and their children with ADHD regarding F-NF and CWMT must be in line with the actual findings; there is not yet a proven benefit of any of both treatment options. Further, in my opinion, the currently insufficiently scientific backing for the efficacy of both treatment options in children with ADHD, questions the (partially) reimbursement of these interventions by health insurance companies.

Directions for Future Research

Resting-state oscillations in ADHD

1) To further diminish inconsistent findings based on noise regarding resting-state oscillations, future studies investigating resting-state oscillations and their neurocognitive and behavioral correlates should use as far as possible similar methodological (e.g., same sample characteristics and the same way of dealing with multiple testing) and technical aspects of the EEG recordings (e.g., EEG registration and analysis, reporting relative rather than absolute power, and measurement of the same condition; eyes-closed and/or eyes-open).
2) To better understand the electrophysiological underpinnings of ADHD, more research focusing on correlation between resting-state oscillations and the core behavioral symptoms of ADHD and neurocognitive functioning is needed. Especially, the role of alpha activity must be further investigated in ADHD. Recent literature further suggesting an inhibitory role for alpha activity in ADHD. This suggestion should be used as a launching pad for future research (Mazaheri et al., 2010; ter Huurne et al., 2013).
3) Technical innovations of EEG, such as independent component analysis may be valuable in strengthen the role of the EEG in ADHD (Loo & Makeig, 2012).
4) Furthermore, other electrophysiological approaches should be applied more in ADHD research, like coherence analyses (Clarke et al., 2007) and event-related potentials (Johnstone, Barry & Clarke, 2013).

Non-pharmacological interventions in children with ADHD

Frequency neurofeedback

1) Future studies should include a larger sample to overcome the power-discussion.
2) In future research projects, the operant learning paradigm may be expanded with a paradigm in which instructions are clearly goal-directed and in which the child is encouraged to actively attempt to reach a certain 'brain-state'.
3) Studies should optimize the facilities to create potential transfer effects.

4) Future research should focus on the question whether there is a neurophysiological background for F-NF that makes F-NF a valuable treatment for children with ADHD. This can be reached by analyzing EEG targets across the sessions and correlations between these neurophysiological measures and behavioral outcome measures. Knowledge from studies with a more experimental set-up may help to further unravel the neurophysiological background, like tNF (Congedo, Lubar & Joffe, 2004; Liechti et al., 2012), MEG-NF (Foldes et al., 2011), and fMRI-NF (Weiskopf, 2012; Sulzer et al., 2013).
5) Non-specific treatment effects must be further investigated. Implementing a third (next to an active and placebo condition), passive control condition would enable to further disentangle the non-specific treatment effects like learning and expectancy effects. If enhanced self-control clarifies (partially) time effects, it would offer great opportunities to develop new treatment modalities without the intermediate role of an EEG.
6) At the same time, research on more innovative methods of NF in children with ADHD can be of great value in developing new treatment modalities and/or enlarging the knowledge about ADHD.

Cogmed working memory training

1) Future studies should include a larger sample to overcome the power-discussion.
2) Future studies should address the potential contributing role of the therapist. A study should be conducted with a comparable design to our study, but than with a more active role for the therapist, providing a context in which it is possible to optimally motivate parents and children throughout the whole training. Unblinding of the therapist should be considered, enabling the therapist to reinforce the child depending on individual training results.
3) Studies should optimize the facilities to create potential transfer effects.
4) As for F-NF and in a similar way, non-specific treatment effects should be further investigated. This can guide future research to develop new treatment modalities.
5) Future research should focus on potential neural correlates of WMT in ADHD by performing methodological sound studies with a wide variety of neurocognitive, behavioral measures, as well as neuroimaging measures.
6) The concern that currently available cognitive training modalities, with among them WMT, may not be able to create sufficient (transfer) effects, may encourage future research to further develop alternative cognitive based training programs for children with ADHD, for example expanding the training focus with other EFs rather than WM alone, or focusing on self-control. This latter is hypothesized to balance between reward-driven and cognitive control systems proposed by Rutledge, van den Bos, McClure & Schweitzer (2012).

For all above mentioned directions, a prerequisite to justify more definitive conclusions is the use of a sufficient large sample. In my opinion, to fulfill this need, at least all academic Mental Health Institutions should have the priority to put effort in including every referred patient in a research project, unless the patient doesn't fit or doesn't want to participate. Lastly, I want to encourage future research to develop efficacious and safe non-pharmacological treatment options, taking into account the expected costs and the cost-effectiveness of such treatments and also the accessibility and availability for the affected child and his/her parents. Especially in this relatively economical hard time, affordable but effective treatments are urgently needed.

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APPENDIX

Samenvatting

Aandachtstekortstoornis met hyperactiviteit (ADHD) komt wereldwijd bij ongeveer 5% van de kinderen voor en is daarmee één van de meest voorkomende neuropsychiatrische aandoeningen die in de kindertijd ontstaat (Polanczyk, de Lima, Horta, Biederman & Rohde, 2007). ADHD is geassocieerd met een verhoogd risico op andere psychiatrische stoornissen op volwassen leeftijd (Biederman et al., 2006), lagere prestaties ten aanzien van onderwijs en opleiding (Kuriyan et al., 2013), een grote belasting voor ouders/verzorgers (Hinojosa, Hinojosa, Fernandez-Baca, Knapp & Thompson, 2012) en hoge financiële kosten op sociaal-maatschappelijk niveau (Pelham, Foster & Robb, 2007).

ADHD kenmerkt zich door een persisterend patroon van inattentie en/of hyperactiviteit/impulsiviteit, dat interfereert met leeftijdsadequaat functioneren, gedefinieerd door de "*Diagnostic and Statistical Manual of Mental Disorders" (fifth ed.; DSM5*; American Psychiatric Association, 2013). Kinderen met deze symptomen worden al drie eeuwen beschreven, maar de naamgeving van deze symptomen samen is door de eeuwen heen gewijzigd door veranderde visies en toegenomen kennis.

Ondanks een opmerkelijke hoeveelheid wetenschappelijk onderzoek, zijn er nog steeds relevante hiaten in de kennis over ADHD. Om bij te dragen aan de kennis over ADHD, behandelde dit proefschrift twee belangrijke onderwerpen, namelijk **hersengolven in rust** en **niet–farmacologische interventies**. Het eerste deel van dit proefschrift (**Hoofdstuk II en III**) onderzocht hersengolven in rust bij ADHD en de relatie tussen hersengolven in rust aan de ene kant en neurocognitief en gedragsmatig functioneren aan de andere kant bij volwassenen en kinderen met ADHD. Het tweede deel van dit proefschrift (**Hoofdstuk IV, V en VI**) beschreef twee gerandomiseerde klinische onderzoeken bij kinderen met ADHD met als doel de effectiviteit van frequentie neurofeedback (F-NF) en Cogmed werkgeheugen training (CWMT) te onderzoeken.

NF is een vorm van biofeedback gericht op het elektro-encefalogram (EEG) en bestaat uit zowel conventionele F-NF als 'slow cortical potential'-NF. NF is een methode waarbij met behulp van electroden op de hoofdhuid registratie plaatsvindt van de hersenactiviteit, die vervolgens wordt teruggekoppeld aan degene die de NF ondergaat (Hammond et al., 2011). De hypothese is dat NF werkt via het operante leerprincipe, waarbij terugkoppeling plaatsvindt door positieve bekrachtiging via visuele en/of akoestische signalen, op het moment dat verandering in de hersenactiviteit plaatsvindt in de gewenste richting. Zodoende kan vrijwillige modulatie van deze hersenactiviteit optreden, gepaard gaande met modulatie van onderliggende processen met als uiteindelijk doel het vergroten van de zelfregulatie (Gevensleben, Rothenberger, Moll & Heinrich, 2012).

CWMT is gebaseerd op het idee dat intensieve training van het werkgeheugen mogelijk andere neurocognitieve functies verbetert en zo - in het geval van ADHD - de ADHD-kern-symptomen vermindert. Het werkgeheugen is een onderdeel van het executief functioneren. Het omvat het vermogen informatie tijdelijk vast te houden en tegelijkertijd te bewerken

(Baddeley, 1986) en wordt gezien als een fundamentele neurocognitieve functie, onderliggend aan andere executieve functies (Klingberg et al., 2005).

Hersengolven in rust bij ADHD

Hoofdstuk II

De 'case-control' studie in **Hoofdstuk II** richtte zich 1) op het onderzoeken van de hersengolven in rust bij volwassenen met ADHD vergeleken met gezonde volwassenen in een ogen-dicht en ogen-open conditie, en 2) op het onderzoeken van correlaties tussen hersengolven in rust en het presteren op een neurocognitieve taak (een 'stop-signal task', die respons inhibitie meet) in volwassenen met ADHD en gezonde volwassenen en correlaties tussen deze hersengolven in rust en de ADHD-kernsymptomen in volwassenen met ADHD. Dit tweede punt was vooral interessant omdat dit de eerste studie was die dergelijke neurocognitieve correlaties bij volwassenen met ADHD onderzocht. Om deze studie uit te voeren, werd het EEG in rust voor 24 volwassenen met ADHD (gecombineerde subtype) en 24 gezonde volwassenen in zowel de ogen-dicht als de ogen-open conditie geanalyseerd. Volwassenen met ADHD lieten een grotere afname zien van de alpha 'power' van de ogen-dicht naar de ogen-open conditie. Er werd geen significante relatie gevonden tussen de hersengolven in rust en de ADHD-kernsymptomen bij volwassenen met ADHD. Voor de correlatie met de neurocognitieve taak bleek de theta/beta 'power' ratio negatief gecorreleerd met de responssnelheid; voor de volwassenen met ADHD ging dit waarschijnlijk ten koste van de nauwkeurigheid.

Hoofdstuk III

De studie in **Hoofdstuk III** richtte zich op het onderzoeken van de invloed van een lage alpha piek frequentie (APF) op de relatie tussen de theta/beta power ratio en de relatieve theta power in rust enerzijds en neurocognitief en gedragsmatig functioneren anderzijds. Deze onderzoeks-focus ontstond naar aanleiding van eerder onderzoek waaruit bleek dat een lagere APF verantwoordelijk was voor de verhoogde theta/beta power ratio in een subgroep bij kinderen met ADHD. Dit leidde tot de suggestie dat verhoogde theta power (als onderdeel van de verhoogde theta/beta power ratio) als meest robuuste bevinding bij ADHD - als het gaat over hersengolven in rust - soms verkeerd wordt geïnterpreteerd. Dit wordt dan veroorzaakt door het pieken van alpha op een lagere frequentie, waardoor deze mee wordt genomen in de schatting van theta power. Om de invloed van de APF te onderzoeken op de correlaties tussen de theta/beta power ratio en de relatieve theta power enerzijds en neurocognitief en gedragsmatig functioneren anderzijds, werden data betreffende hersengolven in rust, neurocognitief functioneren en ADHD-kernsymptomen geanalyseerd. Voor 38 kinderen (8-15 jaar) waren data van hersengolven in rust en scores van ADHD-kernsymptomen beschikbaar. Voor 32 kinderen waren ook neurocognitieve data voorhanden.

De individuele APF werd gemeten door het gebruik van zowel de ogen-open als de ogen-dicht conditie. De frequentiebanden werden geanalyseerd op basis van de ogen-open conditie. Een significant positieve relatie werd gevonden tussen de theta/beta power ratio en de totale score op de ADHD-kernsymptomen en de score op de sub-schaal hyperactiviteit. Tevens werd een significante relatie gevonden tussen relatieve theta power en de sub-schaal hyperactiviteit/impulsiviteit. Beide relaties werden sterker wanneer gecontroleerd werd voor de individuele APF. Acht van de 38 kinderen (21%) lieten een verlaagde APF zien (een APF van 9 Hz of lager), waardoor een overlap ontstond tussen hun individuele alpha-band en de theta-band. Een relatie tussen de theta/beta power ratio en/of relatieve theta power in rust en het neurocognitief functioneren werd niet gevonden. De resultaten van deze studie bevestigden dat de theta/beta power ratio en relatieve theta power inderdaad correleren met de ADHD-kernsymptomen. De bevindingen suggereren verder een belangrijke rol voor de individuele APF in de onderliggende elektrofysiologie bij ADHD.

Niet-farmacologische interventies bij kinderen met ADHD

Frequentie neurofeedback

Hoofdstuk IV beschreef een studie bij kinderen met ADHD naar de effectiviteit van F-NF op de ADHD-kernsymptomen en het globaal klinisch functioneren en de veiligheid, zoals deze gegeven wordt in de dagelijkse klinische praktijk. Dit onderzoek betrof een dubbel-blinde, semi-gerandomiseerde, placebo-gecontroleerde studie. Eenenveertig kinderen (8-15 jaar) met ADHD werden semi-willekeurig toegewezen aan F-NF of placebo-NF voor 30 sessies met een frequentie van tweemaal per week. Stratificatie werd toegepast voor leeftijd, elektrofysiologische staat van 'arousal' en medicatiegebruik. Alle betrokkenen in deze studie, behalve de NF-therapeut, waren blind ten aanzien van groepstoewijzing. Hoewel beide groepen op het niveau van ADHD-kernsymptomen verbetering lieten zien, kon de studie geen superieur effect aantonen voor F-NF groep ten opzichte van de placebo-NF groep. Bovendien werd er ook geen superieur effect gevonden op globaal klinisch functioneren. Er werden geen relevante bijwerkingen gevonden. Haalbaarheid van deze studie-opzet ten aanzien van de geïmplementeerde placebo-NF, waarbij het feedback signaal gebaseerd was op een gesimuleerd EEG signaal, bleek uit de bevinding dat het raden van de groepstoewijzing niet beter was dan op basis van kans. **Hoofdstuk V** omvatte verdere analyses van dezelfde studie met als doel de effectiviteit van F-NF op neurocognitief functioneren te onderzoeken en bevatte tevens een systematische 'review' over dit onderwerp. Daarnaast werd het EEG gedurende de sessies geanalyseerd met als doel te onderzoeken of er toename van neurale regulatie plaatsvond gedurende de F-NF. Een breed palet aan neurocognitieve taken werden voor en na de behandeling afgenomen. Deze neurocognitieve taken waren uitgekozen op grond van de veronderstelde neurocognitieve disfuncties bij kinderen met ADHD (aandacht, executief functioneren, belonings-gerelateerde processen en 'timing').

Zowel op groepsniveau als op individueel niveau werden geen significante effecten gevonden op neurocognitief functioneren ten gunste van F-NF. De systematische review over dit onderwerp liet tevens geen superieur effect zien van F-NF op neurocognitief functioneren. Bovendien werd geen steun gevonden voor toegenomen neurale regulatie na F-NF.
Samenvattend toonden deze studies geen superieur effect aan van F-NF ten opzichte van placebo-NF op de ADHD-kernsymptomen, globaal klinisch en neurocognitief functioneren. Er werd bovendien geen steun gevonden voor de neurofysiologische hypothese van F-NF.

Cogmed werkgeheugen training

Hoofdstuk VI betrof een studie bij jonge kinderen met ADHD naar de effectiviteit van CWMT op de ADHD-kernsymptomen, het neurocognitief, dagelijks executief en globaal klinisch functioneren. Dit onderzoek betrof een triple-blinde, semi-gerandomiseerde, placebo-gecontroleerde studie. Eenenvijftig kinderen (5-7 jaar) met ADHD werden semi-willekeurig toegewezen aan de actieve of placebo conditie van het Cogmed JM training programma voor 25 sessies met een frequentie van vijf keer per week. Stratificatie werd toegepast voor leeftijd en geslacht. Alle betrokkenen in deze studie waren blind ten aanzien van groepstoewijzing. Hoewel kinderen vooruitgang lieten zien op diverse maten, toonde deze studie geen superieur effect aan van CWMT ten opzichte van de placebo conditie op de ADHD-kernsymptomen, neurocognitief, dagelijks executief en globaal klinisch functioneren. Kinderen in de actieve conditie lieten wel verbetering zien op de getrainde werkgeheugentaak, maar geen superieure verbetering op de niet-getrainde taken. Samenvattend kon deze studie geen bewijs vinden voor de effectiviteit van CWMT bij jonge kinderen met ADHD. Met andere woorden, deze studie liet geen transfer-effecten zien.

In de discussie (**Hoofdstuk VIII)** werden de bevindingen van de vijf studies besproken en werd ingegaan op de betekenis van de bevindingen voor de klinische praktijk. De drie belangrijkste lessen van dit proefschrift waren:

1) Hersengolven in rust kunnen mogelijk een belangrijke bijdrage leveren aan onze kennis over ADHD. Echter, de puzzel over de betekenis van deze hersengolven in ADHD is nog helemaal niet opgelost. Alpha power en APF verdienen in elk geval een meer prominente rol in de zoektocht naar de elektrofysiologische achtergrond van ADHD. Correlaties tussen hersengolven in rust enerzijds en ADHD-kernsymptomen en neurocognitief functioneren anderzijds zijn aangetoond; echter inconsistentie van deze bevindingen maken duidelijke conclusies nu (nog) niet mogelijk.
2) De studies naar de effectiviteit van F-NF en CWMT bij kinderen met ADHD in dit proefschrift toonden geen superieur effect aan van de behandelconditie ten opzichte van de placebo conditie. Het is mogelijk dat methodologische en andere tekortkomingen van deze studies oorzaak zijn van het niet vinden van grote specifieke behandeleffec-

ten zoals die gevonden worden bij ADHD-medicatie; hoewel de resultaten niet inconsistent waren, maar significant afwezig waren op alle niveaus. Echter, de beperkingen van beide onderzoeken mogen niet genegeerd worden en moeten worden aangepakt in toekomstig wetenschappelijk onderzoek.

3) Voorlichting aan ouders en hun kinderen met ADHD over F-NF en CWMT dient in lijn te zijn met de actuele onderzoeksresultaten.

Aanbevelingen voor toekomstig wetenschappelijk onderzoek werden vervolgens besproken. Er werd stilgestaan bij de beperkingen van de huidige studies. Het belangrijkste advies voor toekomstig wetenschappelijk onderzoek was het optimaliseren van eerdere studies om de mogelijk specifieke en unieke effecten van F-NF en CWMT verder te onderzoeken, met als doel een meer definitieve uitspraak te kunnen doen over de werkelijke betekenis van beide potentiele behandelmethoden bij kinderen met ADHD.

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Martine van Dongen-Boomsma*, Madelon A. Vollebregt*, Jan K. Buitelaar** & Dorine Slaats-Willemse**. Working memory training in young children with ADHD: A randomized placebo-controlled trial. *Journal of Child Psychology and Psychiatry.*

Submitted for publication

Madelon A. Vollebregt, **Martine van Dongen-Boomsma**, Dorine Slaats-Willemse, Jan K. Buitelaar** & Robert Oostenveld**. How the alpha peak frequency helps to unravel the neurophysiologic underpinnings of behavioral functioning in children with attention-deficit/hyperactivity disorder.

Martine van Dongen-Boomsma*, Madelon Vollebregt*, Dorine Slaats-Willemse & Jan K. Buitelaar. EEG-neurofeedback in children with ADHD; How to resolve the debate about its efficacy?

Madelon A. Vollebregt*, **Martine van Dongen-Boomsma***, Jan K. Buitelaar & Dorine Slaats-Willemse. EEG-neurofeedback bij kinderen met ADHD; gebrek aan overtuigend bewijs?

** joint first authors, ** joint last authors*

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Curriculum Vitae

Martine Boomsma werd geboren op 29 juni 1978 te IJsselstein. Na het behalen van haar Gymnasium diploma (1996) aan het St. Bonifacius College te Utrecht, behaalde zij haar propedeuse HBO-Verpleegkunde (1997) en startte in datzelfde jaar met de studie Geneeskunde aan de Universiteit van Utrecht. Na haar studie (2004), werkte ze als arts-assistent op de afdeling Verloskunde van het Wilhelmina Kinderziekenhuis te Utrecht. Na een klein, inspirerend jaar, besloot zij dat naast de vroegste ontwikkeling van het kind, de gehele ontwikkeling van het kind haar intrigeerde en een centrale plek mocht krijgen in haar uiteindelijke specialisme. Zij besloot kinder- en jeugdpsychiater te willen worden. Zij werkte vervolgens een aantal maanden als art-assistent Psychiatrie bij Altrecht. Vervolgens werd zij per 1 september 2005 aangenomen voor de opleiding tot psychiater aan het UMC St. Radboud en de opleiding tot kinder- en jeugdpsychiater bij Karakter. Beide opleidingen werden gecombineerd met promotieonderzoek onder leiding van professor dr. Buitelaar en dr. Slaats-Willemse, resulterend in dit proefschrift. In oktober 2011 rondde zij haar opleiding af tot psychiater, in 2012 de opleiding tot kinder- en jeugdpsychiater. Sindsdien werkt zij bij Karakter Universitair Centrum als kinder- en jeugdpsychiater en als arts-onderzoeker. Martine is in 2008 getrouwd met Ernst van Dongen en samen hebben zij twee dochters; Nuna (2009) en Laya (2011).