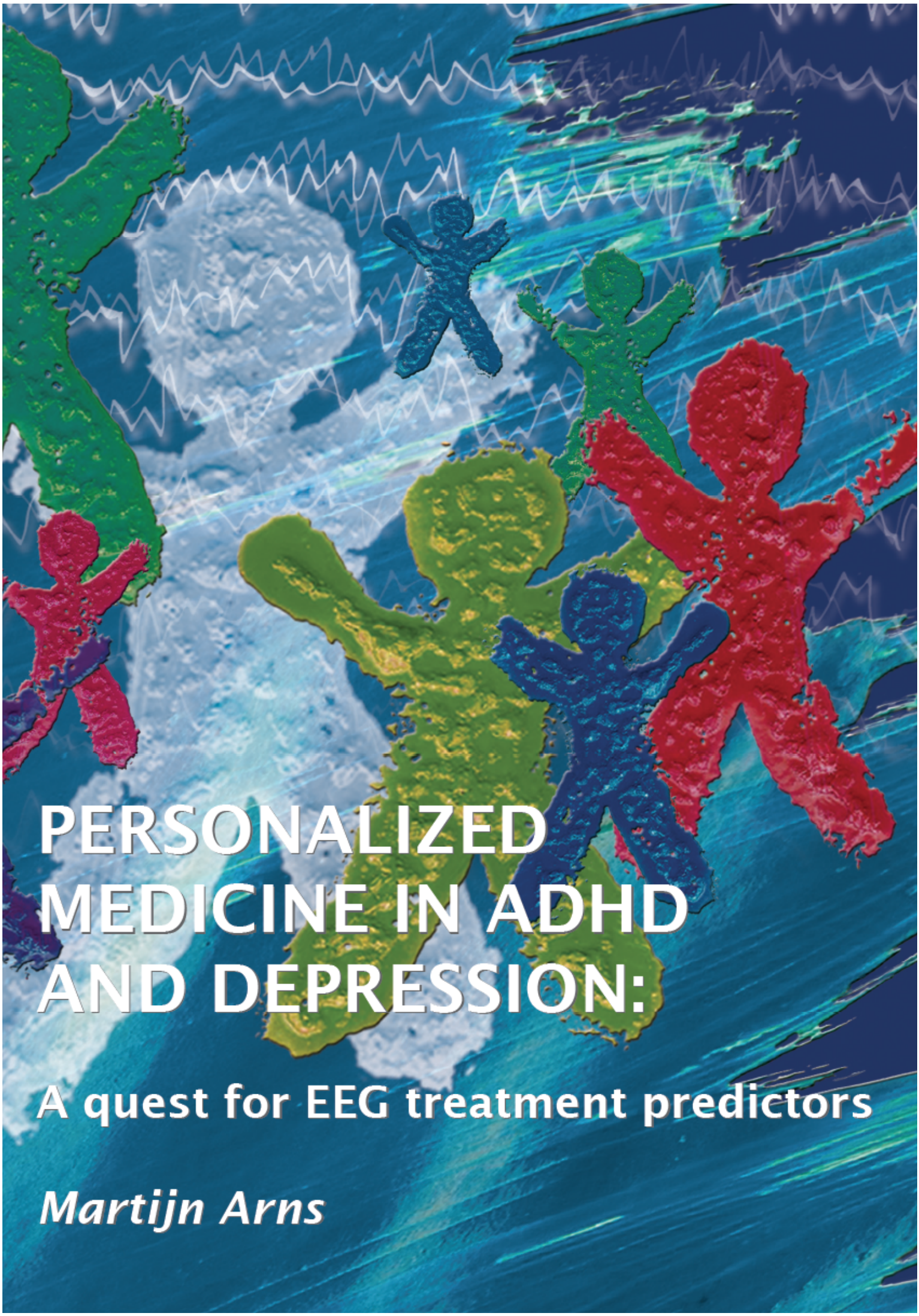


PERSONALIZED MEDICINE IN ADHD AND DEPRESSION:

A quest for EEG treatment predictors

Martijn Arns

PERSONALIZED MEDICINE IN ADHD AND DEPRESSION

A QUEST FOR EEG TREATMENT PREDICTORS

Martijn Arns

Cover: Mathanje Huisman

Printing: Ipskamp Drukkers, Amsterdam

ISBN: 978-94-6191-098

PERSONALIZED MEDICINE IN ADHD AND DEPRESSION:

A QUEST FOR EEG TREATMENT PREDICTORS

EEG gebasseerde personalisatie van behandeling bij Depressie en ADHD.

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op

vrijdag 23 december 2011 des middags te 12.45 uur

door

Martijn Wilco Arns

geboren op 4 december 1974 te Apeldoorn

Promotor: Prof. dr. J.L. Kenemans

Co-promotor: Dr. W.H.I.M. Drinkenburg

Table of contents

Chapter 1: Introduction

Part 1: Treatment prediction in ADHD

Chapter 2 EEG Phenotypes predict treatment outcome to stimulants in children with ADHD

Chapter 3 EEG-vigilance and response to stimulants in paediatric patients with Attention Deficit/Hyperactivity Disorder

Chapter 4 The increase in theta/beta ratio on resting state EEG in boys with attention-deficit/hyperactivity disorder is mediated by slow alpha peak frequency.

Chapter 5 Efficacy of neurofeedback treatment in ADHD: The effects on inattention, impulsivity and hyperactivity: A meta-analysis.

Chapter 6 The effects of QEEG-*informed* neurofeedback in ADHD: An open label pilot study.

Part 2: Treatment prediction in depression

Chapter 7 An investigation of EEG, genetic and cognitive markers of treatment response to antidepressant medication in patients with major depressive disorder: a pilot study

Suppl. 1 EEG Phenotypes in depression

Chapter 8 Repetitive Transcranial Magnetic Stimulation in depression: Protocols, Mechanisms and New Developments

Chapter 9 Potential differential effects of 9 Hz rTMS and 10Hz rTMS in the treatment of depression.

Chapter 10 Neurophysiological predictors of non-response to rTMS in depression

Summary and conclusions

References

Summary in Dutch / Samenvatting in het Nederlands

Acknowledgement / Dankwoord

Curriculum Vitae

Publications

Chapter 1

Introduction

This chapter is adapted from the following book chapter with some updates and modifications:
Arns, M., Gunkelman, J., Olbrich, S., Sander, C., & Hegerl, U. (2010). EEG vigilance and phenotypes in neuropsychiatry: Implications for intervention. In R. Coben & J. Evans (Eds.), *Neuromodulation and neurofeedback: Techniques and applications.* Elsevier.

Introduction

In 1929 Hans Berger reported in an extensive publication his observations on what he termed '*das Elektrenkephalogramm*' (Berger, 1929), which would become the seminal paper highlighting the beginning of research on the human electroencephalogram also abbreviated as EEG. In his first experiments he recorded the EEG from his son Klaus – among others – and described extensively the methods he used and what he observed. Figure 1 below demonstrates 2 graphs from that first publication recorded from his son. The bottom figure represents the rhythm he would eventually call the 'alpha EEG rhythm' and the top figure represents what he would eventually call the 'beta EEG rhythm'. Since that time much research has been dedicated to measuring EEG under different conditions as well as measuring EEG in a variety of disorders ranging from neurological to psychiatric.

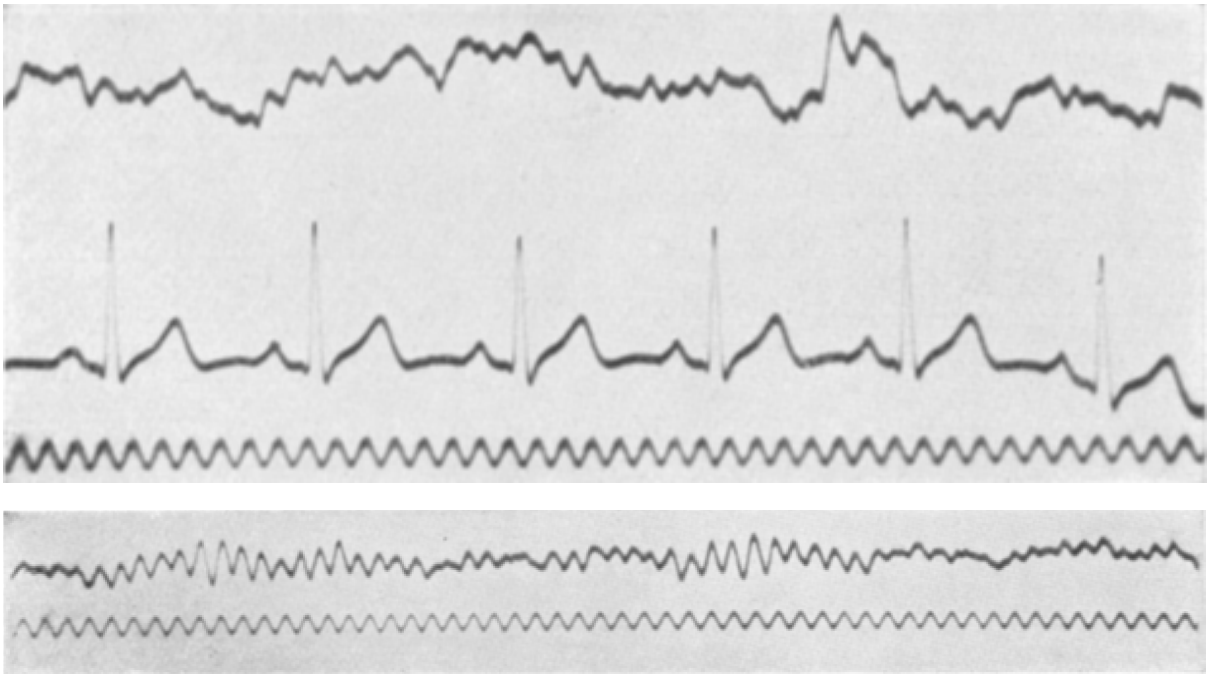


Figure 1: *The first reports of the human EEG from the first publication from Hans Berger (1929). Both represent samples of EEG recorded from his son Klaus (16 years old). The bottom figure represents a sample of what he would later call the 'alpha rhythm' (a sinusoidal rhythm of approximately 10 Hz) and the figure above what he would later call the 'beta rhythm' (or a desynchronized EEG with no obvious rhythmicity). The lowest tracing in both graphs is a generated 10 Hz sine wave, and the middle tracing from the top figure is the ECG. From: Berger (1929).*

In the period between the discovery of EEG in 1929 and the late 1960's EEG was mainly inspected visually until digital equipment became available which made it possible to apply Fourier analysis to EEG data to extract the spectral content – or frequency content - of a signal. This eventually enabled the field of Quantitative EEG (QEEG) as we know it today. In the simplest form one speaks of QEEG when the EEG is submitted to spectral analysis (Niedermeyer & Da Silva, 2004). In this respect some prefer to speak of 'Normative EEG' to emphasize that the EEG should not only be submitted to spectral analysis but also compared to a control group and/or normative database.

The group led by Ross Adey at the UCLA Brain Research Institute in the period 1961-1974 pioneered the use of QEEG. They were the first to use digital computers in the analysis of EEG with the production of brain maps and developed the first normative library of brain maps. See figure 2 for some photos with the first equipment developed to measure EEG in outer space and during driving. As part of the Space Biology Laboratory they studied the effects of outer space and space travel on the brain, to determine whether prolonged space flight would be possible for the human body. As part of this NASA program Graham and Dietlein were the first to coin the term Normative EEG (Graham & Dietlein, 1965). In the last 20 years due to the increasing availability of affordable computer equipment with increasing calculating power, the field of QEEG has expanded even further and has become available for many practicing clinicians and clinics. Along with this, several different normative databases have been developed as well and are available to most clinicians.

Figure 2: *A photo from 1963 showing the equipment developed by Adey et al. to measure EEG in space. Ross Adey – who pioneered QEEG – is the person on the right in the top left picture. (Courtesy of the Computer History Museum)*

In this thesis where we speak of QEEG we focus on normative EEG, or QEEG data that are compared to a control group or normative database. Furthermore, we will restrict our focus to the application of QEEG to neuropsychiatric conditions, whereas more strictly

neurological applications fall beyond the scope of the thesis. In this chapter where we report on EEG power measures we will only report on absolute EEG unless stated otherwise. Relative EEG power measures often obscure findings making it unclear what is actually going on in the EEG, e.g. if the total absolute alpha power is decreased, it might appear as an increased 'relative' beta and theta power.

Personalized medicine: 'Prognostics' rather than 'Diagnostics'

Current conventional treatment in psychiatry is based on behavioral interventions and/or medication ('systemic' approach). Recent large-scale studies increasingly often are showing the limitations of these conventional treatments (both behavioral and drug treatment) in psychiatry. The largest trial to date in 3.671 depressive patients investigating treatment effects in depression (the STAR*D trial) demonstrated limited clinical efficacy of antidepressants and cognitive behavior therapy (CBT) in the treatment of depression with remission rates of 36.8% per single treatment step and 33% treatment resistance after four cumulative treatments (Rush et al., 2006). Some methodological issues potentially limit the extent to which these results can be generalized, such as a selection bias (the fact that most participants in this trial had no health insurance), lack of a placebo control and not checking lithium levels. However, these and other studies (Keller et al., 2000; Kirsch et al., 2008) do demonstrate there is a need for improved efficacy in depression treatment. A similar initiative investigating the effects of different treatment approaches in ADHD (the NIMH-MTA trial) demonstrated a lack of long-term effects for stimulant medication, multicomponent behavior therapy and multimodal treatment beyond 2 years (Molina et al., 2009), although latent class analysis did report a sub-group consisting of children who did demonstrate sustained effects of treatment at 2 years follow up (Swanson et al., 2007). In general, response rates to stimulant medication in ADHD are estimated to be 70% (for an overview see: Hermens, Rowe, Gordon & Williams, 2006).

These conclusions about limitations in efficacy and long-term effects are all based on the interpretation of group-averaged data, but also demonstrate there is a percentage of patients that does respond to antidepressants (Rush et al., 2006) and there is a sub-group of patients that demonstrate long-term effects (Swanson et al., 2007). Personalized medicine promises to move beyond data regarding the average effectiveness of treatment to identify the best treatment for any individual (Simon & Perlis, 2010). In personalized medicine it is the goal to prescribe the right treatment, for the right person at the right time as opposed to the current 'trial-and-error' approach. Genotypic and phenotypic information or 'Biomarkers' lie at the basis of personalized medicine. Usually in this context genetic markers are considered which can predict effects of medication such as the classical example of herceptin. Herceptin is a drug used to treat breast cancer, but only for patients showing an over-expression for a specific protein better known as human epidermal growth factor receptor 2 (HER2) . This drug only works well with this specific sub-group of patients, who are easily distinguished by a genetic test where HER2 is considered the biomarker. At this moment there is no psychiatric disorder, which is completely genetically determined. Furthermore, 2011 marks the 10^{th} year anniversary of the completion of the Human Genome project, which has sparked numerous large scale Genome Wide Association studies

(GWA) and other genotyping studies in psychiatric disorders only accounting for a few percent of the genetic variance (Lander, 2011). This suggests a strictly genetic approach to personalized medicine for psychiatry will be not so fruitful. The notion of personalized medicine suggests *heterogeneity* within a given DSM-IV disorder, rather than *homogeneity*, at least from a brain-based perspective. Therefore a variety of 'endophenotypes' or 'biomarkers' are expected within a single DSM-IV disorder such as ADHD or depression, expected to require a different treatment.

From 'Endophenotypes' to 'Biomarkers'

The concept of endophenotypes has been described as early as in 1966 and originated from a review on geographical distribution in insects where a clear case was made for not only investigating the exophenotype (*"…the obvious and the external…"*) but also the endophenotype (*"…the microscopic and internal"*) (John & Lewis, 1966). This term was further adopted by Gottesman and Shields (1967; 1972) in their studies on schizophrenia as 'biochemical test or microscopic examination' (Gottesman & Gould, 2003). The idea behind an endophenotype is that it is the intermediary step between genotype and behavior and thus is more closely related to genotype than behavior is. Therefore, endophenotypes can be investigated to yield more information on the underlying genotype. Given the interest in the last couple of years for genetic linkage studies, this term has become more topical again. In parallel there have also been many studies using the term biological marker, trait, biomarker etc. Here it is important that in line with Gottesman and Gould (2003), an 'endophenotype' refers to a marker when also certain heritability indicators are fulfilled, whereas a 'Biomarker' simply refers to differences between patient groups, which do not necessarily have a hereditary basis.

In the context of Psychiatry Gordon (2007) proposed the term 'neuro-marker', and Johnstone et al. (Johnstone, Gunkelman & Lunt, 2005) proposed the term 'EEG Phenotype' as examples of biomarkers or intermediate phenotypes. In another context EEG-vigilance regulation has also been proposed as a state-dependent trait (Hegerl, Himmerich, Engmann & Hensch, 2010; Hegerl, Sander, Olbrich & Schoenknecht, 2009). The underlying idea behind these concepts is that neuroimaging data such as from EEG, fMRI, PET scans etc. can be considered stable endophenotypes or biomarkers incorporating both the effects of nature and nurture. This potentially makes such markers ideal candidate biomarkers, which have the potential to predict treatment outcome for treatments such as antidepressants or stimulants, but also for alternative treatments such as rTMS and neurofeedback (explained below). These developments, currently subsumed under the umbrella term 'personalized medicine', are not completely new.

The quest for biomarkers to predict treatment outcome has a long history. For example Satterfield et al. (Satterfield, Cantwell, Saul, Lesser & Podosin, 1973; Satterfield, Lesser & Podosin, 1971) were the first to investigate the potential use of EEG in predicting treatment outcome to stimulant medication (main results outlined further on). In 1957 Roth et al (Roth, Kay, Shaw & Green, 1957) investigated barbiturate induced EEG changes (delta increase) and found this predicted to some degree the long-term outcome (3-6 months) to ECT in depression. This latter finding was replicated measuring delta activity during the

inter-seizure period, and as Fink summarized this finding eloquently: '*Slowing of EEG rhythms was necessary for clinical improvement in ECT*' (Fink, 2010). In this development of personalized medicine the focus is hence more on 'prognostics' rather than 'diagnostics'.

The topic of this thesis is personalized medicine in ADHD and depression with a main focus on neurophysiological techniques such as the EEG and Event Related Potentials (ERPs). In the next section the history of EEG and QEEG findings in ADHD and depression and their promises and limitations for this personalized medicine approach will be reviewed first. In later chapters several studies will be presented which serve to investigate the value of EEG in treatment prediction further. Such predictors are especially relevant for the phenomenon of non-response, since such findings might lead to a better understanding of sub-groups of non-responders and such biomarkers could potentially result in the development of new, personalized treatments for patients irresponsive to current treatments.

In addition to pharmacological treatment, the possible value of alternative non-pharmacological interventions is central to this thesis. In this thesis the application of neurofeedback in ADHD and rTMS in depression is specifically focused on. Neurofeedback is a technique where brain activity is fed back to a patient with the main goal to 'normalize' deviant brain activity, employing principles based on operant conditioning. In chapter 5 and chapter 6 this technique is covered in more depth regarding the application in the treatment of ADHD. Repetitive Transcranial Magnetic Stimulation – also referred to as rTMS – is a technique employing a strong pulsating magnetic field, resulting in electrical stimulation of the underlying cortex. This technique is explained in more detail in chapter 8, and chapter 9 and 10 will focus on predictors for treatment outcome to this technique.

EEG Research in ADHD

ADHD

Attention-Deficit/Hyperactivity Disorder (ADHD) has become one of the most common neurodevelopmental and psychiatric disorders of childhood. The general rate of prevalence is reported between 3% to 7% of school age children (Cormier, 2008). In 40-60% of all cases ADHD persists in adolescence and adulthood (Faraone, Biederman & Mick, 2006). Currently, the disorder is primarily diagnosed by referring to the criteria of the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition Text Revision (DSM-IV, 1994) or the International Statistical Classification of Mental Disorders (ICD-10, World Health Organization, 1992). Attention Deficit Hyperactivity Disorder is not only the most common of the childhood psychiatric disorders but also the best researched disorder (Rowland, Lesesne, & Abramowitz, 2002). According to the DSM-IV-TR (DSM-IV, 1994), the disorder presents itself in three primary subtypes: predominantly inattentive type, predominantly hyperactive-impulsive type and the combined type.

Considerable research has been carried out investigating the neurophysiology of ADHD. The first report describing EEG findings in 'behavior problem children' stems from 1938 (Jasper, Solomon & Bradley, 1938). In those early days Jasper, Solomon and Bradley described an EEG pattern we now call the frontal slow EEG or frontal theta EEG: *"…There were occasionally two or three waves also in the central or frontal regions at frequencies below what is considered the normal alpha range, that is, at frequencies of 5-6/sec…"* (Jasper et al., 1938; p. 644). Hence this observation suggested another EEG rhythm in addition to alpha and beta described earlier by Berger (1929). We now know this rhythm to be Theta, and the term Theta was first introduced in 1944 by Walter and Dovey (Walter & Dovey, 1944). In this group of 'behavior problem children' they described a 'Class 1' as 'hyperactive, impulsive and highly variable' which resembles the current diagnosis of ADHD most closely. The most predominant features in this group were the occurrence of slow waves above one or more regions (as described above) and an 'abnormal EEG' in 83% of the cases. In this Class 1 they also reported an additional sub-group which they termed a 'sub-alpha rhythm' with slow frontal *regular* activity which occurred in a similar way as the posterior alpha (*'…In other cases a 5-6/sec rhythm would predominate in the anterior head regions simultaneous with an 8-10/sec. rhythm from the posterior regions.").* Currently it is known that alpha activity is also observed over frontal regions, which is not due to volume conduction (Broughton & Hasan, 1995). This frontal alpha is often observed during transition to drowsiness, is 1-2 Hz slower than the posterior alpha and is maximal at frontal sites (Broughton & Hasan, 1995; Conneman et al., 2005; De Gennaro et al., 2005). Given the regularity of this signal, according to the authors '*with a regularity equal to those of the normal occipital alpha rhythm*' and the fact they described this rhythm to be '*…normal from the anterior head regions in very young children (below two years) so that it may be related to a lack of maturation…'* suggests this activity is what is currently described as a slow alpha peak frequency (Jasper et al., 1938). Since alpha and slow EEG osscilations such as theta are considered to have different neurophysiological origins it is important to distinguish these accurately (Steriade, Gloor, Llinas, Lopes da Silva & Mesulam, 1990).

Capute et al. (1968) reported that the most common 'abnormality' in MBD was excessive bilateral posterior slowing, which is considered the same as a slowed alpha peak frequency. In this regard it is interesting to note that Cohn & Nardini (1958) described an EEG pattern of bi-occipital slow activity, which they related to aggressive clinical behavior. They stated that this activity: *"…is sometimes sensitive, in a way similar to that of the occipital alpha output, to opening and closing the eyelids... has a distribution that corresponds grossly to that of the occipital alpha activity*." This suggests they also observed a slowed Alpha peak frequency (APF) rather than real occipital theta. Stevens et al. (1968) correlated different EEG abnormalities to behavioral profiles and found that slowing of EEG frequencies (occipital) was related to hyperactivity, difficulty with labeling simple geometric figures and poor figure-ground discrimination. Furthermore, no clear behavioral syndrome was associated with predominant, frontal EEG abnormalities, suggesting that core problems such as hyperactivity are more related to a slowed APF rather than to excess frontal slow activity (theta).

Most older studies investigating the EEG in Minimal Cerebral Dysfunction (MCD) or Minimal Brain Damage (MBD) (the earlier diagnosis for ADHD) reported incidences of around 50% 'abnormal EEG' as compared to control groups showing, on average, 15% 'abnormal EEGs' (for an overview see: Capute, Niedermeyer & Richardson, 1968; Hughes, DeLeo & Melyn, 2000; Stevens, Sachdev & Milstein, 1968). The exact implications of this high prevalence of 'abnormal EEGs' are not very well understood. The presence or absence of an 'abnormal EEG' is of little value in predicting clinical or etiological features (Stevens et al., 1968) and this group also includes children with a 'paroxysmal EEG' or 'epileptiform discharges'.

Paroxysmal EEG abnormalities and epileptiform discharges

The estimated incidences of paroxysmal EEG in ADHD vary between 12-15% (Capute et al., 1968; Hemmer, Pasternak, Zecker & Trommer, 2001; Satterfield et al., 1973) to approximately 30% (Hughes et al., 2000), which is high compared to 1-2% in normal populations (Goodwin, 1947; Richter, Zimmerman, Raichle & Liske, 1971). Note that these individuals did not present with convulsions and thus did not have a clinical diagnosis epilepsy, but simply exhibited a paroxysmal EEG in the absence of convulsions. In autism a prevalence of 46% to 86% for paroxysmal EEG or epileptic EEG abnormalities has been reported (Parmeggiani et al., 2010; Yasuhara, 2010), hence the earlier findings on 'abnormal' EEG might have been partly confounded by a sub-group with autism, since autism was not included as a diagnostic entity in the DSM until 1980 when the DSM-III was released.

The exact implications of this paroxysmal EEG activity in subjects without overt signs of epilepsy are not very well understood and many neurologists will see no need to treat these subjects as epileptics. In a very large study among jet fighter pilots, Lennox-Buchtal, Buchtal and Rosenfalck (1960) classified 6.4% as 'marked and paroxysmally abnormal'. Moreover, they found that pilots with such EEGs were three times more likely to have their plane crashed due to pilot error, indicating that even though these people are not 'epileptic' their brains are 'not normal' and hence the presence of paroxysmal EEG continues to be an exclusion criterion for becoming a pilot. It is interesting to note that several studies found that ADHD patients (Davids, Kis, Specka & Gastpar, 2006; Itil & Rizzo, 1967; Silva, Munoz &

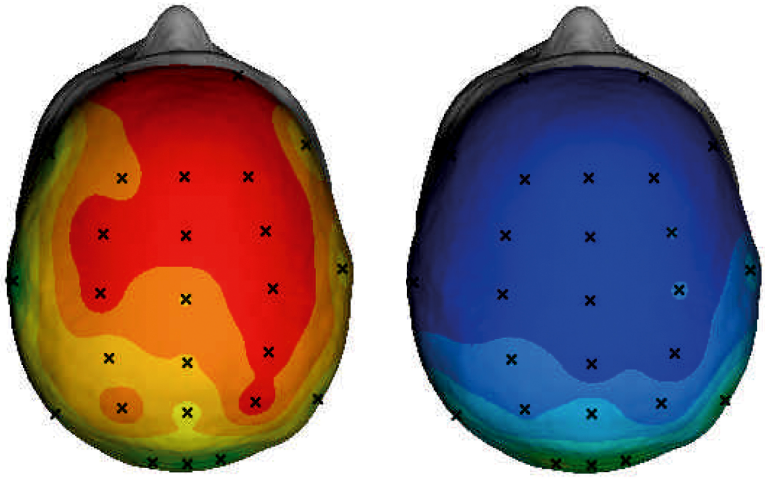
Alpert, 1996) and patients with autism (Yasuhara, 2010) do respond to anticonvulsant medication. The reported effect size for Carbamazepine in the treatment of ADHD was 1.01, which is quite similar to stimulant medication (Wood, Crager, Delap, & Heiskell, 2007). Furthermore, some studies have demonstrated that interictal and/or subclinical spike activity has detrimental effects on neuropsychological, neurobehavioral, neurodevelopmental, learning and/or autonomic functions and some of these children with subclinical spike patterns do respond to anticonvulsant medication both with a reduction of spikes measured in the EEG and with improvements on memory and attention (Mintz et al., 2009). These findings suggest the existence of a sub-group with paroxysmal EEG, who might respond better to anticonvulsant medication; however further research is required to substantiate this.

The era of computerized EEG analysis: QEEG

After the introduction of Quantitative EEG (QEEG) and computerized EEG in the 1960's by the pioneering work of Ross Adey and his group, many more studies have been carried out investigating the neurophysiology of ADHD and depression. The introduction of computerized EEG, simplified the analysis of the EEG since many complex analyses could be performed in an automated fashion.

'Excess Theta' and 'Theta/Beta Ratio'

The most consistent findings reported in the literature on ADHD since the introduction of QEEG are those of increased absolute power in Theta (Bresnahan, Anderson & Barry, 1999; Chabot & Serfontein, 1996; Clarke, Barry, McCarthy & Selikowitz, 1998; Clarke, Barry, McCarthy & Selikowitz, 2001b; DeFrance, Smith, Schweitzer, Ginsberg & Sands, 1996; Janzen, Graap, Stephanson, Marshall & Fitzsimmons, 1995; Lazzaro et al., 1999; Lazzaro et al., 1998; Mann, Lubar, Zimmerman, Miller & Muenchen, 1992; Matsuura et al., 1993) and sometimes increased absolute Delta EEG power (Bresnahan et al., 1999; Clarke, Barry, McCarthy & Selikowitz, 2001a; Kuperman, Johnson, Arndt, Lindgren & Wolraich, 1996; Matsuura et al., 1993). In figure 3 an example is depicted based on 275 unmedicated children with ADHD compared to a matched control group. On the left the increased 'Theta' EEG power is clearly visible specifically in frontocentral brain areas.



Absolute 'Theta' EEG power Relative 'Beta' EEG power

Figure 3: *The averaged brain activity of 275 ADHD patients compared to a matched control group (based on the data from: Williams et al., 2010a) is shown in this figure. The figure left shows the increased theta (p<.0001) and right the decreased relative Beta power (p<.0001) where blue indicates decreased activity and orange to red indicates increased activity. This figure illustrates the most consistent finding of increased 'theta' EEG power in ADHD.*

Lubar in 1991 laid the foundation for the concept of the Theta/Beta power ratio as a measure, which could discriminate 'normal' children from children with ADD, learning disorders and ADHD (Lubar, 1991). Many others investigated this measure further, with the clearest replication from Monastra et al. (1999) who demonstrated in a multi-center study in 482 subjects that using a single electrode location (Cz) they could classify with an accuracy of 88% children with ADHD based on the Theta/Beta power ratio. Since these initial findings many groups have further investigated the EEG in ADHD, mainly using computerized power spectral EEG analysis (FFT) and coherence. Boutros et al. (2005) using a meta-analysis incorporating more than 1100 subjects with ADHD/ADD concluded that increased theta activity in ADHD is a sufficiently robust finding to warrant further developing as a diagnostic test for ADHD, with data suggesting that relative theta power is even a stronger predictor.

In contrast to the results described in the previous section on historical findings in the EEG from the pre-QEEG era, almost none of the recent studies report on alpha peak frequency (APF), but only on spectral power measures using fixed frequency bands in ADHD, whereas in the earlier studies clear relations have been reported between a slowed APF and behavioral measures such as hyperactivity (Stevens et al., 1968). It is well known that the frequency of alpha matures with age. Children 4 months of age have an APF of 4 Hz, those at age 12 months one of 6 Hz and those at age 3 years one of 8 Hz. A 10 Hz frequency on average is observed at 10 years of age (Niedermeyer & Lopes da Silva, 2004). Even in subjects older than 10 years of age a substantial variability in the individual APF is present

where in some cases the APF might overlap with the fixed frequency bands labeled as 'theta' (4-8 Hz), which was already pointed out by Steriade et al. (Steriade, Gloor, Llinás, Lopes de Silva & Mesulam, 1990) and has prompted some researchers to individualize frequency bands based on the individual APF (Doppelmayr, Klimesch, Pachinger, & Ripper, 1998; Klimesch, 1999). Therefore, the often-reported excess theta in ADHD likely consists of both a slowed APF and real excess slow activity (theta). In chapter 2 (Arns et al., 2008) and chapter 4 (Lansbergen, Arns, van Dongen-Boomsma, Spronk & Buitelaar, 2011) this will be addressed in more detail, and the results will demonstrate that it is indeed the case that the frequently reported excess theta actually consist of 2 sub-groups, 1) excess theta and 2) a slowed APF sub-group.

Increased or decreased beta?

The literature is less consistent about the finding of decreased absolute beta in ADHD (Callaway, Halliday & Naylor, 1983; Mann et al., 1992; Matsuura et al., 1993), although relative decreased beta has been reported more often (also see figure 3). Decreased absolute beta was not found in several other studies (Barry, Clarke, Johnstone & Brown, 2009; Clarke et al., 2001a; Lazzaro et al., 1999; Lazzaro et al., 1998) and was actually found to be increased in one study (Kuperman et al., 1996). Furthermore, some studies have also reported a specific sub-group in ADHD with excess beta ranging from 13% (Chabot & Serfontein, 1996) to 20% (Clarke et al., 1998; 2001b), and most prevalent in males with ADHD. Clarke et al. (2001c) also reported that about 10% of the excess beta group in ADHD showed beta spindles, and Arns et al. (2008) reported that 16% had beta spindles. In summary, several studies point to the existence of an ADHD sub-group with excess beta rather than a decreased beta power.

EEG as a prognostic tool: Subtypes and treatment prediction in ADHD

Satterfield and colleagues (Satterfield et al., 1973; Satterfield et al., 1971) were the first to investigate the potential use of EEG in predicting treatment outcome to stimulant medication. They found that children with excess slow wave activity and large amplitude evoked potentials were more likely to respond to stimulant medication (Satterfield et al., 1971) or more general that abnormal EEG findings could be considered a predictor for positive treatment outcome (Satterfield et al., 1973). Chabot et al. (Chabot, di Michele, Prichep & John, 2001; Chabot, Orgill, Crawford, Harris & Serfontein, 1999) found that ADHD and ADD children with excess relative alpha or beta power were likely to show behavioral improvement, whereas the relative excess theta group showed a worse response to medication. Their group exhibiting this 'excess Theta' was described as: '*generalized excess of theta absolute and relative power, decreased alpha mean frequency, and frontal theta hypercoherence*'. Note the mentioning of decreased alpha mean frequency, suggesting that in fact they were looking at a combined group of excess theta and slowed APF.

In contrast, Clarke et al. (2002) and Suffin and Emory (1995) showed that in ADHD and ADD good responders to stimulant medication were characterized by increased theta and increased theta/beta ratios. Furthermore, Clarke et al. (2003b) demonstrated that an excess beta group also responded well to stimulants, in agreement with Chabot et al., (1999) and

Hermens et al. (2005). However, Clarke et al. (2003b) noted that there were few EEG normalizations.

Depression

Major depression is a common disorder with millions of sufferers around the world and a lifetime prevalence of about 13% in men and 21% in women (Blazer, Kessler, McGonagle & Swartz, 1994). The World Health Organization has predicted that depression will globally become the 2nd largest burden of disease by 2020, following cardiovascular conditions (Murray & Lopez, 1997). Individuals with depression experience a wide range of symptoms including a loss of interest or pleasure, feelings of sadness, guilt, low self-esteem, disturbances in sleep and appetite, poor concentration and suicidal ideations (DSM-IV, 1994).

Lemere published the first description relating EEG findings to depression in 1936 (Lemere, 1936). After inspecting the EEG's of healthy people and several psychiatric patients he concluded: "*…The ability to produce "good" alpha waves seems to be a neurophysiological characteristic which is related in some way to the affective capacity of the individual*". This increased alpha power is to date still considered a hallmark of depression (for an overview also see Itil (1983)) and recent studies suggesting this endophenotype to be the mediator between the BDNF Val66Met polymorphism and trait depression (Gatt et al., 2008). A large body of research into alpha power in depression has been dedicated to 'frontal alpha asymmetry', which will be addressed in the next section.

Frontal alpha asymmetry in depression

In 1973 d'Elia & Perris were the first to investigate parietal alpha power asymmetry in depression (psychotic depression in this case) and reported that the left to right ratio correlated to the depression score both before and after ECT (d'Elia & Perris, 1973). Furthermore, the treatment effects of ECT were mainly reflected in left hemisphere changes.

In 1983 a group led by Richard Davidson started publishing pioneering work on frontal alpha asymmetry in depression. They reported a relative hyperactivation of the right frontal cortex, which was not found for the parietal cortex (Schaffer, Davidson & Saron, 1983). In their 1990 paper Henriques and Davidson laid a further foundation for the concept of frontal alpha asymmetry in depression (Henriques & Davidson, 1990), where they consider 'approach' and 'withdrawal' as the essential basis for this asymmetry. *"…The approach system facilitates*

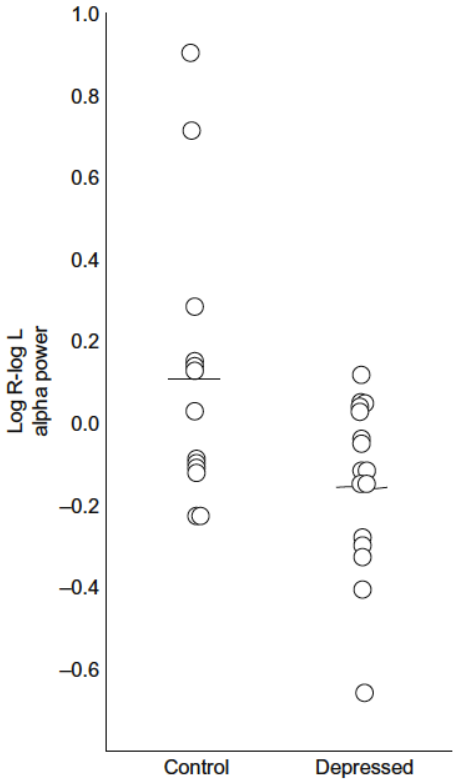


Figure 4*: This figure shows the initial results from the Henriques and Davidson paper (1990) demonstrating the diferences in 'frontal alpha asymmetry' between healthy controls and depressed subjects, where the depressed subjects exhibit more relative left frontal alpha, interpreted as decreased left frontal activity. Note the large overlap between these 2 groups.*

appetitive behavior and generates certain forms of positive affect. The withdrawal system facilitates the withdrawal of an organism from sources of aversive stimulation and generates certain forms of negative affect…" (Davidson, 1998). These two systems have been conceptualized as relatively orthogonal. They interpreted the decreased left-sided frontal activation as a deficit in the approach system, and hence subjects with this condition are more prone to certain negative affective states and depressive disorders, given a certain level of environmental stress. On the other hand, they suggested that the right-sided frontal activation is related to withdrawal related emotion and psychopathology such as anxiety disorders (Henriques & Davidson, 1990). Support for the Approach-Withdrawal model comes from many correlational studies (for an overview see Davidson, 1998) but also from some studies involving manipulation of frontal EEG asymmetry by neurofeedback (Allen, Harmon-Jones & Cavender, 2001; Baehr, Rosenfeld & Baehr, 1997; Choi et al., 2011). Besides these frontal deficits Henriques and Davidson (1990) also reported a decreased right-parietal activation found in both previously and currently depressed patients. They related this to selective spatial cognitive deficits which are reported to accompany depression and which might also explain some of the symptoms in affective disorders which require the decoding of non-verbal, expressive behavior (Henriques & Davidson, 1990).

In the often cited Henriques and Davidson (1991) paper, these researchers used data from 15 depressed and 13 controls. They reported significant differences in alpha asymmetry between depressive patients and controls. They reported that only 2/13 normals (15%) deviated significantly from the depressive asymmetry scores and only 1/15 depressives (7%) deviated significantly from the normal asymmetry scores (based on a Cz montage). Therefore, there is more overlap between groups than there are differences – also see figure 4 from the Henriques and Davidson publication showing the individual data. This clearly demonstrates that these data cannot be used for diagnostic and/or prognostic purposes, which is also acknowledged by Davidson (1998) in contrast to the 'over-interpretation' of this finding in many QEEG and neurofeedback practices.

Measures of frontal asymmetry in depressed patients are only moderately stable over time (Debener et al., 2000; Tomarken, Davidson, Wheeler & Kinney, 1992), leading the Davidson group to average frontal alpha asymmetry measures over at least 2 occasions (separated by weeks) in their more recent work (Davidson, 1998). Furthermore, eyes open and eyes closed data are also averaged (weighted average) in order to obtain more stable estimates of EEG asymmetry (Davidson, 1998). The finding that this measure is only moderately stable over time has led some authors to question the 'stable trait' status of alpha asymmetry (Debener et al., 2000). Most studies investigating the frontal alpha asymmetry did not find any correlation between alpha asymmetry and measures of mood such as depression severity (Debener et al., 2000; Henriques & Davidson, 1991). On the other hand some have suggested that resting frontal alpha asymmetry reflects the joint contribution of a trait that is superimposed on state-like factors (Tomarken et al., 1992). Hagemann et al supported this empirically (Hagemann, Naumann & Thayer, 2001) who found that about 60% of the variance of frontal alpha asymmetry was explained by a latent trait and about 40% was due to state-like fluctuations. Allen et al. (Allen, Coan & Nazarian, 2004) showed that about 60% of the variance in alpha asymmetry is stable across time, despite substantial clinical improvements over time. Finally, several studies have demonstrated that alpha asymmetry was also influenced by differences in cranial and brain parenchymal asymmetries in bone

thickness (Myslobodsky et al., 1989) and different EEG montages (Hagemann et al., 2001; Hagemann, Naumann, Becker, Maier & Bartussek, 1998; Reid, Duke & Allen, 1998) whereas Henriques and Davidson (1990) found the effects to be consistent using different EEG montages. In an excellent review of methodological problems with frontal alpha asymmetry measures by Hagemann (2004) many other confounding factors are discussed such as the effect of situational factors (e.g. gender of the experimenter in relation to the gender of the subject, montages, etc.). Furthermore for a good review of structural skull deviations and their potential of confounding frontal alpha asymmetry variables, see Myslobodsky, Coppola & Weinberger (1991).

Alpha activity is traditionally defined as a sinusoidal rhythm occurring over posterior regions of the brain, which attenuates with eyes open (Chatrian et al., 1974). As Hagemann et al. (2001) suggest, the above-mentioned contradictory findings also may be explained in terms of signal-to-noise ratios. Since alpha activity is not maximal at frontal sites and sometimes there is little to no alpha at those sites, the signal of interest – alpha – can be too low for a reliable estimation of alpha asymmetry. Finally, EEG vigilance could also play a role in some of the contradictory findings since studies measuring short EEG segments (2-3 min.) more often find alpha asymmetry as compared to studies measuring longer EEG segments (e.g. 8 minutes) (Davidson, 1998; Reid et al., 1998). A recent study calculated frontal alpha asymmetry employing personalized alpha bandwidths based on the individual APF (using the same method which is also used in chapter 4), and failed to find a difference in alpha asymmetry between depressed patients and controls by either fixed frequency bands or individualized alpha frequency bands (Segrave et al., 2011).

In summary many studies have investigated the relation between frontal alpha asymmetry and depression, but have demonstrated little value as a diagnostic marker in depression and low heritability (Anokhin, Heath, & Myers, 2006; Smit, Posthuma, Boomsma, & De Geus, 2007). Furthermore, two studies from the same group investigated the prognostic value of alpha asymmetry and found conflicting results (Bruder et al., 2001; Bruder et al., 2008). Hence this measure holds little value in predicting treatment outcome to antidepressant treatment and as Segrave concluded: "*…anterior alpha asymmetry lacks the sensitivity to differentiate MDD from controls in the manner of an endophenotype."* (Segrave et al., 2011)

EEG as a prognostic tool: Treatment prediction in depression

Various clinical and demographic characteristics such as ethnicity and age have been found to be *related* to antidepressant treatment outcome (Trivedi et al., 2006; Kemp, Gordon, Rush & Williams, 2008; Kozel et al., 2008), however the clinical utility of these measures, remains poor and at this moment none of these predictors have clinical use in predicting treatment outcome to various antidepressant treatments (Bagby, Ryder & Cristi, 2002; Simon & Perlis, 2010).

One of the first attempts at using the EEG as a prognostic tool in depression stems from 1957. Roth et al. (1957) investigated barbiturate induced EEG changes (delta increase) and found this predicted to some degree the long-term outcome (3-6 months) of ECT in depression.

In quantitative EEG (QEEG) research, various pre-treatment differences in EEG measures have been reported to be associated with improved antidepressant treatment outcomes. Biomarkers associated with poor antidepressant response which have at least been replicated once include:

1) Decreased parieto-occipital alpha power: (SSRI: Bruder et al., 2008; TCA: Ulrich, Renfordt, Zeller & Frick, 1984) and decreased frontal alpha power (Suffin & Emory, 1995).
2) Increased Slow EEG power at baseline: Increased Theta (TCA: Knott, Telner, Lapierre, Browne & Horn, 1996), Increased Relative Theta (SSRI & SNRI: Iosifescu et al., 2009) and increased Delta power (SSRI: Knott, Mahoney, Kennedy & Evans, 2000; TCA-trend: Knott et al., 1996). However, Cook et al. (1999) found no differences in theta for responders and non-responders to fluoxetine.
3) A slow individual alpha peak frequency (iAPF) for antidepressant medication (Ulrich, Renfordt, Zeller & Frick, 1984) and rTMS treatment (Arns, Spronk & Fitzgerald, 2010; Conca et al., 2000).
4) A reduced P300 amplitude (SSRI: Bruder et al., 2001; Bruder et al., 1995; ECT: Ancy, Gangadhar & Janakiramaiah, 1996; Gangadhar, Ancy, Janakiramaiah & Umapathy, 1993). Bruder et al (2001) found that the P300 amplitude was specifically reduced in non-responders at frontal sites (F7, F8, FT9 and FT10) but not at more posterior sites. Furthermore, a prolonged P300 latency has been found to be associated with a poor treatment outcome (Kalayam & Alexopoulos, 1999; Vandoolaeghe, van Hunsel, Nuyten & Maes, 1998).

The above biomarkers are all based on baseline measures. However, in depression much research has also been dedicated to 'treatment emergent biomarkers'. Treatment emergent biomarkers measure the physiological response to a given treatment and hence at least two assessments are required. These biomarkers are thought to pick up early neurophysiological changes associated with clinical response. Below this is summarized further focusing on 'EEG Cordance' and the 'Antidepressant Treatment Response' or ATR.

EEG Cordance

The EEG cordance method was initially developed by Andrew Leuchter and colleagues to provide a measure, which had face-validity for the detection of cortical deafferentation (Leuchter et al., 1994). They observed that often the EEG over a white-matter lesion exhibited decreased *absolute* theta power, but increased *relative* theta power, which they termed 'discordant'. Therefore the EEG Cordance method combines both absolute and relative EEG power and negative values of this measure (discordance) – specifically in theta or beta - reflect low perfusion or metabolism, whereas positive values (concordance) – specifically in alpha - reflect high perfusion or metabolism (Leuchter et al., 1994; Leuchter et al., 1994). In a subsequent study they further confirmed this by comparing cordance EEG with simultaneously recorded PET scans reflecting perfusion (Leuchter, Uijtdehaage, Cook, O'Hara & Mandelkern, 1999).

In a first study it was found that depressive non-responders to an SSRI were characterized by a 'discordant' brain state at baseline – reflective of low perfusion (Cook et al., 1999).

Subjects were classified as 'discordant' if >30% of all electrodes exhibited discordance or if fewer electrodes that are highly deviant. Furthermore, central (Cz, FC1, FC2) theta cordance was related to treatment outcome after ECT (Stubbeman et al., 2004). More recent studies have focused on EEG Cordance in the Theta frequency band at pre-frontal electrodes (Fp1, Fp2, Fpz) and have essentially found that the *change* in Theta Cordance (*decrease*) after being medicated for 48 hours to 2 weeks predicted longer-term treatment outcome (SSRI & SNRI: Cook et al., 2002; Cook et al., 2005). In an independent replication Bares et al. (2008; 2007) also found that responders were characterized by a decrease in prefrontal (Fp1, Fp2, Fz) Theta cordance after 1 week (Bares et al., 2007: SSRI, SNRI, TCA; Bares et al., 2008: SNRI).

Pre-frontal Theta Cordance *increase* was found in placebo-responders (Leuchter, Cook, Witte, Morgan & Abrams, 2002). A more recent study from this group refined this further by examining right-medial frontal sites (FPz, Fz, FP2, AF2, F4 and F8) and found that Theta Cordance after 1 week of treatment was only decreased in the medication remitters but not in the placebo-remitters (Cook, Hunter, Abrams, Siegman & Leuchter, 2009), hence demonstrating specificity of this measure related to treatment outcome only and not to placebo response.

ATR: Antidepressant Treatment Response

The ATR measure was also developed by Andrew Leuchter (Leuchter et al., 2009; Leuchter et al., 2009) and Iosifescu (2008) and is commercialized by Aspect Medical Systems. The first results of this measure were published by Iosifescu et al. (2009), demonstrating the ATR measure was able to predict treatment outcome to an SSRI or Velafaxine with an accuracy of 70% (82% sensitivity; 54% specificity). Recently the results of a large clinical trial (BRITE-MD) investigating the ATR were published. This measure is based on EEG recorded from Fpz (FT7 and FT8) and is the non-linear weighted combination of 1) combined relative alpha and theta (3-12 Hz/2-20 Hz) at baseline and 2) the difference between absolute alpha-1 power (8.5-12 Hz) at baseline and absolute alpha-2 power (9-11.5 Hz) after 1 week of treatment (Leuchter et al., 2009). It was demonstrated that a *high ATR* value predicted response to an SSRI with 74% overall accuracy (58% sensitivity, 91% specificity; Leuchter et al., 2009). Interestingly, in another study, they reported that patients with a *low ATR* responded better to the atypical antidepressant Bupropion which has a clear dopaminergic affinity (Leuchter et al., 2009) thereby demonstrating this measure identified 2 sub-groups of depressive patients with subsequent implications for 2 types of antidepressants with a different mode of action.

The disadvantage of this method is that patients already need to be prescribed the medication before any prediction can be made and this method could not be used on 15% of the patients due to ECG artifacts (Leuchter et al., 2009).

Summarizing, at this moment there is a lot of promising research demonstrating that there are EEG measures which might predict treatment outcome to antidepressant treatments. However, none of these baseline measures have achieved a level of research warranting its use in clinical practice. Most likely for this purpose an integrative approach is required using data from multiple domains such as EEG, ERP, neuropsychology and genetics as a recent pilot-study demonstrated (Spronk, Arns, Barnett, Cooper & Gordon, 2011). Furthermore, at

this moment given the wealth of data there is a need for a theory or model which integrates these findings and can make better predictions on the use of EEG in predicting treatment outcome and explaining the relationship between such EEG predictors and the behavioral complaints in depression and ADHD.

EEG and QEEG: Models and theory

There are several models and theories that make an attempt at integrating the different findings or relating EEG patterns to treatment outcome. More specifically these are the 'EEG Phenotype model' initially developed and published by Jack Johnstone, Jay Gunkelman and Joy Lunt (Johnstone et al., 2005) and the 'EEG Vigilance Model' which was initially developed by Dieter Bente (Bente, 1964) and which is currently further investigated and developed by Ulrich Hegerl and his group (Hegerl et al., 2010; Hegerl, Olbrich, Schönknecht & Sander, 2008). In the following sections these models are explained in more detail focused on their application in ADHD and depression.

EEG Vigilance model

The regulation of vigilance and its flexible adaptation to internal and environmental needs are of fundamental importance for all higher organisms. Vigilance has to be adapted to the respective environmental situation, ensuring a high vigilance level in situations of danger and a reduced vigilance level during times of recreation. However, the interplay between environment and vigilance regulation also works the other way around: The environment actively created by a person can also depend on vigilance regulation. If the capacity of the brain to maintain a high vigilance level is reduced, a person will normally feel sleepy and thus seek an environment with low external stimulation and a chance to sleep. However, under certain circumstances such an unstable vigilance regulation can also induce a compensatory behavioral pattern termed here as 'vigilance autostabilization behavior'. Hyperactivity, sensation seeking and other behavioral patterns create a highly stimulating environment. The resulting increase in external stimulation counteracts the impending vigilance decline and leads to a stabilization of vigilance. An everyday example would be the hyperactive, "high-spirited" behavior of overtired children. Related to this, mania has been described as sensation seeking gone out of control. By contrast, in times of a tonically high vigilance level, a person might avoid additional external stimulation and withdraw himself as autoregulatory behavior. The proposed concept of vigilance autostabilization behavior is related to earlier theories of brain function (Bente, 1964; Ulrich, Renfordt & Frick, 1986; Wundt, 1896), personality (Zuckerman, 1985) and sensation seeking (Eysenck, 1990).

EEG-vigilance algorithm "VIGALL"

In parallel to the transition from active wakefulness to deep sleep the human brain takes on different global functional states. These functional states are reflected in the spectral composition and topography of the EEG and have been termed vigilance stages. These states correspond to different levels of alertness at the behavioral level. Several stages can

be separated during the transition from tense to relaxed wakefulness and further on to drowsiness until sleep onset.

In 1937, Loomis et al. (1937), later modified by Roth (1961), Bente (1964) and others (e.g. (Klimesch, 1999; Ulrich & Frick, 1986); proposed classifications for vigilance stages occurring during transition from active wakefulness to sleep onset. They are based on the following EEG phenomena during eyes closed, which have been demonstrated in several studies:

A1) Posterior alpha mostly seen after eye-closing with a frequency of 8-12 Hz and an occipital focus. This oscillation has been referred to as "idling rhythm" (Niedermeyer, 1997) because it marks a state of relaxed wakefulness, corresponding to vigilance stage A1 according to Bente (1964) and Loomis (Loomis et al., 1937).

A2-A3) Alpha power anteriorisation occurs increasingly after several minutes of relaxed wakefulness. Alpha peak frequency shows a slight decrease. This phenomenon is reported to occur during transition to drowsiness (Broughton & Hasan, 1995; Connemann et al., 2005; De Gennaro, Ferrara, Curcio & Cristiani, 2001; De Gennaro et al., 2004; De Gennaro et al., 2005; Pivik & Harman, 1995) and corresponds to vigilance stage A2 and A3 (Bente, 1964; Loomis et al., 1937).

B1) Low voltage EEG is increasingly observed during lower vigilance stages. The alpha rhythm disappears (*alpha drop-out*) and beta power increases (De Gennaro et al., 2001; Tanaka, Hayashi & Hori, 1996; Tanaka, Hayashi & Hori, 1997). This EEG pattern corresponds to vigilance stage B1 (Roth, 1961). The EEG in this state is similar to the EEG during intense mental activity and eyes open condition.

B2-3) Increased delta and theta activity is observed in parallel with increasing subjective drowsiness (Strijkstra, Beersma, Drayer, Halbesma & Daan, 2003; Tanaka et al., 1996; Tanaka et al., 1997), corresponding to vigilance stages B2 and B3 (Roth, 1961).

C) The occurrence of K-complexes and sleep spindles mark the beginning of definite sleep (Cash et al., 2009; De Gennaro & Ferrara, 2003; Tanaka et al., 1997).

Based on these EEG features a computer-based algorithm has been created for separating different EEG-vigilance stages (also see figure 4) for consecutive EEG segments. The first version of the algorithm "VIGALL" (Vigilance Algorithm Leipzig) was based upon the Fast Fourier-derived power of the four main EEG frequency bands alpha, beta, delta and theta during two-second segments of continuous EEG data at different sites. An improved second version of the algorithm now takes into account the intracortical source power (derived by Low Resolution Tomography-LORETA) of different regions of interest (ROIs).

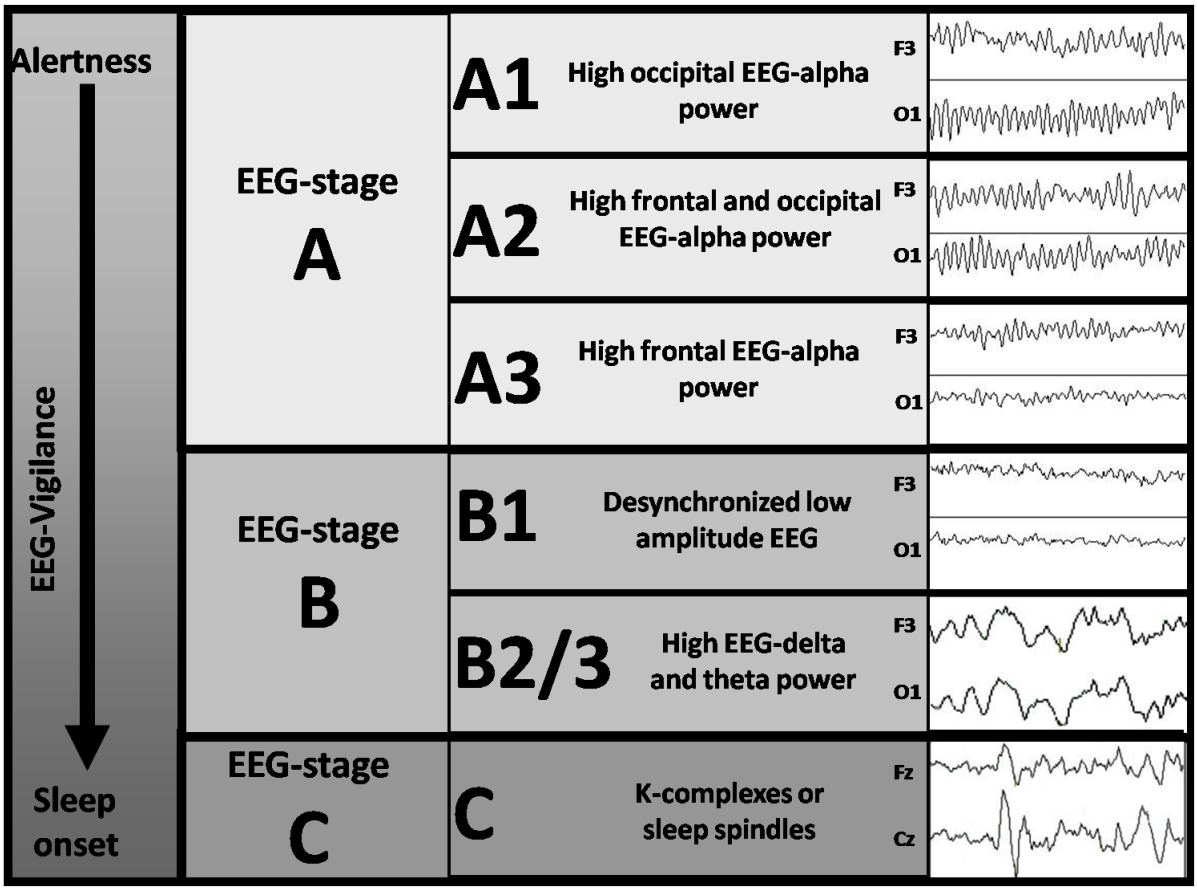


Figure 4: *EEG-vigilance stages on the continuum from high to low vigilance levels (left column): The main criteria of the EEG-vigilance classification algorithm are given for six distinct EEG-vigilance stages (middle columns). Examples of typical two-second EEG curves are presented in the right column.*

Several studies have further validated the EEG Vigilance model. Given the above stages and their relation to Vigilance, it is expected that switches between neighboring stages occur more often than switches to more distant stages, which was clearly demonstrated to be the case by (Olbrich et al., 2009) also see figure 5. This study demonstrated that switches between neighboring stages occurred significantly more often than a random process would reveal. These findings underline that the vigilance stage sequences during rest follow a certain order and give further validity to the EEG-vigilance algorithm VIGALL. Furthermore, Olbrich et al. (2009) also demonstrated that autonomic measures such as heart rate, also was lower for lower vigilance stages (e.g. B stages) as compared to higher vigilance stages (e.g. A stages).

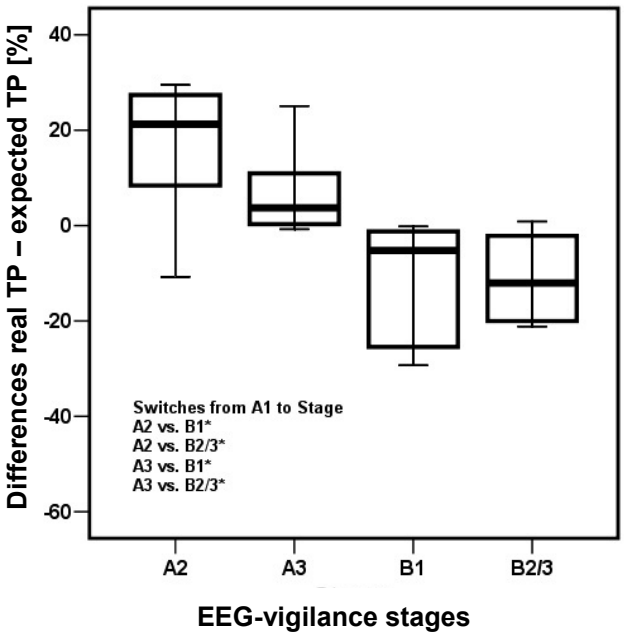


Figure 5: *The differences between real (rTP) and expected (eTP) transition probabilities for stage A1 were significantly higher for switches to stages A2 and A3 than for switches to stages B1 and B2/3. This indicates that vigilance decline is a gradual process with switches between neighboring EEG-vigilance stages occurring more often than switches between distant vigilance stages.*

EEG vigilance regulation in psychiatric disorders

As described earlier, changes in vigilance are also related to behavior. A decrease in vigilance or an 'unstable' vigilance regulation can lead to 2 different behaviors, 1) the organism decides to go to sleep and the vigilance reverts to sleep stages or, 2) the organism exhibits 'autostabilization behavior' to counter regulate their vigilance level such as hyperactivity and sensation seeking behavior. Figure 6 depicts this process in more detail. A physiological or 'normal' Vigilance regulation decreases over time. However, there are two deviating patterns of vigilance regulation – as can be seen below – namely the 'rigid regulation' and the 'labile regulation'. The first example of rigid regulation is characterized by an inability to down-regulate one's vigilance level and this person might avoid additional external stimulation and withdraw himself as autoregulatory behavior. This is a behavioral pattern, which is also often seen in depression. In contrast to this, individuals characterized by a labile regulation have an inability to maintain their vigilance level and/or exhibit unstable vigilance regulation. This type of vigilance regulation could induce a vigilance autostabilization behavior characterized by hyperactivity, sensation seeking and other behavioral patterns aimed at creating a highly stimulating environment. The resulting increase in external stimulation counteracts the impending vigilance decline and leads to a stabilization of vigilance. An everyday example would be the hyperactive, "high-spirited" behavior of overtired children. This behavioral pattern matches aspects of the behavior also seen in ADHD and mania.

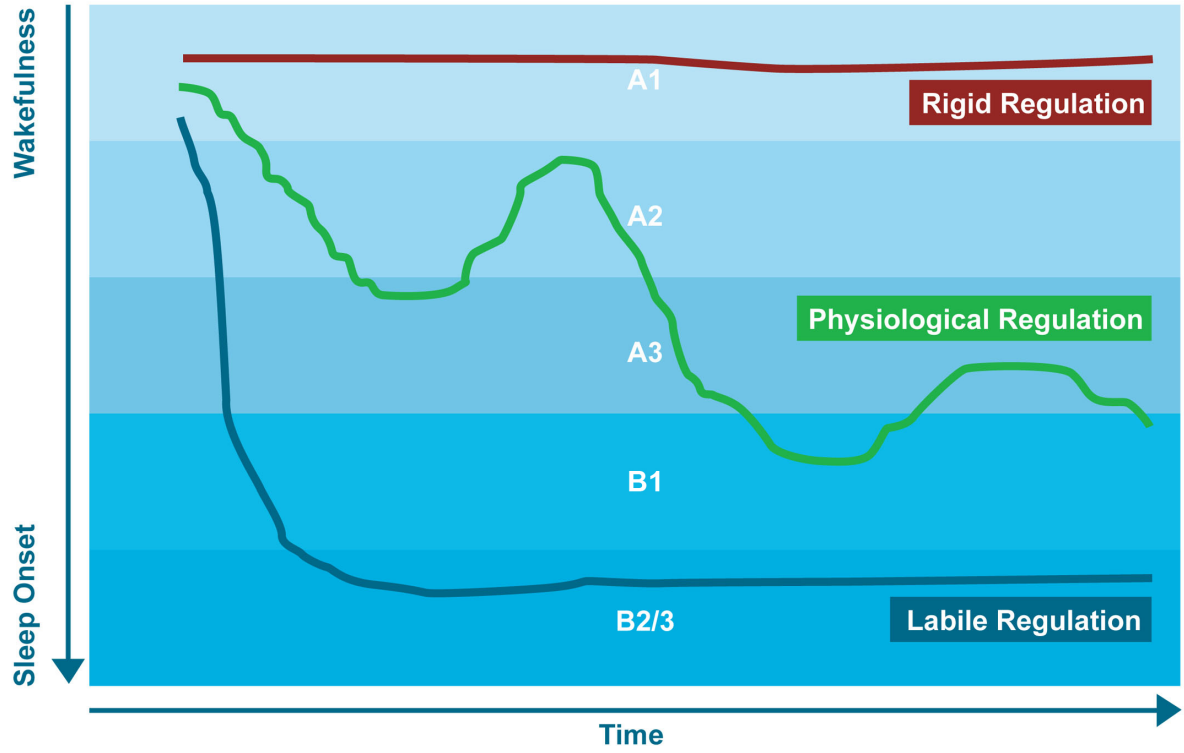


Figure 6: *This figure shows the different modes of vigilance regulation, namely the rigid regulation, a physiological or 'normal' regulation and a labile vigilance regulation.*

Mania and depression

Manic patients do not appear to be sleepy or tired. When evaluating EEG recordings of such patients, one would expect to find signs of a cortical hyperarousal. However, when studied under resting conditions with eyes closed, acutely manic patients consistently show rapid declines in vigilance within the first minute of EEG recording (Bschor, Müller-Oerlinghausen & Ulrich, 2001; Ulrich, Haug & Fähndrich, 1994; Van Sweden, 1986); a sub-group (19%) even shows signs of micro sleeps (defined as abrupt intrusion of sleep spindles) within the first 10 seconds into the EEG recording (Small, Milstein & Medlock, 1997). This finding generally has been neglected in theories on the pathophysiology of mania and is difficult to incorporate into current concepts. It does not appear to be a mere consequence of the sleep deficits often occurring within manic episodes. Instead, a causal role of the vigilance impairment in the pathomechanism of mania is suggested by the fact that sleep deficits can trigger or worsen hypomanic and/or manic syndromes in patients with bipolar disorders (BD) (Barbini, Bertelli, Colombo & Smeraldi, 1996; Hegerl et al., 2008; Wehr, 1992). Some symptoms of mania can be interpreted as autoregulatory reactions of the organism aimed to counteract the vigilance instability by increasing the level of external stimulation. While this might lead to vigilance stabilization, in many cases a vicious circle is initiated since this behavioral syndrome and the associated lack of sleepiness may aggravate the sleep deficit as well as the instability of vigilance regulation resulting in a vicious circle. According to this concept, most publications on treatment of mania using vigilance stabilizing agents such as Ritalin and modafinil reported an improvement within one or two hours of first dose

(Beckmann & Heinemann, 1976; Brown & Mueller, 1979; Schoenknecht, Olbrich, Sander, Spindler & Hegerl, 2010)

In contrast to the unstable vigilance regulation in mania, a hyperstable vigilance regulation is observed during depressive episodes (Ulrich et al., 1994; Hegerl, Wilk, Olbrich, Schoenknecht & Sander 2011), in line with the earlier presented findings of increased alpha (thus reflective of high vigilance) in depression (Itil, 1983; Lemere, 1936; Pollock & Schneider, 1990). This goes in parallel with a difficulty falling asleep, an inner restlessness and a hyperactivity of the hypothalamic-pituitary-adrenal axis often found in depressed patients. One could hypothesize that depressive symptomatology with sensation avoidance and withdrawal may serve an autoregulatory function to counteract a hyperstable vigilance regulation. Also see figure 7 below for a case example of a bipolar patient recorded in his manic episode (top) and depressive episode (bottom) and the obtained EEG Vigilance stages. This example clearly demonstrates that – within subject – a labile vigilance regulation is associated with the manic phase, whereas a rigid vigilance regulation is associated with the depressive phase of the disorder.

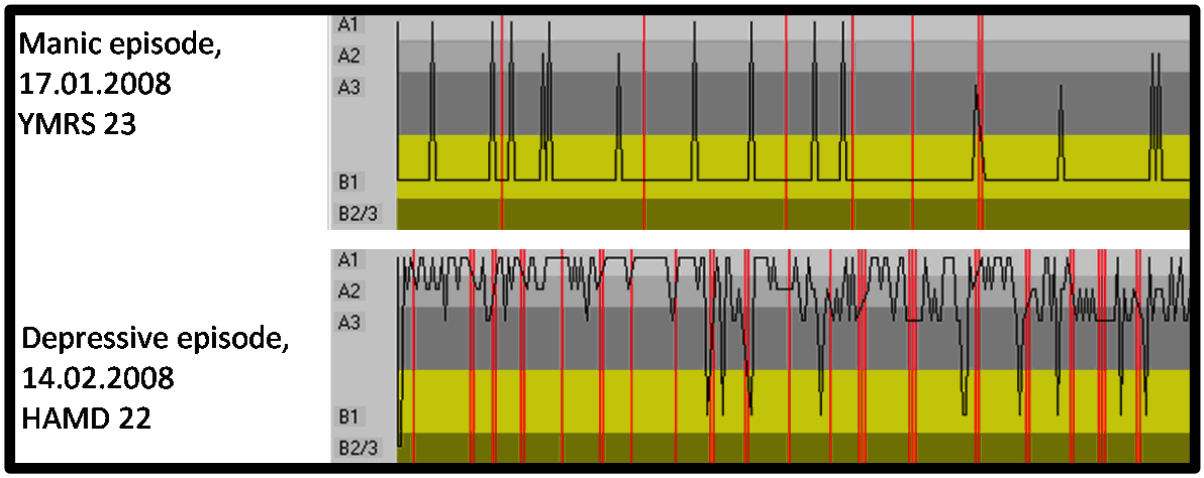


Figure 7: *Time course of EEG-vigilance stages for consecutive two second segments of a ten minute resting EEG in a patient with bipolar affective disorder during a manic episode (top; Young Mania Rating Scale 23) and during a depressive episode (bottom; Hamilton depression Score 22). Labile vigilance regulation is found during the manic state while during the depressive state the vigilance level does not drop to low vigilance stages. Vertical red lines mark segments with artifacts.*

Vigilance regulation in ADHD

Support for an unstable vigilance regulation in ADHD is provided by the fact that this disorder is associated with sleepiness, shortened sleep latency (Golan, Shahar, Ravid & Pillar, 2004), primary sleep disorders, sleep related movement disorders and parasomnias (Chervin et al., 2002; Konofal, Lecendreux & Cortese, 2010; Walters, Silvestri, Zucconi, Chandrashekariah & Konofal, 2008) and ADHD-like behavior can be induced in children by sleep restriction (Fallone, Acebo, Arnedt, Seifer & Carskadon, 2001; Golan et al., 2004). Recently, Van Veen (Van Veen et al., 2010) reported in a sample of adult ADHD patients that 78% had sleep-onset insomnia, confirmed by actigraphy and associated with a delayed

nighttime melatonin onset. A similar rate of 73% sleep onset insomnia has been reported in children with ADHD (Van der Heijden, Smits, Van Someren & Gunning, 2005) and normalizing this sleep onset insomnia by for example melatonin or chronotherapy results in clinically meaningful improvements in ADHD/ADD symptomatology (Dahl, Pelham & Wierson, 1991; Hoebert et al., 2009).
Taken together, these data – along with the earlier reported EEG findings found in ADHD - suggest that a labile vigilance regulation is a pathogenic factor in ADHD. Some symptoms of ADHD can be seen as a direct result of the unstable vigilance regulation (deficits in sustained attention, distractibility), while other symptoms (e.g. hyperactivity, "sensation seeking") can be interpreted as vigilance stabilizing syndrome, as is summarized in figure 8 below. Therefore, the well-documented effectiveness of psychostimulants in pediatric ADHD (Faraone & Buitelaar, 2009; Pliszka, 2007) is most likely explained by its vigilance stabilizing property.

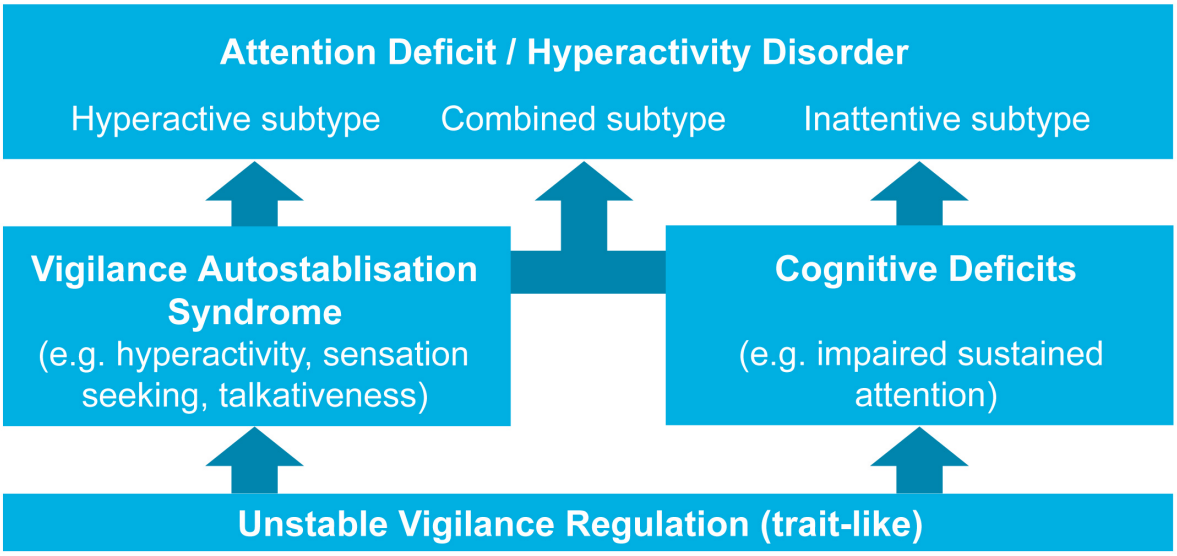


Figure 8: *This figure provides an overview of the relation between an unstable vigilance regulation and the behavioral symptoms of ADHD (adapted from Hegerl et al. 2009).*

EEG Phenotype model

As described earlier, the concept of endophenotypes was coined as early as in 1966 by John and Lewis (1966) and further developed based on studies in schizophrenia by Gottesman and Shields (1967; 1972). The idea behind an endophenotype is that it is the intermediary step between genotype and behavior and thus is more closely related to genotype than behavior is. Endophenotypes can be investigated to yield more information on the underlying genotype. In parallel there have also been many studies using the term biological marker, trait, biomarker etc. Here it is important that in line with Gotessman and Gould (2003), an 'endophenotype' refers to a marker when also certain heritability indicators are fulfilled, whereas a 'Biomarker' simply refers to differences between patient groups, which do not necessarily have a hereditary basis.

In 2005 Jay Gunkelman and associates submitted a paper proposing a set of EEG patterns as "EEG phenotypes" when the genetic links were known, and as "candidate EEG phenotypes" when the linkage to genetics remained unknown (Johnstone et al., 2005). These proposed EEG-based phenotypes are stable states of neurophysiological function, and can be identified from the raw EEG waveforms. The authors proposed a framework, which permitted researchers and clinicians to describe much of the observed EEG variance with a small number of categories of phenotypical divergence. These groupings are not identical to the DSM-IV groupings, and they are observed to cut across the DSM-IV categories. Unlike the DSM-IV, these phenotypes were observed to predict an individual's response to both neurofeedback and medication approaches to therapy.

The literature on medication response prediction suggests that a phenotypic perspective may help enhance efficacy when prescribing medication, as seen in the work by Suffin & Emory (1995) who demonstrated that patients with frontal theta responded better to stimulant medication and patients with frontal alpha responded better to an antidepressant, irrespective of their DSM diagnosis. This method is referred to as referenced EEG or rEEG, and its efficacy has recently been replicated in a larger controlled study (Debattista et al., 2010). Furthermore, Prichep et al. (1993) found the same results in Obsessive Compulsive Disorder (OCD) where OCD patients with excess alpha responded better to an SSRI, as compared to OCD patients with excess theta. Improved outcomes may also be seen in neurofeedback, as demonstrated in the clinical outcome improvement reported by Wright and Gunkelman (1998) when they added the EEG phenotype approach to guide neurofeedback. Using a slightly different approach, Monastra, Monastra and George (2002) demonstrated that using a pre-selection on excess theta/beta ratio in an ADHD population also improved treatment outcome to neurofeedback (resulting in a doubling of the effect size) employing theta/beta neurofeedback, further supporting this notion.

Table 1: *A summary of the EEG Phenotypes originally proposed by Johnstone, Gunkelman and Lunt (2005). The top part of the table represents EEG Phenotypes for which hereditability and/or genetic linkages have been reported (also summarized below) and the bottom part reflects 'candidate EEG phenotypes' for which more research is required to establish clear hereditability and/or genetic linkages.*

'EEG Phenotypes'	
1) Low-voltage fast:	Low-voltage EEG with relative beta dominating
2) Frontal lobe hypoperfusion, Frontal alpha:	Frontal theta, slow alpha, or alpha activity
3) Persistent eyes-open alpha:	Alpha does not attenuate by at least 50% with eyes open as compared to eyes closed.
4) Faster alpha variants:	Alpha peak frequency greater than 11-12 Hz parietally
5) Spindling excessive beta:	Rhythmic beta with a spindle morphology (beware of medication effects, especially benzodiazepines)
6) Epileptiform:	Transient spike/wave, sharp waves, paroxysmal EEG
'Candidate EEG Phenotypes'	
Frontal asymmetries:	Frontal asymmetry (generally measured at F3, F4).
Diffuse slow activity:	Increased delta and theta (1-7 Hz) with or without slower alpha
Mixed fast and slow:	Increased slower activity, lack of organized alpha, increased beta
Focal abnormalities:	Focal slow activity or focal lack of EEG power
Excess temporal lobe alpha:	Increased temporal alpha activity (Kappa)

Many studies have investigated the heritability of the EEG in twin studies and family studies (see: Martinović, Jovanović, & Ristanović, 1997; Vogel, 1970), and found that many aspects of the EEG are heritable. In a meta-analysis van Beijsterveld and van Baal (2002) demonstrated high heritability for measures such as the APF (81%), alpha EEG power (79%), P300 amplitude (60%) and P300 latency (51%), all suggesting that EEG and ERP parameters fulfill the definition of an endophenotype. Table 1 shows an overview of the original EEG Phenotypes proposed by Johnstone, Gunkelman and Lunt (2005). Below a summary is provided about what is currently known about the specific EEG Phenotypes as proposed by Johnstone, Gunkleman and Lunt (2005) and their underlying genetics and heritability:

1) Low-voltage (alpha) EEG: This is the most well described EEG phenotype to date and was first described by Adrian and Matthews (Adrian & Matthews, 1934). The latter author exhibited an EEG in which alpha rhythm *'…may not appear at all at the beginning of an examination, and seldom persists for long without intermission.'* (Adrian & Matthews, 1934: page 382). The low-voltage alpha EEG has been known to be heritable (autosomal dominant) and the heritability of alpha power is estimated at 79-93% (Anokhin et al., 1992; Smit et al., 2010; Smit, Posthuma, Boomsma, & De Geus, 2005; Vogel, 1970; Beijsterveld & van Baal., 2002). Low-voltage EEG is a well-

described endophenotype in anxiety and alcoholism (Ehlers, Garcia-Andrade, Wall, Cloutier, & Phillips, 1999; Enoch, Schuckit, Johnson, & Goldman, 2003; Bierut et al., 2002; Enoch et al., 1999; Pine & Pine, 1953). Alpha power and LVA have been successfully associated with a few chromosome loci (Enoch et al., 2008) but also with single genes: a serotonin receptor gene (HTR3B) (Ducci et al., 2009), corticotrophin releasing binding hormone CRH-BP (Enoch, White, Waheed, & Goldman, 2008), a gamma-amino butyric acid (GABA)-B receptor gene (Winterer et al., 2003) and with the BDNF Val66Met polymorphism in depression (Veth, Arns, Drinkenburg, et al., in preparation).

2) Frontal alpha: In addition to the high heritability of parieto-occipital alpha power referred to above, heritability of alpha at frontal sites is also high (85-87%) (Anokhin et al., 2006) but generally lower as compared to parieto-occipital sites (van Beijsterveldt & van Baal, 2002).
3) Persistent eyes open alpha: Vogel (1970) also described a 'Monotonous High Alpha Waves' pattern, a characteristic that is heritable in a simple autosomal dominance manner. The description of this EEG pattern ('Kontinuität') is very similar to the 'hyperrigid' EEG described in the EEG Vigilance model.
4) Faster alpha variants: The alpha peak frequency (APF) has been shown to be the most reproducible and heritable EEG aspect (Posthuma, Neale, Boomsma, & de Geus, 2001; Smit et al., 2005; van Beijsterveldt & van Baal, 2002) and has been associated with the COMT gene, with the Val/Val genotype being marked by a 1.4 Hz slower APF as compared to the Met/Met group (Bodenmann et al., 2009); this difference could explain a considerable amount of variability in this measure.
5) Spindling excessive beta: Family studies have shown that frontal and fronto-central beta spindles and excess beta exhibit an autosomal dominant mode of inheritance in healthy persons, but these patterns can also occur as a result of brain damage. Furthermore, the pattern of fronto-precentral beta has a lower frequency in Japanese (Vogel, 1970). A strong linkage between beta frequencies and GABA-A receptor genes has been reported, in line with the often-reported medication effects of benzodiazepines resulting in a 'beta buzz' (Porjesz et al., 2002).
6) Epileptiform EEG: Several types of paroxysmal EEG or epileptic EEG have also been demonstrated to be heritable and genetically linked (Haug et al., 2003; Kaneko, Iwasa, Okada & Hirose, 2002; Vaughn, Greenwood, Aylsworth & Tennison, 1996), however as mentioned before neurological EEG falls outside the scope of this thesis.

The EEG phenotype model demonstrates overlap with the EEG vigilance model, where in the EEG Phenotype model an EEG is described as its predominant feature (e.g. frontal alpha, frontal theta) the EEG vigilance model describes these as part of a continuum of vigilance. This thesis will investigate both models and aims to integrate findings from both models in their relation to predicting treatment outcome in ADHD and depression.

One critical point must be remembered when viewing the listing in table 1: the various phenotypes may coexist. The various combinations of the phenotypes are too numerous to be handled completely in this limited chapter presentation. Thus, this list should not be construed as a replacement for professional assistance in designing a neurofeedback intervention or in prescribing medication, nor in any way can this be used to fully characterize an individual's EEG/QEEG.

Concluding

At this time there is no single framework, theory or approach, which can be used to interpret EEG and QEEG findings and its role in predicting treatment outcome in ADHD and depression. In this chapter it was attempted to explain a small part of the large spectrum of related findings, and provide a theoretical framework based on the EEG Vigilance model, and its relationship to EEG and behaviors and the EEG Phenotype model.

In the following chapters these models will be investigated further, and several of the previous findings on biomarkers associated with treatment outcome will be tested further. The focus will be on predictors for non-response, since such findings might lead to a better understanding of sub-groups of non-responders and potentially result in the development of new treatments for patients unresponsive to current treatments.

Outline of this thesis

The primary aim of this thesis is to investigate what the value of neurophysiological measures such as EEG and ERP are in aiding prediction of treatment outcome in ADHD and depression. Part 1 of this thesis (chapter 2 to 6) specifically focuses on ADHD whereas part 2 (chapters 7 to 10) focuses specifically on depression. Additionally, this will be investigated for several different treatments both pharmacological (ADHD: chapter 2 and 3, depression: chapter 7) as well as non-pharmacological. In ADHD the non-pharmacological application of neurofeedback is summarized and a meta-analysis presented in chapter 5, and in chapter 6 the possibilities of personalizing neurofeedback treatment in ADHD, in accordance with the above-described EEG-subtypes of ADHD is investigated. In depression the non-pharmacological application of rTMS is summarized in chapter 8. The possibility of personalizing rTMS stimulation parameters to the EEG is investigated in chapter 9 and neurophysiological predictors of treatment outcome, specifically non-response, are investigated in chapter 10.

The validity of the EEG phenotype model and the value of this model in predicting treatment outcome will be investigated in ADHD in chapter 2 and in depression in chapter 7, supplementary material. In addition the validity of the EEG vigilance model and the value of this model in predicting treatment outcome to stimulant medication in ADHD will be addressed in chapter 3.

As was summarized earlier in this introduction, the concept of ‘Theta/Beta’ ratio has been very well investigated in ADHD, however a discrepancy with the old qualitative literature was found where more often a slowed APF was reported. Given that the APF and theta represent a difference in underlying neurophysiology and might be differentially related to treatment outcome, in chapter 4 this discrepancy related to the specificity of the theta/beta ratio in ADHD is further investigated. Furthermore, several chapters also investigate more specifically if the APF has a relation to treatment outcome in ADHD (Medication: chapter 2 and neurofeedback: chapter 6) and depression (rTMS: chapter 9 and 10). Finally the summary and conclusions will summarize the chapters and try to integrate the obtained findings using the different approaches as outlined in this chapter to asses the value of EEG and ERPs in predicting non-response to treatment in ADHD and depression.

Part 1

Prediction of treatment response in ADHD

Chapter 2

EEG Phenotypes predict treatment outcome to stimulants in children with ADHD

Arns, M., Gunkelman, J., Breteler, M., & Spronk, D. (2008). EEG phenotypes predict treatment outcome to stimulants in children with ADHD. *Journal of Integrative Neuroscience*, *7*(3), 421-38.

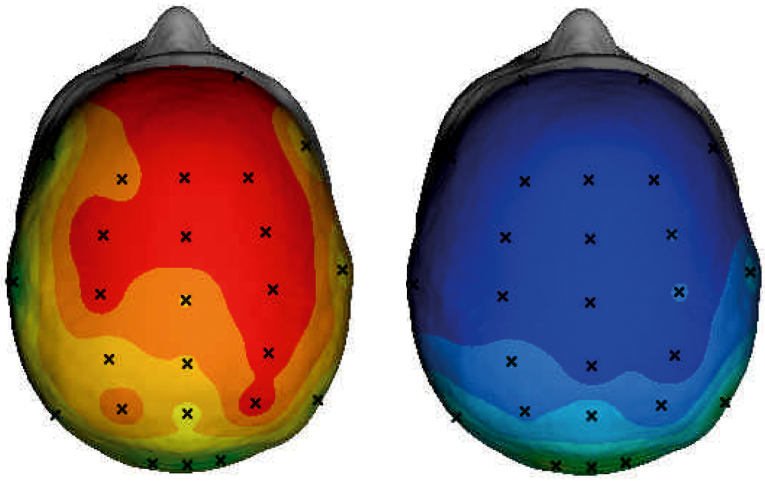
Abstract

This study demonstrates that the EEG Phenotypes as described by Johnstone, Gunkelman & Lunt (2005) are clearly identifiable EEG patterns with good inter-rater reliability. Furthermore, it was also demonstrated that these EEG phenotypes occurred in both ADHD subjects as well as healthy control subjects. The Frontal Slow, the Slow Alpha Peak Frequency and the Low Voltage EEG Phenotype seemed to discriminate ADHD subjects best from the control group, however not significantly. The Frontal Slow group responded to a stimulant with a clinically relevant decreased number of false negative errors on the CPT. The Frontal Slow and Slowed Alpha Peak Frequency phenotypes, have very different etiologies as evidenced by the treatment response to stimulants. In previous research the slowed alpha peak frequency has most likely erroneously shown up as a Frontal Theta sub-group. This implies that future research employing EEG measures in ADHD should avoid using traditional frequency bands, but clearly dissociate slowed alpha peak frequency from frontal theta by taking the individual alpha peak frequency into account. Furthermore, the divergence from normal of the frequency bands pertaining to the various phenotypes is greater in the clinical group than in the controls. Investigating EEG Phenotypes seems to be a promising new way to approach EEG data, explaining much of the variance in EEG's, and thereby potentially leading to more specific prospective treatment outcomes.

Introduction

Neurophysiological studies in ADHD based on group data have shown a quite consistent picture for ADHD. Most of these studies have found increased slow (theta) EEG activity (Bresnahan et al., 1999; Chabot & Serfontein, 1996; Clarke et al., 1998; Clarke et al., 2001b; DeFrance et al., 1996; Janzen et al., 1995; Lazzaro et al., 1999; Lazzaro et al., 1998; Mann et al., 1992; Matsuura et al., 1993) and decreased fast (beta) EEG activity in resting conditions (Callaway et al., 1983; Mann et al., 1992; Matsuura et al., 1993). Minor differences have been found in several studies between the DSM-IV TR (DSM) ADHD and ADD diagnosis, mainly showing a less severe pattern of deviation in the ADD group as compared to the ADHD group (Barry et al., 2003; Chabot & Serfontein, 1996).

Figure 1 shows an example from the Brain Resource International Database based on 275 non-medicated ADHD patients. This averaged data shows increased theta and decreased beta with a frontocentral localization.



Absolute 'Theta' EEG power Relative 'Beta' EEG power

Figure 1: *The average Brain activity of 275 ADHD patients compared to a matched control group. The figure left shows the increased theta (p<.0001) and right the relative decreased beta power (p<.0001). Note the frontocentral localization.*

However, a different picture emerges when looking at the individual data (see figure 2). Figure 2 shows the individual data from 36 ADHD patients from this exact same dataset from the Brain Resource International Database, showing the individual data underlying the average data shown above in figure 1. The quantitative EEG's (qEEGs) of these patients – were compared to a normative database consisting of more than 5000 healthy controls, allowing an individual comparison. These data show that indeed 47% of these ADHD patients showed increased EEG activity in the theta frequency band. However, only 5.6% showed decreased beta whereas 22% showed increased beta. These data suggest a large variability in QEEG profiles within a 'behaviorally homogenous population' of children with ADHD. This was also pointed out by Barry et al. (2003) stating that *"…a limitation of most EEG studies is that they assume their clinical groups are homogenous. If this is not so, the*

reported group differences may not accurately reflect the nature of EEG deviance in individual children with AD/HD."

Subject #	Theta	Beta
2014	↑	
2193	↑	↑
2306		
2395		
2418		
2520		
2553	↑	
2575		
2744	↑	↑
2777	↑	
3149		
3251	↑	
3330	↑	
3521		
3532		
3576	↑	
3813		
3846	↑	↑

Subject #	Theta	Beta
3824		
3857	↑	
4061		
4151	↑	↑
4162	↑	↑
4409	↑	
4397		↓
4465		
4476		↑
4487	↑	
4926		
5163		↑
5118	↑	
5208		
5400	↑	
5411		↑
5422	↑	↓
5332		

Figure 2: *Data of 36 patients with ADHD (4-digit ID codes) from the exact same dataset as in figure 1. However, here the individual data are depicted. Arrows up and down indicate increased or decreased power of the frequency band involved. Indeed some subjects showed increased theta (47%), however only 5.6% of these subjects showed a decreased beta and even 22% showed increased beta. This demonstrates the contrast between group-average data vs. individual data.*

Several studies have investigated EEG defined sub-types in ADHD. Chabot and Serfontein (Chabot & Serfontein, 1996) identified a sub-group with increased beta in about 13%. Clarke et al. (Clarke et al., 1998; Clarke et al., 2001c; Clarke et al., 2003b) also reported on such an EEG sub-group with increased beta in ADHD with a slightly different behavioral profile (increased rate of temper tantrums and moody behaviors) present in about 20% of children with ADHD. This seems in line with the above observation of increased beta in 22% of ADHD children. Furthermore, both Chabot and Serfontein (Chabot & Serfontein, 1996) and Clarke et al. (2001b) reported on different EEG clusters in ADHD where besides the excess beta subtype, a 'cortical-hypoarousal' subtype and a 'maturational-lag' subtype could be identified (see for an overview: Barry et al., (2003)).

The fact that Ritalin does not have a clinically significant effect in 20-40% of patients with ADHD (Gordon et al., 2007; Swanson et al., 1993) could well be related to the above reported EEG-Subtypes in ADHD, assuming that some sub-types respond better to medication than others. Several studies have shown that these EEG subtypes are indeed related to favorable outcome of stimulant drugs. For example Ritalin responders are characterized by increased frontal slow (Delta and Theta (Clarke et al., 2002d; Satterfield et al., 1973; Suffin & Emory, 1995)). However, for the excess beta group described above it was found that they too respond favorably to stimulant medication (Clarke et al., 2003b)

which was also found by Hermens et al. (2005). Chabot et al. (1999) found that both alpha and beta excess were predictors of behavioral improvement, whereas excess theta was predictive of both positive and negative treatment responses, with the negative treatment responses characterized my a more severe excess theta. In a study by Suffin and Emory (Suffin & Emory, 1995) a group of attentionally disturbed clients were studied, where they showed that stimulants were efficacious with the theta clusters (excess frontal theta), but antidepressants were efficacious with the alpha clusters (excess frontal alpha), regardless whether they were categorized as ADHD or depressed using DSM standards. Similar findings were also published by Simeon et al. (Simeon , Ferguson & Fleet, 1986) who found that children with ADHD, who had increased alpha EEG power, responded well to the atypical antidepressant Buproprion.

Most of the above mentioned studies have investigated relative EEG power measures, which can sometimes give a misrepresentation (i.e. when there is excess absolute theta, the relative power of other bands will be decreased due to this theta excess). Furthermore, in all studies the traditional EEG frequency bands (like theta, alpha and beta) were investigated. Based on the work by Klimesch (1999) on the individual alpha frequency and the fact that the individual alpha peak frequency matures during development up to the age of 10 years, it is conceivable that in some cases where studies referred to 'excess theta' they might have been referring to 'excess alpha' due to a slower individual alpha peak frequency. This is especially true for ADHD/ADD studies where children in the range of 6 to 18 years are often studied. Also, Clarke et al. (2001c) and Johnstone et al. (2005) make mention of 'Beta Spindles' which might be qualitatively different from general increased beta (Niedermeyer & Da Silva, 2004). The recently published paper by Johnstone et al. (2005) on EEG Phenotypes provides an interesting framework to perform individual classifications of EEG, taking the above issues in mind. Therefore, in this study we aim to further investigate the concept of EEG phenotypes and their predictive value for treatment outcome using stimulant medication in ADHD. In addition we also investigated arousal measures such as Heart Rate (HR) and Heart Rate Variability (HRV) and their relation to these EEG Phenotypes, since the main effects of stimulants are considered to be through increasing arousal.

Method

Subjects

Data from 49 children with ADHD (all male, average age = 11.33; range 6 – 17) and 49 control children (matched on age, gender and education; average age = 11.92; range 7 – 18) were drawn from the Brain Resource International Brain Database (Gordon, 2003). All subjects were medication free (at least 48 hours) at the time of assessment. The 49 children with ADHD were recruited from the Sydney metropolitan region. All ADHD subjects were referred by two pediatricians and a diagnosis was confirmed using a semi-structured interview based on DSM-IV criteria for ADHD and Connors Parent Rating Scales (T-scores 1.0 SD above the norm in either Inattentive or Hyperactive/Impulsivity indices). The average

scores and SD's for the ADHD group on these subscales were: Inattentive: Mean =8.00; SD=0.19; Hyperactive/Impulsive: Mean=5.28; SD=0.43 and Impulsive: Mean=1.91; SD=0.20.

Twenty-two subjects met DSM-IV criteria for the Combined subtype of ADHD, 22 met the criteria for ADHD of the predominantly inattentive subtype and 2 individuals met the criteria for ADHD of the predominantly hyperactive-impulsive subtype. For 3 subjects these data were missing.

Exclusion criteria included a personal or family history of Axis 1 psychiatric disorder (other than ADHD), physical brain injury, neurological disorder, genetic disorder or other serious medical condition and/or a personal history of drug or alcohol addiction. All subjects were asked to refrain from drinking caffeine and smoking cigarettes for two hours before the study session and all subjects and/or their guardians provided written informed consent to participate in the study, in accordance with National Health and Medical Research Council guidelines.

Procedure

ADHD subjects were tested on two separate occasions. The first occasion was pre-medication. All subjects were medication free (at least 48 hours) at the first occasion and 30 subjects of these were medication naïve. For the second occasion (post-medication) all ADHD subjects were taking their prescribed course of stimulant medication (38 Methylphenidate, 7 dexamphetamine and 4 Strattera) for a period of at least four weeks and were required to take their typical dose 60 minutes before the testing session commenced.

Subjects were seated in a sound and light attenuated room, controlled at an ambient temperature of 24°C. Electroencephalographic and neuropsychological assessments were completed in order (first the EEG for Eyes Open and Eyes Closed was taken followed by the CPT test). Details of these procedures have been published elsewhere (Gordon, 2003; Gordon et al., 2007).

Psychophysiological data acquisition

EEG data were acquired from 26 channels: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz and O2 (Quickcap; NuAmps; 10-20 electrode international system). Data were referenced to averaged mastoids with a ground at Fpz. Horizontal eye-movements were recorded with electrodes placed 1.5cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3mm above the middle of the left eyebrow and 1.5cm below the middle of the left bottom eye-lid. Skin resistance was < 5 K Ohms and above 1K Ohm for all electrodes. A continuous acquisition system was employed and EEG data were EOG corrected offline (Gratton, Coles & Donchin, 1983). An additional ECG lead was placed on the arm. The sampling rate of all channels was 500 Hz. A low pass filter with attenuation of 40dB per decade above 100 Hz was employed prior to digitization.

Eyes Open (EO) and Eyes Closed (EC) resting conditions
Subjects were asked to rest quietly with their eyes open for the duration of the recording, and were told that this condition would last for 3 minutes. Following this, subjects were asked to rest quietly with their eyes closed for the duration of the recording, and were told that this condition would last for three minutes.

Continuous Performance Test (CPT)
Performance on the Continuous Performance Test was used as a measure of treatment effect and was assessed for the ADHD group both pre- and post-medication. Subjects were presented with a series of letters (B, C, D and G) on the computer screen for 20 msec, with an interstimulus interval of 2.5 sec. Subjects were instructed to simultaneously press two buttons with each index finger, when the same letter appeared twice in a row. Speed and accuracy of response were equally stressed in the task instructions. There were 125 stimuli in total: 85 background letters and 20 pseudo-randomly presented target letters (i.e. repetitions of the previous letter). In addition to the letters, 20 distracter stimuli (black and white 1 X 1 cm checkerboards) were randomly interwoven with the letter stimuli. Subjects were instructed to ignore the "checkerboards". Subjects were given a brief practice session to clarify the task instructions. Subjects were told that this task would last for 8 minutes.

Reliability and validity data of these tasks are reported elsewhere (Clark et al., 2006; Paul et al., 2005; Williams et al., 2005).

Psychophysiological variables
Average power spectra were computed for 28 epochs during the eyes open and closed conditions. Each two-minute epoch was divided into adjacent intervals of four seconds. Power spectral analysis was performed on each four-second interval by first applying a Welch window to the data, and then performing a Fast Fourier Transform (FFT), next the average power spectra were calculated. Epochs were rejected if the signal at three or more sites exceeded 100 μV for that particular epoch. A low pass filter at 100 Hz was used.

The Heart Rate (HR – beats per minute) and Heart Rate Variability (HRV: Standard Deviation of the Heart Rate) were obtained from an ECG lead at the wrist during Eyes Open and Eyes Closed condition.

EEG Phenotype Rating
For all 98 subjects a full individual report was obtained with the EOG corrected (Gratton et al., 1983) raw EEG for EO and EC condition. Furthermore, a Brain Resource Company 'Neurofeedback' report was obtained containing individual data compared to the International Brain Database consisting of 5000 normative subjects. Data were first rated by the first author and after that by the second author. Rating was not blind with respect to diagnosis, so raters were aware of the subject's diagnosis, though both raters were blind to medication response. Subjects could be rated to have 1 or more EEG Phenotypes. See Johnstone et al. (2005) for an elaboration of all EEG Phenotypes. Below find a brief description of the EEG Phenotypes and the exact definitions used in this study:

1) 'Normal EEG': the EEG could not be classified into any of the other EEG Phenotypes. Therefore, this type is a normal EEG type showing neither abnormalities nor the presence of EEG Phenotypes.

2) Frontal Slow: Real frontal slow required a visual inspection of the raw EEG. The finding of slow activity, which could not be considered either frontal alpha or a slowed alpha peak frequency as per Niedermeyer & Lopes da Silva (2004). This EEG phenotype is also often called frontal theta (excess 4-8 Hz activity) and in the Johnstone et al. (2005) paper this one is mentioned under 'Frontal Lobe Disturbances'.
3) Low Alpha Peak Frequency (Low APF): Alpha Peak Frequency findings were interpreted dependent on age in agreement with Niedermeyer & Lopes da Silva (2004). An alpha peak frequency of lower than 9 Hz was considered a slow alpha peak frequency. For ages below 9 years of age this was interpreted with caution and an APF needed to be lower than 8.5 Hz. Location was Pz.
4) Frontal Beta Spindles: at least 1-2 occurrences of frontal beta spindles exceeding amplitude of 20 μV (as per definition of Niedermeyer & Lopes da Silva (2004)) and center frequency higher than 14 Hz.
5) Low Voltage: This phenotype was classified when the EEG power in all frequency bands was reduced as evidenced by a significant decrease in most frequency bands (delta, theta, alpha and beta) according to the subject's individual report. In the Johnstone et al. paper (2005) this subtype is called Generally Low Magnitudes.
6) Frontal Alpha: This phenotype was classified when there was a clear presence of frontal alpha, further evidenced by a significant increase in the alpha content (8-12 Hz or lower frequency range for younger ages) at frontal regions according to the subject's individual report. A distinction was made between frontal alpha and frontal slow, by taking the individuals IAF (individual alpha frequency) into account as per the research of Klimesch (1999).
7) Persistent Alpha EO: This phenotype was classified when there was a less than 50% decrease in alpha power during EO as compared to EC, with Pz as the standard site.
8) Temporal Alpha: This phenotype was classified as showing clear presence of alpha at one of the temporal sites (T3, T4, T5 or T6) in the raw EEG, where the presence of alpha occurred in the temporal sites independent from occipital or parietal alpha.
9) High Alpha Peak Frequency (High APF): An Alpha Peak Frequency of 11 or greater at site Pz was considered a fast alpha peak frequency.

Treatment

All ADHD subjects were treated with a stimulant (Dexamphetamine or Methylphenidate) or Strattera. Four were treated with Strattera, and were hence excluded from the analysis, in order to focus the treatment outcome results specifically on stimulant medication. All remaining 45 subjects were treated with a stimulant: Methylphenidate (n=38) or Dexamphetamine (n=7). No control subjects received medication.

Statistical analysis

The inter-rater reliability at classification for all 98 subjects' phenotypes was calculated using Cohen's Kappa.

The subjects were first classified into EEG Phenotype groupings, with the additional label of ADHD or Control. Chi-square tests were used to test significant differences in the occurrence of EEG Phenotypes between the ADHD group and the control group (e.g. percentage of frontal slow in Controls vs. percentage of frontal slow in ADHD).

One-way ANOVA's were used to test differences in age between the 'Normal EEG' group and the different EEG Phenotypes.

Repeated measure tests were used to test the medication effect with pre-medication and post-medication as the repeated measure and CPT performance as the dependent variable.

Univariate tests were performed using as the fixed factor both Group (ADHD vs. Control) and EEG Phenotype (present vs. not present) and as the dependent variable autonomic measures (HR or HRV).

Results

Inter-rater reliability

The inter-rater reliability between the two raters (first and second author) were generally high, suggesting that these EEG Phenotypes can be reliably identified by two raters, with Kappa values around .90 or better, though with the persistent eyes open alpha and frontal alpha phenotypes showing the lowest inter-rater reliability. Table 1 shows the number of subjects per EEG Phenotype sub-group, together with the exact Kappa values. Note that for this study phenotype classification was used only when both raters agreed on the EEG Phenotype classification.

Table 1: *This table shows the number of subjects in the different EEG Phenotype groups and the inter-rater reliabilities for the different EEG Phenotypes.*

	N- ADHD	N-Controls	Inter-rater reliability
'Normal EEG'	5	11	Kappa: .90; p<.000
Frontal Slow	13	9	Kappa: .94; p<.000
Low APF	13	5	Kappa: .90; p<.000
Frontal Beta Spindles	8	10	Kappa: .97; p<.000
Low Voltage	6	1	Kappa: .93; p<.000
Frontal Alpha	8	4	Kappa: .47; p<.000
Persistent Alpha EO	7	5	Kappa: .64; p<.000
Temporal Alpha	5	6	Kappa: .89; p<.000
High APF	3	5	Kappa: .94; p<.000

Prevalence of EEG phenotypes

Figure 3 shows the prevalence of the different EEG Phenotypes in ADHD and Normal controls. There were no significant age differences between the EEG Phenotype groups. The ADHD group tended to show a higher occurrence of 'Frontal Slow', 'Slow Alpha Peak Frequency' and 'Low Voltage EEG' as compared to the control group. However, the Chi-square tests failed to show any significant differences between the ADHD and Control groups. Only the difference for low voltage EEG (p=.050) and slow alpha peak frequency (p=.074) tended towards significance. This lack of effect is probably due to the low subject numbers per subgroup.

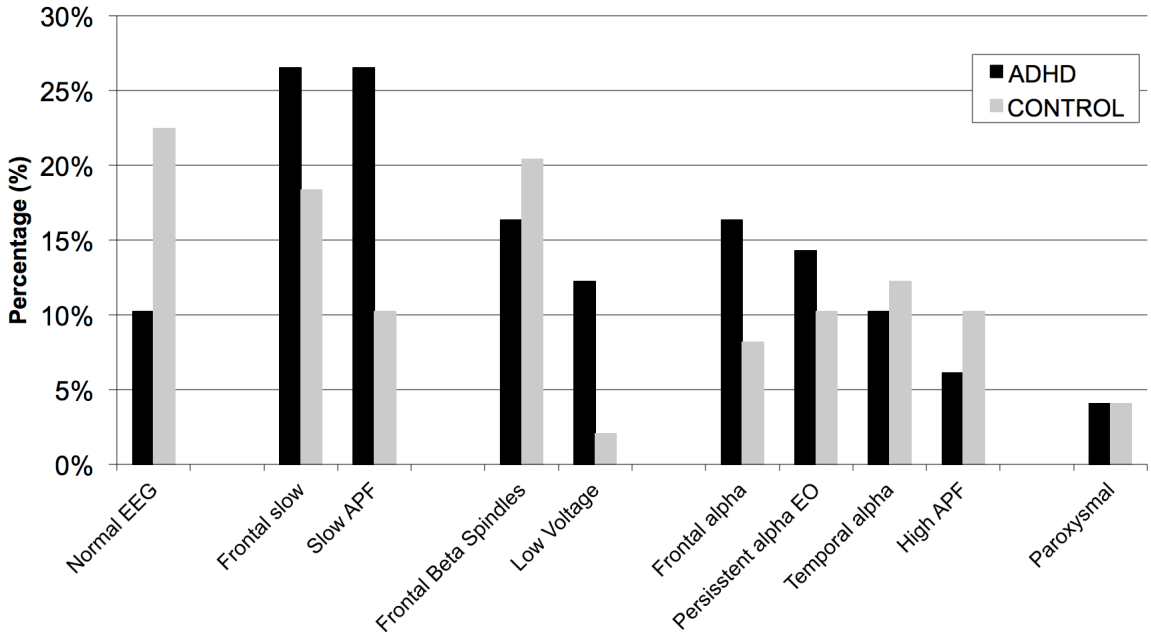


Figure 3: *The occurrence of the different EEG Phenotypes for both ADHD and the matched Control group. Note the higher occurrence of Frontal Slow, Slow Alpha Peak Frequency and Low Voltage EEG in the ADHD group. Also note that the Control group had occurrences of several EEG phenotypes. Only 25% displayed a 'normal' EEG.*

Figure 4 below shows the Eyes Open spectral plots for 3 different EEG phenotypes. This figure illustrates that although these EEG Phenotypes also occur in healthy controls, that EEG Phenotypes are more expressed in the clinical grouping. In the Frontal Slow phenotype, the ADHD group has more frontal slow EEG power when compared to the Control group. Additionally, the Slow Alpha Peak Frequency for the ADHD group (red vertical line) is slower compared to the Control group's peak alpha frequency (black vertical line).

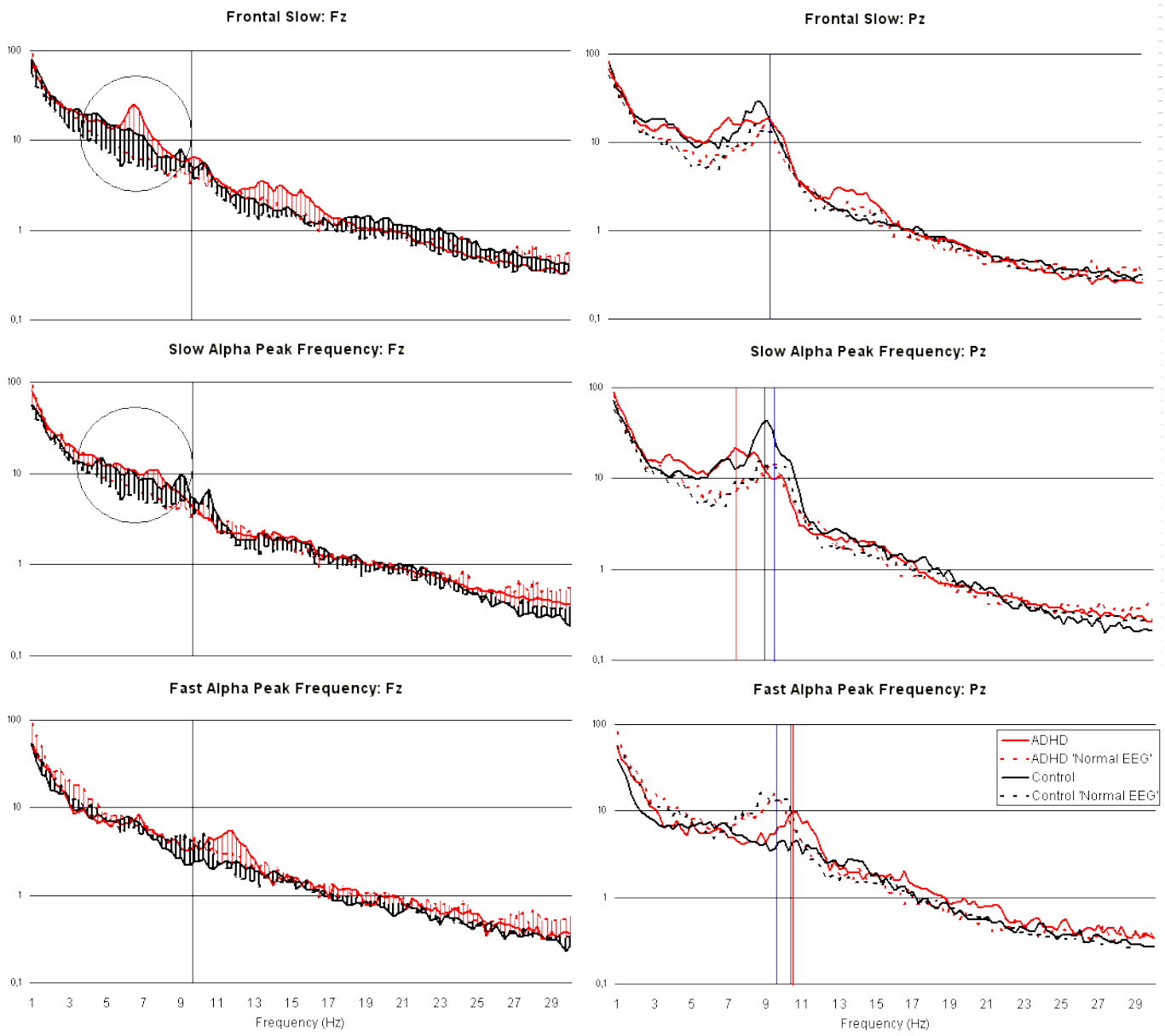


Figure 4: *The average FFT´s for Eyes Open for the Frontal Slow Phenotype (Top), The Slowed Alpha Peak Frequency Phenotype (Middle) and the Fast Alpha Peak Frequency EEG Phenotype (Bottom). Red depicts the ADHD group and Black the controls group, dashed lines represent the 'Normal EEG' sub-group averages. Left pictures are Fz and right pictures are Pz. The vertical lines in the right graphs (Pz) indicate the Alpha Peak Frequency for the ADHD (red), Control (black) and 'Normal EEG' (blue) groups. Note the similarity of the power in the 'theta frequency band' (or 4-7.5 Hz) for both the Frontal Slow and the Slow Alpha peak Frequency group. Also note how similar the 'Normal EEG' sub-groups are for both ADHD and Controls, indicating that most of the variance is explained by the EEG Phenotype. Finally, note the exaggeration for the respective EEG Phenotypes in the ADHD group as compared to the Control group (as demonstrated by the shadowed black or red area in the left graphs showing the difference between the 'Normal EEG group' vs. the respective 'Phenotype' group).*

Treatment effect on CPT performance

Figure 5 shows the treatment effects on the CPT for EEG Phenotypes. The Fast Alpha Peak Frequency, Temporal Alpha, Low Voltage and Persistent Alpha EO groups have been omitted due to small sample sizes (N<8). For the False Positive errors there was a significant treatment effect for the Frontal Alpha Group (F=10.454; df=1, 6; p=.018). The number of false positive errors was significantly larger in the pre-treatment (mean = 4.125; SEM=1.125) as compared to the post-treatment assessment (mean = 0.857; SEM = 0.26).

Patients with the frontal slow phenotype demonstrated a significantly improved performance on the CPT task. They demonstrated a significant treatment effect for the False Negative errors (F=6.972; df=1, 10; p=.025) The frontal slow phenotype hence made more false negative errors pre-treatment (mean = 5; SEM = 1.19;) as compared to post-treatment (mean = 2; SEM = 0.52;).

Interestingly, as can be seen in figure 5 the Frontal Slow and Slow Alpha Peak frequency phenotypes both made many errors as compared to the other groups, but only the Frontal Slow group responded to treatment with a stimulant. There were no significant medication effects on reaction times in the CPT.

In Table 2 below, the percentages of ADHD-subtypes Inattentive, Combined and Hyperactive/Impulsive for the different EEG Phenotypes are shown. It can be seen that there is no 100% relation between the EEG Phenotypes and the ADHD-subtypes based on behavior although there is a trend that the Inattentive sub-type is more associated with the Slow APF and Frontal Alpha EEG subtypes.

Table 2: *Percentage of ADHD-subtypes for the different EEG Phenotypes. As can be seen here there is no 100% relation between the different EEG Phenotypes and ADHD-subtypes, showing that the behavioral sub-types do not correlate 100% with the EEG Phenotypes.*

	'Normal'	Frontal Slow	Slow APF	Frontal Alpha	Frontal Beta Spindles
Inattentive	50%	55%	73%	86%	50%
Combined	50%	45%	27%	14%	37%
Hyperactive/ Impulsive	0%	0%	0%	0%	13%

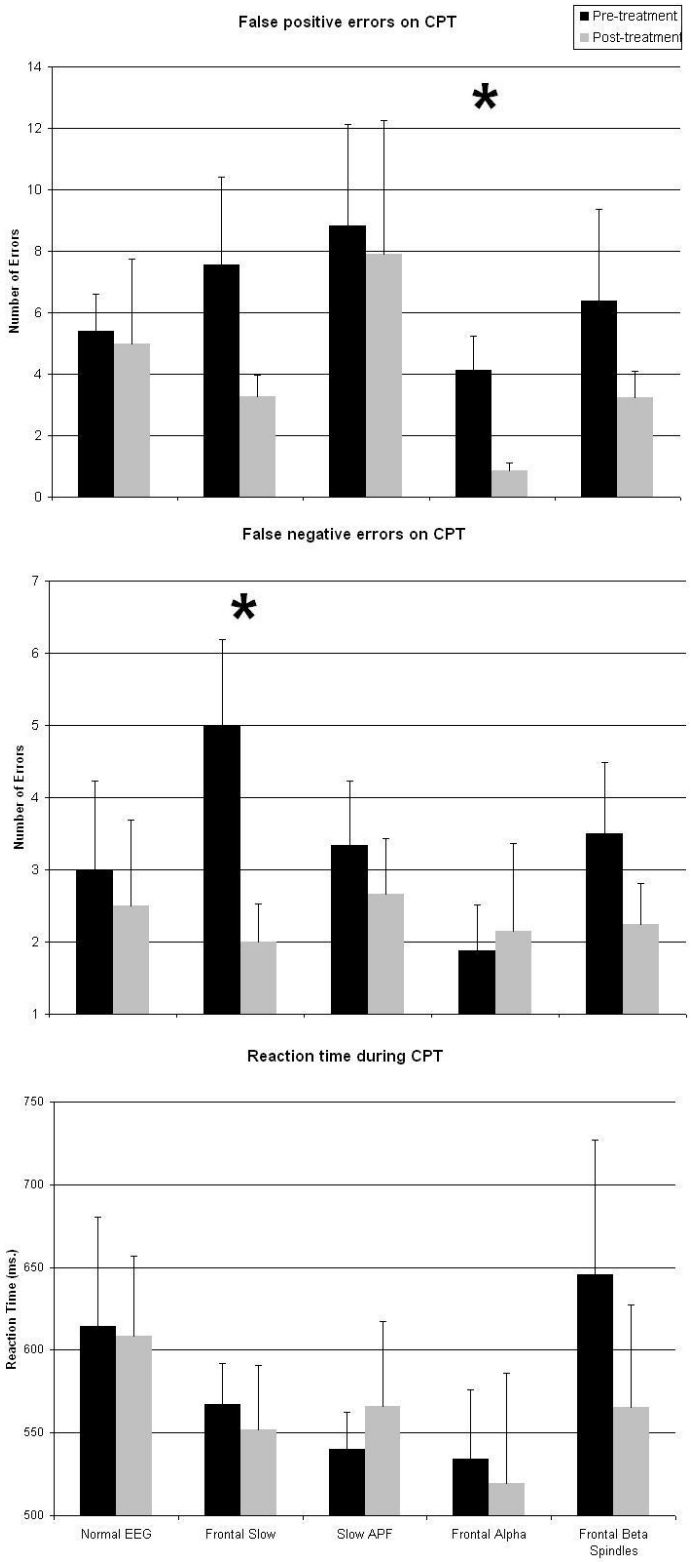


Figure 5: *Pre-treatment and post-treatment performance for the ADHD group only on different CPT measures (False Positive errors, false negative errors and reaction time) for EEG Phenotypes (N=45). Note that the Frontal Slow and Slow Alpha Peak frequency groups make more errors as compared to the other groups, and that only the Frontal Slow group responds to treatment with a stimulant (*: P<.05). Also note that there were no treatment effects on reaction times.*

Autonomic arousal

Only the Frontal Slow EEG Phenotype showed significant increased Heart Rate during Eyes Open (F=6.627, df=1; p=.015) and Eyes Closed (F=4.351, df=1; p=.045) conditions as compared to the 'Normal EEG' group for both ADHD and the controls group (EEG Phenotype effect). The overall group effects were also significant indicating ADHD patients in the 'Normal EEG' and 'Frontal Slow' sub-groups have significantly decreased Heart Rate during Eyes Open (F=12.158; df=1; p=.001) and Eyes Closed (F=6.156; df=1; p=.018) as compared to the control group. There were no other significant relationships between EEG Phenotypes and HR or HRV in Eyes Open and Eyes Closed conditions.

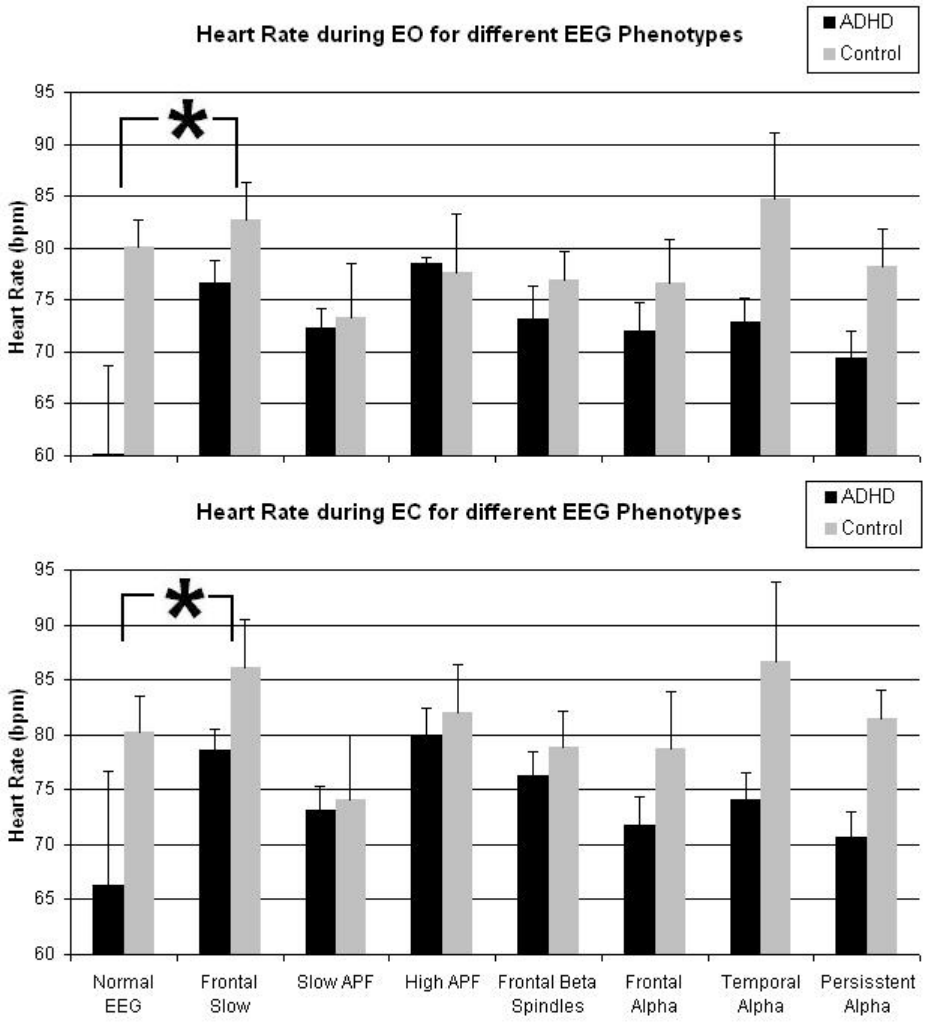


Figure 6: *The interrelationships between Heart Rate (HR) during Eyes Open and Eyes Closed conditions and the different EEG Phenotypes. The Frontal Slow EEG Phenotype (for both ADHD and Control group) showed an increased HR during resting conditions. Furthermore, ADHD children in general seem to have a decreased HR as compared to the Control group.*

Discussion

This study used the EEG Phenotype classification postulated by Johnstone, Gunkelman & Lunt (2005) in a group of 49 children with ADHD and 49 matched controls. The identification of these EEG Phenotypes by two raters was reproducible in individual data, with high Kappa values mostly exceeding .90. Only for Persistent Alpha and Frontal Alpha the inter-rater reliability scores were lower, indicating a lower agreement for those EEG Phenotypes, which could also be due to the lower occurrence of these EEG Phenotypes (<10%). The Phenotype ratings were not blind to diagnosis, which could have affected the ratings. However, given the small differences between the ADHD and Control group in prevalence of EEG Phenotypes this most likely did not have a dramatic effect.

As pointed out in the introduction a large qualitative heterogeneity existed in EEG Phenotypes in the ADHD group as well as in the control group. From table 2 it also became clear that the differences in EEG Phenotypes could not be explained completely by behaviorally diagnostic differences such as ADD or ADHD diagnosis. Indeed more subjects from the control group exhibited a 'normal EEG' as compared to the ADHD group; however this was only 25%. ADHD subjects more often showed a frontal slow – 'frontal theta' – EEG Phenotype. However, the Slow Alpha Peak Frequency tended to discriminate between both groups even better.

To our knowledge this is the first study assessing individually scored alpha peak frequency as a subgroup in ADHD. Previous studies e.g. Chabot and Serfontein (1996) did assess the Alpha Mean Frequency, however this is different from assessing the individual APF. The alpha mean frequency is the mean frequency between 8-12 Hz, whereas the individual APF is the peak frequency which can be 7 Hz or lower or sometimes higher than 12 Hz (Klimesch, 1999). The average APF of the Slow APF group was 8.2 Hz and when using the traditional theta frequency band (4-7.5 Hz), it becomes clear that this group will show up as 'increased theta EEG power'. This is also demonstrated in figure 4 where for the slow APF groups there is an increased power in the frontal 'theta band'. Therefore, we speculate that the subjects from our Slowed APF group in previous studies have shown up as a frontal slow EEG. However these two patterns have completely different etiologies as described in the IFCN report on the basic mechanisms of EEG rhythmicity (Steriade et al., 1990). This is also further evidenced by the results from this study where the frontal slow group responded well to stimulants with a substantial decrease in the number of false negative errors on the CPT and the lack of a treatment response in the slowed APF group.

This could partly explain the contradictory findings with some studies finding good medication response in excess frontal slow EEG sub-types (Clarke et al., 2002d; Satterfield et al., 1973; Suffin & Emory, 1995) and other studies finding good medication response in excess alpha EEG sub-types (Chabot et al., 1999). For future studies it is therefore important to clearly dissociate frontal slow from slowed APF by taking the individual APF into account.

We also found that the frontal alpha sub-group responded to stimulant medication, although on a different measure: False positive errors. The frontal alpha sub-group already performed better than most other EEG Phenotypes, hence this effect could reflect a non-specific floor-effects. The Frontal Slow and Slow APF groups both performed worst on most CPT measures, implicating that the effect for the Frontal Slow group is clinically most

relevant. False positive errors can be regarded as a measure of impulsivity (commission errors) whereas false negative errors can also be regarded as inattention (omission errors). In this context it might be argued that ADHD children with frontal slow are specifically those with the inattentive component, which also responds very well to stimulant medication. However, table 2 does not confirm this, since the occurrence of inattentive was 55% and combined 45% for the Frontal Slow group. Furthermore, ADHD children with a frontal alpha could be considered the least impulsive (see figure 6) since they already make the fewest False Positive errors, and with a stimulant they even make fewer false positive errors. This is confirmed from table 2 showing that in the Frontal Alpha group 86% had a diagnosis inattentive, without the impulsive component.

It is a surprising finding that the prevalence of the different EEG Phenotypes is comparable between the ADHD and Control group. However, in figure 4 it can be seen that the expression of a given EEG Phenotype is more excessive for the ADHD group as compared to the Control group.

Interestingly, both groups contained two subjects who displayed Paroxysmal EEG activity, whereas these subjects were not diagnosed with Epilepsy.

Autonomic interrelations

In general, subjects with ADHD showed decreased heart rate at rest as compared to the control group. The frontal slow EEG phenotype was specifically associated with an increased resting heart rate during eyes open and eyes closed condition as compared to the 'normal EEG' groups for both children with ADHD and the control group, suggesting a lower vagal nerve tone associated with a frontal slow EEG (irrespective of ADHD or control group). This relationship was found for only the frontal slow phenotype and not for the slow alpha peak frequency, showing another functional dissociation between these two EEG phenotypes, which are the most common patterns in ADHD. This finding is especially interesting to note since most studies report that stimulants such as Methylphenidate have been found to 'normalize' excess theta (Cooper et al., 2005; Zahn, Abate, Little & Wender, 1975) and cause a task-related increase in heart rate in healthy volunteers (Brumaghim & Klorman, 1998; Coons et al., 1981). The frontal slow (or frontal theta) phenotype already exhibited an increased heart rate as compared to the other EEG Phenotypes for both the ADHD and Control group. Therefore, the increased heart rate caused by drugs such as methylphenidate could be considered an unwanted effect for subjects in the frontal slow EEG phenotype, whereas clinically they respond the best (also see figure 6; the ADHD children with the frontal slow phenotype seem to have a heart rate comparable to the control group for other phenotypes).

Limitations of this study

In spite of the high Kappa reliability values, it must be noted that the raters were not blind to the status of the subjects. Thus the apparently increased severity of the phenotypes in

the ADHD group may be due to a rater's bias. Therefore, this result must be considered preliminary until this finding is replicated by other groups using blinded ratings.

Another limitation lies in the small number of subjects involved, also due to the sub-grouping. On the one hand this means that the results may be biased due to selection of subjects. On the other hand the small number of subjects may cause a lack of explanatory power, thus precluding conclusion with regard to smaller effects. Finally, no Connors or other outcome measures were available at follow-up. Thus, the clinical relevance of the findings needs further elaboration.

This study demonstrated that the EEG Phenotypes as described by Johnstone, Gunkelman & Lunt (2005) are clearly identifiable EEG patterns, which can be classified with good reliability by two raters. Furthermore, it was also demonstrated that these EEG phenotypes occurred in both ADHD subjects as well as healthy control subjects. The Frontal Slow, the Slow Alpha Peak Frequency and the Low Voltage EEG Phenotype seemed to discriminate ADHD subjects best from the control group, however not significantly. Interestingly, only the Frontal Slow EEG Phenotype showed a clinically relevant treatment response to stimulant medication, whereas the Slowed Alpha Peak Frequency group did not respond to stimulant medication as measured by the performance on a CPT.

The data suggest that the two most prevalent EEG Phenotypes: Frontal Slow and Slowed Alpha Peak Frequency may have shown up in previous studies most likely as a Frontal Theta group, whereas these two EEG Phenotypes have very different etiologies as evidenced by the treatment response to stimulants. This implicates that all future research employing EEG measures in ADHD should avoid using traditional frequency bands only, but clearly dissociate frontal slow from slowed APF by taking the individual APF into account. Furthermore, the severity of the phenotype divergence from normal is greater in the clinical group than in the controls. This is an area of potentially high yield for a subsequent study, since it will be interesting to investigate the 'severity' of a given EEG phenotype and it's relation to behavior rather than the presence or absence of an EEG phenotype.

Investigating EEG Phenotypes or Neuromarkers seem to be a promising way to classify EEG data, explaining much of the variance, and thereby potentially leading to more specific prospective treatment outcomes.

Acknowledgements

Data from The Brain Resource International Database was generously provided by the Brain Resource Company Pty Ltd. We would also like to thank local BRC clinics for data collection of the control group. All scientific decisions are made independent of Brain Resource Companies commercial decisions via the independently operated scientific division - BRAINnet - which is overseen by the independently funded Brain Dynamics Centre and scientist members.

Chapter 3

EEG-vigilance and response to stimulants in paediatric patients with Attention Deficit/Hyperactivity Disorder

Sander, C., Arns, M., Olbrich, S., & Hegerl, U. (2010). EEG-Vigilance and response to stimulants in paediatric patients with attention deficit/hyperactivity disorder. *Clinical Neurophysiology*, *121*, 1511-1518.

Abstract

A recently proposed concept interprets some ADHD symptoms (e.g. hyperactivity) as reflections of an autostabilisation process counteracting an instable vigilance regulation. In a pilot study, we investigated whether assessment of vigilance regulation is useful for prediction of treatment outcome.

Methods: Resting EEG recordings of 49 unmedicated ADHD patients and 49 age-matched controls were analyzed. Vigilance was determined using a computer-based classification algorithm. Treatment outcome was measured as changes in CPT performance from baseline after at least 4 weeks of medication.

Results: Compared to healthy controls, ADHD patients spend less time in higher vigilance stages (A1: ADHD=66% Controls=81%). Patients with signs of an instable vigilance regulation achieved worse pre-treatment but better post-treatment results compared to patients with more stable vigilance regulation. Still, these differences did not reach significance.

Conclusions: Signs of a vigilance instability where found in ADHD patients compared to controls. Those patients with a higher degree of vigilance instability seemed to benefit more from stimulant medication.

Significance: To our knowledge, this is the first investigation of EEG-vigilance in ADHD-patients. Our results are limited by the shortness of the analyzed EEG-data but merit further investigation of the vigilance regulation in patients with ADHD.

Introduction

Attention deficit/hyperactivity disorder (ADHD) is one of the most prevalent psychiatric disorders in children and adolescents, affecting 3-7 % of school-aged children (Cormier, 2008). It has been shown, that in many cases symptoms will remain into adulthood (Davidson, 2008). Children with ADHD have a high risk of developing comorbid disorders e.g. affective disorders or substance abuse (Bukstein, 2008; Daviss, 2008; Young, 2008) and the disorder is associated with impairments in educational, neuropsychological and social functioning.

Considerable research has been done on the neurophysiology of ADHD (reviewed by: di Michele, Prichep, John & Chabot, 2005). Studies using quantified EEG have consistently shown a distinct profile, characterised by an increase in slow activity (i.e. theta and delta) and decreased power in fast (i.e. beta) frequencies (Clarke et al., 1998; Lazzaro et al., 1998); reviewed by (Barry et al., 2003). The elevation of theta activity was found to remain present from childhood to adulthood (Bresnahan & Barry, 2002; Bresnahan et al., 1999).

Patients with ADHD do not represent a homogenous group from the neurophysiologic perspective. Arns et al. (2008) have demonstrated that ADHD patients showing increased slow wave qEEG activity (i.e. raised theta) might consist of 2 sub-groups: a group where a slowed alpha peak frequency (APF) is actually measured as increased slow EEG power vs. a group with real elevated theta. Also, whereas a reduction in fast beta activity is characteristic for ADHD, in about 20 % of patients an excess in beta-power has been found (Arns et al., 2008; Chabot & Serfontein, 1996; Clarke et al., 2001c). Several EEG-defined subtypes of ADHD have been put forward – besides the excess beta type, a maturational lag-type and a cortical hypoarousal-type have been described (Chabot & Serfontein, 1996; Clarke et al., 2001b; Clarke, Barry, McCarthy, Selikowitz & Croft, 2002).

Nowadays, ADHD can effectively be treated with neurofeedback, psychotherapeutic and pharmacological interventions (Arns et al., 2009; Ghuman, Arnold & Anthony, 2008; Knight, Rooney & Chronis-Tuscano, 2008). In the latter case psychostimulants are considered the first line approach (Pliszka, 2007; Soileau Jr, 2008). Although their effectiveness and safety has been proven (Lerner & Wigal, 2008; Rostain, 2008) a considerable number of patients does not clinically respond to stimulant medication (Greenhill, Halperin & Abikoff, 1999; Swanson et al., 1993).

Therefore, many attempts have been made to use the EEG as a predictor for treatment response (Satterfield et al., 1973; Chabot et al., 1999; Hermens et al., 2005; Arns et al., 2008; reviewed by Loo & Barkley, 2005). Overall, medication with psychostimulants has been shown to result in a normalization of EEG activity towards the pattern found in healthy controls (Clarke et al., 2002; Clarke et al., 2003a; Hermens et al., 2005). The usefulness of EEG for response prediction is underlined by findings that subgroups of ADHD patients with different EEG profiles do respond differently to stimulant medication (Arns et al., 2008; Clarke et al., 2002d; Suffin & Emory, 1995).

Recently, Hegerl et al (Hegerl et al., 2010; Hegerl et al., 2008; Hegerl et al., 2009) proposed a pathogenetic model focusing on the instable vigilance regulation found in patients with mania or ADHD. This concept is based on the description of vigilance stages (e.g. Ulrich,

1994), which refer to distinct global states of brain activation (Olbrich et al., 2009), observable on the continuum reaching from full wakefulness and sleep onset. Several classifications have been proposed, which are based on characteristic EEG features of these stages. The following stages can be separated (Loomis et al., 1937) further developed by (Bente, 1964; Roth, 1961):

An activated state with a lack of alpha activity

Stage A with dominant alpha activity corresponding to relaxed wakefulness (further divided into sub-stages A1, A2, A3 according to the degree of alpha anteriorisation)

Stage B with low amplitude non-alpha (sub-stage B1) and increasing theta and delta activity (sub-stages B2 & B3) corresponding partly with stage I according to Rechtschaffen and Kales (Rechtschaffen & Kales, 1968)

Stage C with sleep spindles, characterizing sleep onset and corresponding to stage II according to Rechtschaffen and Kales (Rechtschaffen & Kales, 1968)

According to Hegerl et al. (Hegerl et al., 2009), vigilance instability might result in a vigilance autostabilisation behavior, which is reflected in hyperactivity, sensation seeking, and distractibility. An instable vigilance regulation would result in more frequent declines to lower vigilance stages, which are characterized by a decline in alpha activity and increase in theta and delta activity mainly in frontal areas. The quantitative EEG profile of someone remaining in lower vigilance stages throughout an EEG recording would thus appear as what has consistently been shown in ADHD – decreased alpha and increased theta activity. The therapeutic effect of psychostimulants is seen to result from their vigilance enhancing properties.

The present paper aims to investigate the association of vigilance regulation and effect of psychostimulants in ADHD. We therefore reanalyzed data published by Arns et al. (2008). The study is of pilot nature, yet to our knowledge it is the first investigation of EEG-vigilance in ADHD. The following hypotheses will be tested:

States of lower vigilance will occur more often in patients with ADHD as compared to healthy controls, which will more often remain in higher vigilance stages.

Those ADHD patients with a lower vigilance level will benefit more from treatment with vigilance stabilizing agents such as psychostimulants.

Methods

Subjects

Data from 49 boys with ADHD (average age = 11.33; range 6 – 17) and 49 control boys (matched on age, gender and education; average age = 11.92; range 7 – 18) were drawn from the Brain Resource International Brain Database (see : Gordon, 2003; 2005). Exclusion criteria were a personal or family history of mental illness, brain injury, neurological

disorder, serious medical condition, drug/alcohol addiction; and a family history of genetic disorders. All subjects voluntarily gave written informed consent.

The ADHD patients had been referred by a pediatrician and their diagnosis was confirmed by a semi-structured interview based on DSM-IV criteria for ADHD and T-scores 1 SD above the norm for Inattentive or Hyperactive/Impulsive indices of the Connors Parent Rating Scales. Data were missing for three participants. For the other patients mean scores and SDs on the subscales were: Inattentive: mean = 8.909, SD = 1.27; Hyperactive/Impulsive: mean 5.28; SD = 2.90 and Impulsive: mean = 1.91; SD = 1.16. Twenty-two subjects met DSM-IV criteria for ADHD of predominantly inattentive sub-type, two subjects met criteria for ADHD of predominantly hyperactive-impulsive sub-type and twenty-two subjects met criteria for the combined ADHD sub-type.

Procedure

ADHD subjects were assessed on two separate occasions (before medication and after at least 4 weeks of medication); control subjects were assessed only once. They were seated in a sound and light attenuated room, controlled at an ambient temperature of 22°C and data was collected using the Brain Resource LabNeuro platform. During each session electroencephalographic and neuropsychological assessments took place in the following order: EEG data was recorded for two minutes with eyes open (EO) and for two minutes with eyes closed (EC). During the EO condition, subjects were asked to sit quietly and to fix their eyes on a red dot presented on a computer screen.

Afterwards, all subjects performed a Continuous Performance Test (CPT), which was used as a measure of treatment effect in the ADHD group. During the CPT series of letters (B, C, D and G) were presented for 20 msec with an interstimulus interval of 2.6 sec. When the same letter appeared twice in a row, subjects had to press two buttons with each index finger. The CPT contained 125 stimuli in total: 20 of which were pseudo-randomly presented target letters, 85 background letters, and 20 additional distractor stimuli (black and white checkerboards), which were randomly interwoven with the letter stimuli but had to be ignored by the subjects. The test was fully computerized, presented on a touch screen monitor and subjects' responses were recorded via touch-screen presses. The task instruction equally stressed response accuracy and speed. Subjects were told that the task would be 8 minutes long and performed a brief practice session. Reliability and validity data of these tasks are reported elsewhere (Clark et al., 2006; Paul et al., 2005).

Treatment

At the time of the first assessment ADHD patients were medication naïve (n=30) or free of medication for at least 48 hours (n=19). No control subjects received medication. At the second assessment all ADHD patients had been taking a prescribed medication for at least four weeks. 45 subjects were treated with psychostimulants (methylphenidate: n=38; dexamphetamine: n=7), while 4 patients were treated with atomoxetine. Patients were required to take their prescribed dose 60 minutes before the testing session. When analyzing treatment effects on CPT performance, those 4 patients treated with atomoxetine will be excluded.

Psychophysiological data acquisition

EEG data were acquired from 26 channels: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz and O2 (Quickcap; NuAmps; 10-20 electrode international system). Data were referenced to averaged mastoids with a ground at Fpz. Horizontal eye-movements were recorded with electrodes placed 1.5cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3mm above the middle of the left eyebrow and 1.5cm below the middle of the left bottom eye-lid. Skin resistance was below 5 K Ohms and above 1K Ohm for all electrodes. A continuous acquisition system was employed and EEG data were EOG corrected offline (Gratton et al., 1983). An additional ECG lead was placed on the arm. The sampling rate of all channels was 500 Hz. A low pass filter with attenuation of 40dB per decade above 100 Hz was employed prior to digitization.

Vigilance Classification

Only data from the EC condition was used for vigilance classification, since the current classification criteria refer to resting conditions with closed eyes. For vigilance analysis we used BrainVision Analyzer (Brain Products GmbH, Germany) software. After reading the data into the Analyzer we applied a low pass (>70 Hz), high pass (< 0.5 Hz) and notch (50 +/- 2.5 Hz) filter and divided the EEG recording into 2-second segments, resulting in 60 segments for each data set. The segmented EEGs underwent a semi-automatic artifact correction, focusing mainly on those channels crucial for vigilance analysis (F3, F4, O1, and O2). Segments containing muscle, movement or technical artifacts were marked and not classified into a vigilance stage but not excluded in order to maintain the original time course. On average 8.98 % of all segments (SD = 7.98) were marked as containing artifacts. One subject from the control group had to be excluded from further analysis since artifacts were found in 35 % of all 2-sec-segments.

As next step, each data set was visually scanned for periods of sleep. No subject exhibited signs of actual sleep onset, thus no segments were classified as stage C. Power spectral analysis was then performed by applying a Welch window to the data, and then performing a Fast Fourier Transformation (FFT) on each segment which were then averaged.

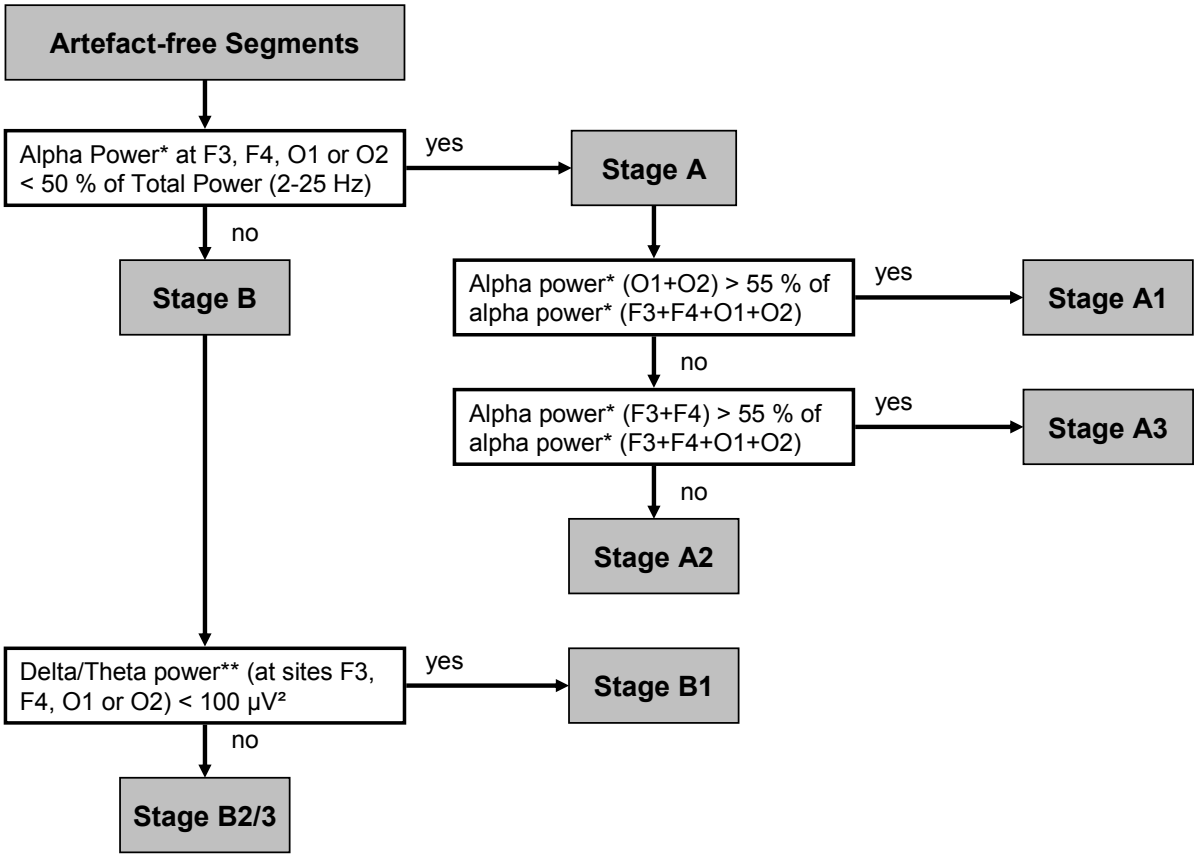


Figure 1: *Overview over the algorithm used to classify continuous 2-second EEG-segments from 2 minutes of resting-EEG with eyes closed. Segments containing artifacts were not classified.*

**, ** Frequency bands were not fixed, but adapted to individual alpha peak frequency (APF). Alpha band was considered as the 4 Hz window around the individual APF (+/- 2 Hz). The frequency spectrum above 2 Hz until start of the alpha band was considered as theta band, while beta band was defined as the frequency range above the individual alpha band until 25 Hz.*

Classification of vigilance stages A and B was executed using a validated, in house built computer algorithm (Hegerl et al., 2008; Olbrich et al., 2009), which uses the frequency spectrum from 2 to 25 Hz and calculates power in the four main frequency bands (delta, theta, alpha, beta). Extend of the frequency bands was not fixed (besides delta at 2-4 Hz) but adapted to the individual alpha peak frequency (APF) at occipital sites. APF was determined by searching the interval from 7.5 to 12.5 Hz in 0.5 Hz steps for the frequency range with the highest power. Individual APF was set as mean peak frequency at sites O1 and O2. Afterwards a window of 4 Hz was put around the individual APF (+/- 2 Hz). The resulting frequency range was considered the alpha band. Range of theta and beta bands were then determined according to the alpha band (Theta = 4 Hz to beginning of alpha band; beta = end of alpha band to 25 Hz). Each segment was then assigned to a respective vigilance stage based on the proportion of power in the four frequency bands, comparing power in frontal (F3 & F4) to occipital (O1 & O2) sites (see figure 1).

Statistics

For each vigilance stage its mean percentage of all non-artifact segments was calculated. Differences in the prevalence of vigilance stages was tested using a General Linear Model (GLM) with group (ADHD vs. Controls) as intersubject factor and vigilance stage (A1, A2, A3, B1, B2/3) as intrasubject factor. Post-hoc analyses were performed with Bonferroni-Correction.

Subjects were classified to vigilance types according to the most prevalent vigilance stage. In cases of equal amount of two or more vigilance stages no classification was performed. Chi-square tests were used to test differences in the occurrence of vigilance types between the ADHD group and controls.

CPT error scores (false positives, false negatives, total errors) were subjected to a square-root transformation in order to reduce skew in the distribution. Since many subjects made zero mistakes, we follow a recommendation of Freeman & Tukey (1950) and used the equation X' = X ** 0.5 + (X+1) ** 0.5.

Medication effects on CPT scores were tested using repeated measurement ANOVAs with time (pre vs. post treatment) as intrasubject factor and vigilance type (low vs. high vigilance) as intersubject factor.

Results

Table 1: *Differences in the amount of vigilance stages in ADHD patients as compared to Controls. For each vigilance stage its mean proportion during the 60 segments of the whole recording (corrected for artifacts) are shown, as they were found in the ADHD and Control group respectively. When age was included as a covariate, this had no effect on the results.*

	ADHD (n = 49)	Controls (n = 48)	p (1tailed)a	Co-variable (Age) p (1tailed) a
A1-Stages	66.2994	81.0050	.008 **	.007 **
A2-Stages	4.2906	1.4469	.015 *	.012 *
A3-Stages	1.9755	1.0015	.128	.126
B1-Stages	3.4563	2.2125	.297	.267
B2/3-Stages	23.9782	14.3331	.035	.037

a Bonferroni-corrected significance level set at p(5%) = .01, p(10%) = .02.

Table 2: *Changes in the pre- and post-treatment Continuous Performance Test Scores of 40 ADHD patients receiving stimulant treatment*.

		Pre	Post	T	P (2-tailed)
Reaction Time (in ms, RT)	M	609.45	579.48	1.025	.312
	SD	176.72	158.36		
Standard Deviation (in ms, SD)	M	263.00	199.50	2.733	.009
	SD	135.65	91.417		
False positive Errors (FP)*	M	5.11	4.17	2.946	.005
	SD	2.73	2.79		
False negative Errors (FN)*	M	3.64	2.76	2.729	.009
	SD	1.77	1.40		
Total errors (TE)*	M	6.35	5.09	3.600	.001
	SD	2.81	2.69		

* Square root transformed data.

Prevalence of EEG-vigilance stages

During the 2 minutes of resting EEG with eyes closed, A1-stages were most prevalent in both groups (ADHD: 66.3%; Controls: 81.0%), followed by B2/3 stages (ADHD: 24.0%; Controls: 14.3%), whereas stages A2, A3 and B1 were rarely found. GLM analysis confirmed a significant main effect of vigilance stage ($F = 487.6$; $p = .000$), no significant main effect for group ($F = 2.0$; $p = .160$), but a significant vigilance * group interaction ($F = 2.7$; $p = .037$). As expected, post hoc analyses with Bonferroni Correction (see table 1) showed that ADHD patients spent significantly less time in A1-stages than controls, and tended to remain longer in A2-stages. Comparable results were found when age was included as a covariate. As can be seen in figure 2, these differences remained stable over the whole recording period: There was no detectable decrease in the prevalence of A1-stages, neither in the ADHD group nor in the control group during the 2 minutes of recording.

Subjects were classified according to the predominant vigilance stage over the whole recording period. 38 subjects in the ADHD group (77.6 %) and 43 subject in the control group (89.6 %) were classified as “A1-type”, 10 ADHD patients (20.4 %) and 4 Controls (8.3 %) as “B2/3-type”, and 1 subjects from both groups was classified as “B1-type”. Chi^2-Tests revealed no significant differences in the relation of these vigilance types between the ADHD and Control group ($Chi^2 = 2.870$, $p=.238$).

Table 3: *Effects of treatment (pre vs. post treatment with psychostimulants) and vigilance type (low vigilance vs. high vigilance) on performance in the Continuous Performance Test. Shown are results of repeated measurement ANOVAs with two-sided significance testing*.

	Vigilance type	Pre	Post	time	vigilance	time * vigilance
Reaction Time (in ms, RT)	Low	618.00	566.40	p = .283	p = .954	p = .675
	High	606.60	583.83			
Standard Deviation (in ms; SD)	Low	295.80	189.30	p = .006	p = .650	p = .291
	High	252.07	202.90			
False positive Errors (FP)*	Low	6.07	4.22	p = .001	p = .483	p = .100
	High	4.79	4.16			
False negative Errors (FN)*	Low	3,95	2.44	p = .006	p = 1	p = .260
	High	3.53	2.86			
Total errors (TE)*	Low	7.27	4.93	p = .000	p = .586	p = .071
	High	6.04	5.14			

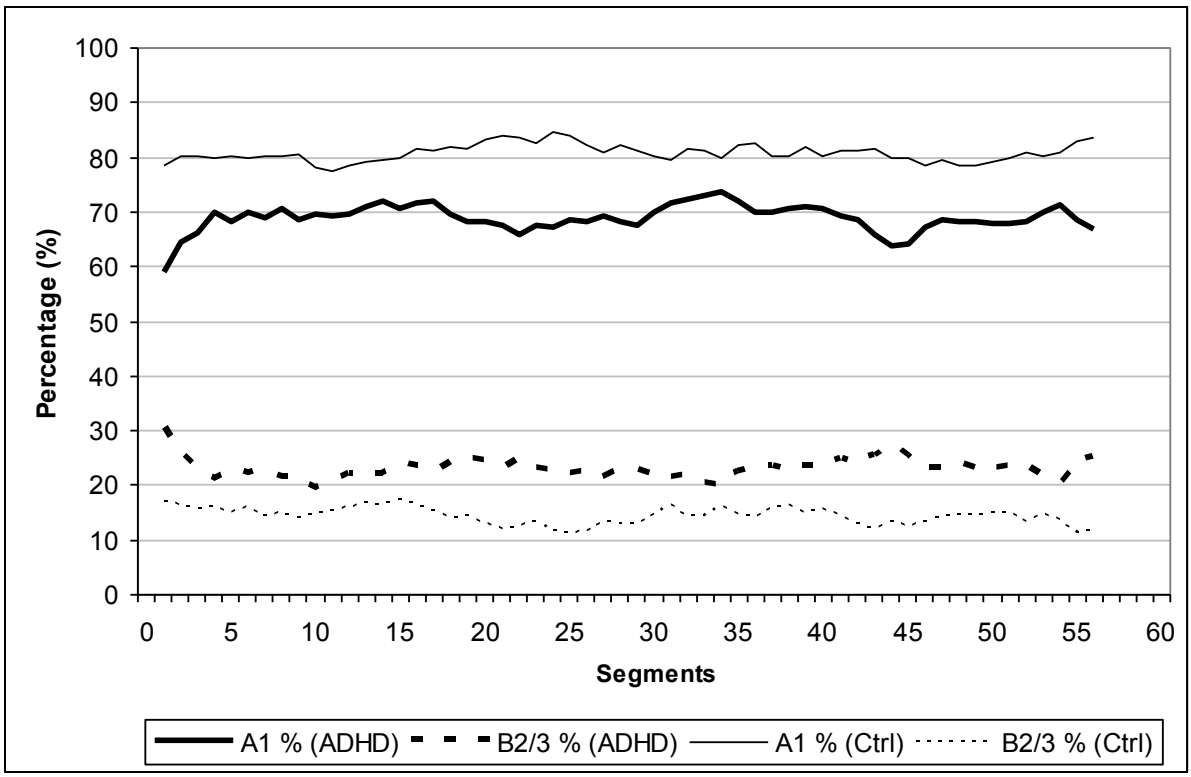


Figure 2: *Time course of vigilance stages A1, A2 and B2/3 in ADHD-patients compared to healthy controls during 2 min of resting-EEG with closed eyes. On the x-axis, consecutive sliding average-epochs are presented, which have been calculated from the 60 2 to second segments (epoch 1: averaged amount of vigilance stages from segments 1-5, epoch 2: segments 2-6, epoch 3: segments 3-7, ..., epoch 56: segments 56-60).*

Changes in Continuous Performance Test (CPT)

For all analyses concerning the impact of vigilance regulation on CPT performance and response to psychostimulants, ADHD patients, who had remained predominantly in B2/3-stages during the resting EEG (low vigilance) were compared to those, who showed mostly A1-stages (high vigilance). Those four patients treated with atomoxetine were excluded (including the one patient with predominant B1-stages) as well as five patients who did not complete the CPT a second time. Therefore all following analyses comprised data of 40 ADHD patients only.

After treatment a significant reduction in the amount of false positives, false negatives and total errors was found. Also, the standard deviation of the reaction time did significantly decline; while there was no significant reduction in reaction time (see Table 2). When performing a median split of the pre-treatment reaction times (slow group: RT < 565 msec; fast group: RT =/> 565 msec), a regression to the mean became evident – those who exhibited faster pre-treatment reaction times (fast group, n = 22) tended to slow down under stimulant medication (Mpre = 491.50, Mpost = 558.68, T = -1.863, p = .077) whereas those who had rather slow pre-treatment reaction times (slow group, n = 18) significantly accelerated their performance (Mpre = 753.61, Mpost = 604.81, T = 4.997, p = .000). However, Chi^2-Tests (Chi^2 = .240; p = .887) revealed no association of reaction time (slow vs. fast group) with ADHD subtypes (inattentive vs. hyperactive/impulsive vs. combined).

Pre- and post-treatment CPT-results were compared between the “low vigilance” (n=10) and the “high vigilance” (n=30). Numerically, the “low vigilance” group achieved worse pre-treatment results as compared to the “high vigilance” group on all CPT scores (slower RT with higher SD, more FP, FN and ER) and, after stimulant medication, improved more on all scores, resulting in better post-treatment performance as compared to the “high vigilance” group (see figure 3). However, repeated measurement ANOVAs showed a main effect of time (pre vs. post treatment) for all CPT results besides the reaction times, but no significant main effect of vigilance group. For total errors, there was a tendency for a vigilance * time interaction (see Table 3).

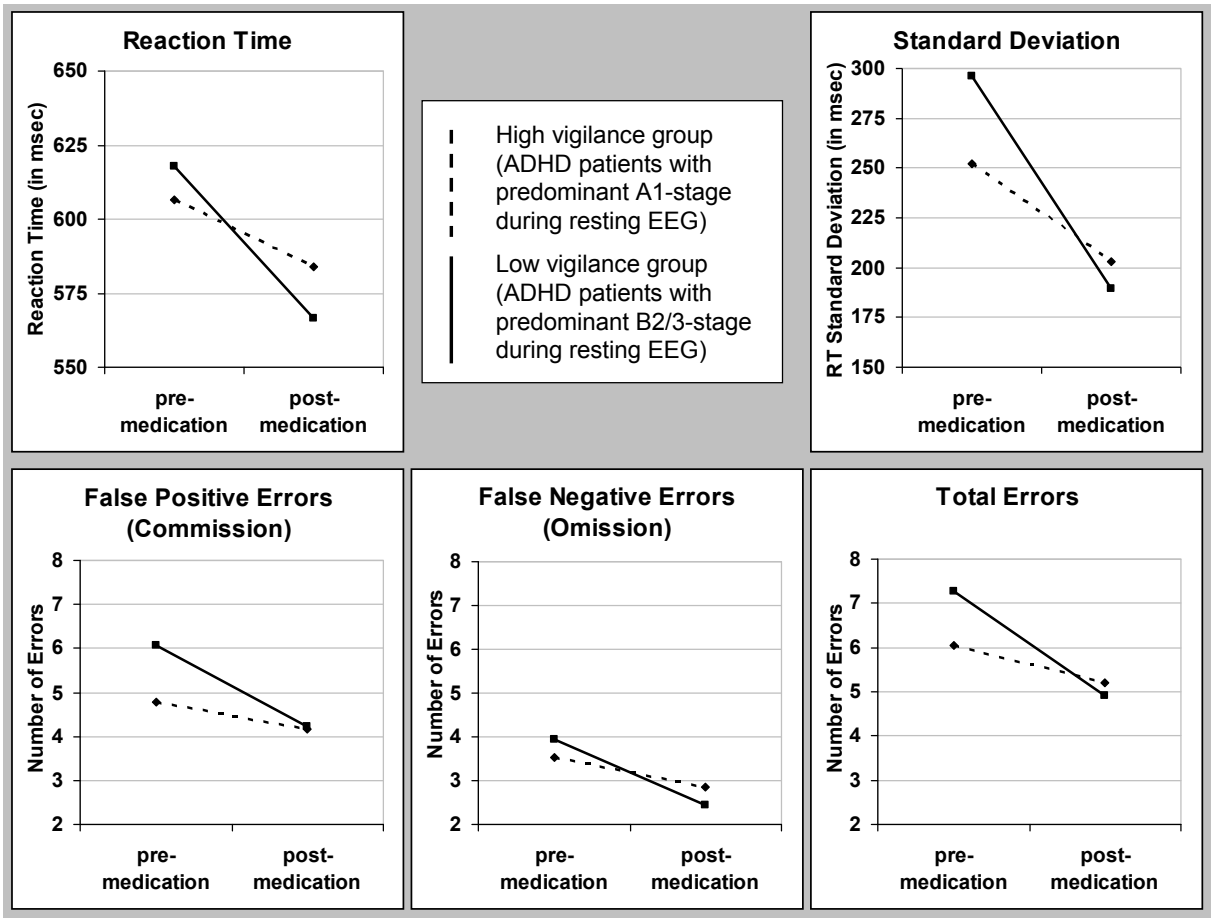


Figure 3: *Results of the ADHD group in the Continuous Performance Test (CPT). Subjects performed the CPT in unmedicated state (pre-treatment) and after at least 4 weeks of medication with stimulants (methylphenidate, dexamphetamine). Shown separately are the results of those ADHD patients whose resting-EEG showed signs of an instable vigilance (low vigilance group, n=10), resulting in a higher proportion of time spend in lower vigilance stages, compared to those ADHD patients who exhibited predominantly A1-stages during the 2 minutes of resting-EEG (high vigilance group, n=30).*

Discussion

In this work, we aimed to investigate the vigilance regulation of patients with ADHD. It has been put forward that an instable vigilance regulation is a trait characteristic of ADHD and that some ADHD symptoms, e.g. hyperactivity, might be part of an autoregulatory vigilance stabilization behavior (Hegerl et al., 2009). Since vigilance-stabilizing agents such as psychostimulants have repeatedly been shown as effective in the treatment of ADHD, we assumed that those patients with more pronounced vigilance instability should benefit the most from stimulant treatment.

We could confirm the first hypotheses as ADHD patients were found to exhibit less A1-stages compared to healthy controls, thus remaining shorter in stages of higher vigilance. A critical interjection could be that our results might be due to maturation effects. This argument is based on the fact that cortical rhythms such as alpha develop in a certain temporal order during youth and adolescents. It could be argued that vigilance stages are not classifiable in children and possibly in adolescents, since the definition of vigilance stages is bound to the spatio-temporal distribution of cortical rhythms, mainly the occurrence (or non-occurrence) of alpha. However, according to Niedermeyer (Niedermeyer & Da Silva, 2004), a stable alpha rhythm can be found in children aged 6-10 years, but only gradually reaches the mature frequency of 10/sec. A vigilance classification depending on a rigid definition of the alpha band (8-12 Hz), would therefore underestimate the occurrence of A-stages, since a slowed alpha would be considered as theta. This was taken into account when the individual APF was used as basis for vigilance classification. However, interspersions of posterior slow activity might be found quite often between alpha waves in younger children. Whether or not slow EEG-activity is reflecting lower vigilance or immaturities cannot be answered from this study (for a detailed discussion see: Ulrich, (1994)).

Changes in Continuous Performance Test (CPT) results were used to assess medication response. A reasonable approach according to Swanson (Swanson, 1985), who recommended objective laboratory measures of inattention as appropriate measures for monitoring pharmacological effects in children. Comparing results of repeated CPT performances of unmedicated ADHD patients, Soreni et al. (Soreni, Crosbie, Ickowicz & Schachar, 2009) found the CPT to yield a reliable measure of inhibitory control (false positive errors) and acceptable reliability estimates for reaction times and reaction time variability.

When CPT performance in unmedicated state was compared to CPT performance after medication with psychostimulants (methylphenidate, dexamphetamine), we found a reduction in omission (false negative) and commission (false positive) errors, with results showing that stimulant medication showed a regression to the mean for reaction time. These findings are in accordance to existing data on stimulant effects on CPT performance (Losier, McGrath & Klein, 1996; Riccio, Waldrop, Reynolds & Lowe, 2001). We also found a reduction in the variability of reaction times, but no significant change in reaction times. In general, ADHD patients have mostly been shown to have slower and more variable reaction times compared to controls, with medication resulting in faster reaction times with reduced variability (Kavale, 1982; Riccio et al., 2001).

One explanation for the lack of change in reaction times might be that there have been agonistic effects in our population. When patients with slower baseline reaction times were compared to patients who exhibited faster reaction times at baseline, the former were found to become faster under medication, whereas the latter tended to get slower. This might simply reflect a regression to the mean but could also be sign of a reduction of impulsivity in the fast group and more attentional focus in the slow group. Teicher et al. (Teicher, Lowen, Polcari, Foley & McGreenery, 2004) classified the attentional state of patients during CPT performance and could show that these state measures provided a robust differentiation between controls and ADHD patients, who were less often on task and showed more shifts between attentional states. In the presence of generally short reaction times, such attentional lapses do result in instances of prolonged reaction times (Leth-Steensen, Elbaz & Douglas, 2000), making it difficult to detect changes with the usual statistics (Castellanos & Tannock, 2002; Hervey et al., 2006).

Although attentional lapses are consistent with the thesis of an instable vigilance regulation as the main reason for performance deficits in prolonged tasks, we were not able to verify our second hypothesis, that an instable vigilance regulation could predict response to stimulant medication. In general, those ADHD patients, who at baseline demonstrated more signs of an instable vigilance, achieved numerically worse results in the CPT during the baseline condition. After four weeks of medication with methylphenidate or dexamphetamine they seemed to perform better than those patients, who had demonstrated a higher vigilance level at baseline. The fact that these differences did not reach significance, suggests that the study might have been underpowered concerning this aspect. Still, especially concerning error rates floor effects have to be considered. Many patients made very little mistakes even in the unmedicated baseline assessment. Yet, if there is no room to improve performance, any attempt to predict such improvement is bound to fail.

Still, in a previous publication using the same dataset, Arns et al. (2008) found that treatment outcome could be predicted using an EEG Phenotype approach based on the pre-treatment EEG. It was shown that the frontal slow EEG-Phenotype predicted treatment outcome to stimulant medication, which led to speculation about whether frontal slow EEG should be considered a stable trait (EEG Phenotype) or a state (vigilance state). In figure 2 it can be seen that the differences in vigilance stages were present over the full 2-minute EEG recording and there seemed to be a baseline difference rather than a time effect. This tends to suggest that in ADHD the frontal slow EEG could be regarded as a stable trait (EEG-Phenotype), which is supported by the fact that the EEG-Phenotype approach did predict treatment outcome. However, the exact cause of the frontal slow EEG is not clear yet, and might still be a result of an unstable vigilance regulation. An important fact is the shortness of the available EEG-data. Usually, EEG-vigilance classification is based on recordings of 10 minutes or longer, since differences between groups of instable or stable vigilance regulation do manifest themselves only after sufficient time. Hegerl et al. (2008) compared the EEG-vigilance of unmedicated patients with borderline personality disorder (BPD) or obsessive-compulsive disorder (OCD) and healthy controls. BPD patients showed a lower vigilance from the first minute on, controls progressively declined to lower vigilance levels, and OCD patients showed a stable and high vigilance level during five minutes of resting EEG with eyes closed. Yet, during the 5 minutes these differential time courses did not reach

significance. By analyzing vigilance during 2 minutes of resting EEG in this study, only slight differences could be detected between ADHD patients and healthy controls. Assuming that ADHD patients do generally present with trait-like vigilance instability, one has to argue that it was not possible to distinguish patients with more or less severe vigilance instability, which may have been easier if longer EEG recordings would have been available. Therefore, further research employing longer recordings should be conducted to investigate vigilance regulation in ADHD.

There are other limitations to acknowledge, most of them a result of the pilot nature of this study. Post-hoc analyses were performed on existing data; therefore some conditions could not be constructed as potentially required. There was no second EEG-recording after medication with stimulants to verify changes in vigilance regulation and no change sensitive rating scale for ADHD symptomatology were available. Also, the study might have been underpowered for detecting differences between patients with stable versus instable vigilance regulation concerning their response to methylphenidate.

Acknowledgement

We would like to acknowledge that the data used in this study were generously provided by the Brain Resource Company LLC in Sydney using the Brain Resource LabNeuro platform. We would especially like to acknowledge the support from Evian Gordon and Kylie Barnett in providing us with all these data. Furthermore, we like to acknowledge Werner van den Bergh and Jay Gunkelman for the fruitful discussions on this topic.

Financial disclosure:

C.S., M.A. and S.O. report no potential conflicts of interest.
U.H. has been or is participating in advisory boards of Lilly, Wyeth, Lundbeck and Sanofi-Aventis. He received financial support for an Investigator Initiated Trial from Lundbeck. He received honoraria for single lectures as well as sponsoring for symposia and an internet service from Cephalon and other pharmaceutical companies, health insurances and other parties.

Chapter 4

The increase in theta/beta ratio on resting state EEG in boys with attention-deficit/hyperactivity disorder is mediated by slow alpha peak frequency.

Lansbergen, M., Arns, M., van Dongen-Boomsma, M., Spronk, D., & Buitelaar, J. K. (2011). The increase in theta/beta ratio on resting state EEG in boys with attention-deficit/hyperactivity disorder is mediated by slow alpha peak frequency. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *35*, 47-52.

Abstract

Attention-deficit/hyperactivity disorder (ADHD) was found to be characterized by a deviant pattern of electrocortical activity during resting state, particularly increased theta and decreased beta activity. The first objective of the present study is to confirm whether individuals with slow alpha peak frequency contribute to the finding of increased theta activity in ADHD. The second objective is to explore the relation between resting-state brain oscillations and specific cognitive functions. From 49 boys with ADHD and 49 healthy control boys, resting-state EEG during eyes open and eyes closed was recorded, and a variety of cognitive tasks were administered. Theta and beta power and theta/beta ratio were calculated using both fixed frequency bands and individualized frequency bands. As expected, theta/beta ratio, calculated using fixed frequency bands, was significantly higher in ADHD children than control children. However, this group effect was not significant when theta/beta ratio was assessed using individualized frequency bands. No consistent relation was found between resting-state brain oscillations and cognition. The present results suggest that previous findings of increased theta/beta ratio in ADHD may reflect individuals with slow alpha peak frequencies in addition to individuals with true increased theta activity. Therefore, the often-reported theta/beta ratio in ADHD can be considered a non-specific measure combining several distinct neurophysiological sub-groups such as frontal theta and slowed alpha peak frequencies. Future research should elucidate the functional role of resting-state brain oscillations by investigating neurophysiological sub-groups, which may have a more clear relation to cognitive functions than single frequency bands.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; BRID = Brain Resource International Database; CPRS = Conners' Parent Rating Scale; CPT = Continuous performance test; EEG = electroencephalography, IAF = individual alpha peak frequency; SPHERE-12 = Somatic and Psychological Health Report questionnaire.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common psychiatric disorder in childhood, affecting 5-10 % of all children worldwide (Faraone, Sergeant, Gillberg & Biederman, 2003). In 40-60% of all cases ADHD persists in adolescence and adulthood (Faraone, Biederman & Mick, 2006). Electrophysiological studies have revealed consistent evidence for abnormal brain oscillations during resting state in individuals with ADHD (Barry et al., 2003). The EEG of the majority of children with ADHD is characterized by a deviant pattern of baseline cortical activity, specifically increased slow-wave activity, primarily in the theta band, and decreased fast-wave activity, primarily in the beta band, often coupled (i.e., increased theta/beta ratio; (Barry et al., 2003)). A meta-analysis of EEG and ADHD including 9 studies (1498 participants) reported significant effect sizes for theta and beta power, and theta/beta ratio (effect size = 1.31, -0.51, 3.08, respectively; Snyder & Hall, (2006)). However, recently, it has been suggested that at least two different EEG subtypes in ADHD, a subgroup with true frontal slow EEG (i.e., enhanced theta activity) and a subgroup with slow alpha peak frequency, might lead to the finding of increased 'theta' power (Arns et al., 2008), and thus increased theta/beta ratio, in ADHD. Moreover, these two EEG subtypes differed in their response to stimulant medication (Arns et al., 2008). So, the robust finding of increased theta and theta/beta ratio in ADHD may largely depend on a subgroup of children with ADHD who have a slow alpha peak frequency. In earlier studies, based on visual inspection of EEG data, it has already been reported that slow alpha peak frequency was correlated to hyperactive behavior, whereas the frontal EEG abnormalities such as frontal slow EEG showed no relation to the ADHD symptomatology (Stevens et al., 1968). When EEG power is calculated from individual adjusted frequency bands (based on the individual alpha peak frequency) rather than from fixed frequency bands (Klimesch, 1999), the finding of increased theta power in one group relative to another group is not contaminated by participants with slow alpha peaks. Especially in children it is known that the alpha peak frequency matures starting at 4-6 Hz at age 2-12 months to 10 Hz at 10 years of age (Niedermeyer & Da Silva, 2004), and hence the use of individual adjusted frequency bands is especially important. So far, all studies comparing resting-state EEG between children with and without ADHD used fixed frequency bands to estimate EEG power. The first objective of the present study is to address the question whether the robust findings of increased theta activity in ADHD are still present when controlling for children who exhibit slower alpha peak frequencies.

Few studies have addressed the functional role of resting-state brain oscillations. Do specific resting state brain oscillations relate to specific cognitive functions?

Decades of research have established well-replicated findings of several cognitive deficits in attention-deficit/hyperactivity disorder (ADHD) such as attention deficits, working memory problems and deficient inhibitory control (Nigg, 2005). However, the question remains whether cognitive impairments may relate to abnormal brain oscillations.

It has been argued that alpha activity reflects arousal (i.e., "the current energetic level of the organism") and theta and beta activity reflect task- or situation-specific activation changes resulting from stimulus processing (Barry, Clarke, Johnstone, Magee & Rushby, 2007). Based on findings from animal and human research, it has been suggested that task-

induced increases in theta power and the phase relationship between theta and gamma oscillations are important for memory processes, particularly episodic long-term memory and working memory (Knyazev, 2007; Sauseng, Griesmayr, Freunberger & Klimesch, 2010). Recently, it has also been postulated that theta oscillations reflect a "more general brain integrative mechanism" rather than an integrative mechanism specific for memory processes (Sauseng et al., 2010). Event-related increases in alpha power have been associated with top-down inhibitory control processes of visual information (Jensen, Gelfand, Kounios & Lisman, 2002).

Klimesch (1999) argued that low levels of theta activity and high levels of alpha activity during resting state predict increased theta power and decreased alpha power during task performance, that subsequently lead to improved cognitive performance. However, few studies investigated directly the relation between brain oscillations in a resting human (not during task performance) and subsequent cognitive performance. Consistent with the hypothesis of Klimesch (1999), increased theta power and increased alpha power at rest have been related to impaired cognitive performance in children with ADHD as well as in control children (Hermens et al., 2005; Loo & Smalley, 2008; Sumich et al., 2009). However, discrepant findings have also been reported (Swartwood et al., 1998; Wienbruch, Paul, Bauer & Kivelitz, 2005). So, the functional role of EEG oscillations during resting state is still unclear. One possible explanation for the inconsistent findings is the wide variety of behavioral paradigms that have been used, which all tap different cognitive functions. The second goal is to explore the relation between resting-state brain oscillations (calculated using individualized frequency bands) and task performance on a variety of cognitive tasks. By setting this goal, the present study may reveal baseline EEG markers of specific neurocognitive dysfunctions in ADHD, and give more insight into the functional role of resting-state EEG.

Based on previous independent findings of increased slow-wave and decreased fast-wave activity as well as impaired cognitive performance in ADHD, we expect that increased theta power, decreased beta power, and increased theta/beta ratios will be associated with decreased cognitive performance in ADHD patients. Based on the assumption of Klimesch et al. (1999) that increased alpha activity at rest predicts decreased event-related alpha activity which reflects increased cognitive performance, we hypothesized that alpha power at rest correlates positively with cognitive performance.

Method

Participants

Forty-nine boys diagnosed with ADHD (M = 12.2 years; SD = 3.0; range 6-18) were matched on age, gender, and education with 49 healthy control boys (M = 12.5 years; SD = 2.8; range 7-18). Performance on the Spot-the-Real-Word Test, which is a good indicator of premorbid IQ (Paul et al., 2005), did not differ significantly between the groups (36.8 and 37.4 for the ADHD and control group, respectively; $F(1,91) < 1$). The data from the participants in the present study were acquired as part of the Brain Resource International Database (BRID; http://www.brainresource.com) and have already partially been published (Arns et al.,

2008). Data acquisition for the BRID is performed in a standardized manner with identical hardware, software, paradigms, and experimental procedures (Gordon, 2005).

All children were recruited from the Sydney metropolitan region. Two pediatricians evaluated the children with ADHD using a semi-structured interview based on DSM-IV criteria for ADHD (Williams et al., 2010a) and Conners' Parent Rating Scale (CPRS; Conners, Sitarenios, Parker & Epstein, (1998)) (T-scores 1 SD above the norm for either inattentive or hyperactive/impulsive subscores). Twenty-one participants met criteria for ADHD combined subtype, 22 met the criteria for ADHD predominantly inattentive type, and 2 boys met the criteria for ADHD predominantly hyperactive/impulsive subtype. The classification of ADHD subtype was missing for 3 participants. The average number of inattentive and hyperactive/impulsivity DSM-IV symptoms for the ADHD group were 8.0 (SD = 1.3) and 5.2 (SD = 2.9), respectively. The average scores on the cognitive problems/inattentive, hyperactive, and impulsive subscales of the CPRS were 70.3 (SD=7.4), 73.5 (SD=14.9), and 73.0 (SD=9.8), respectively.

Exclusion criteria for ADHD and healthy control children included a personal history of physical brain injury, neurological disorder, genetic disorder, or other serious medical condition and a personal history of substance abuse or dependency. Additionally, ADHD children were excluded if they had an Axis I psychiatric disorder (other than ADHD), assessed by two pediatricians in a semi-structured interview. Children in the control group were excluded if the Somatic and Psychological Health Report questionnaire (SPHERE-12; Hickie, Davenport, Naismith & Scott, (2001)) revealed an Axis 1 disorder. All children were medication free for at least 48 h before testing. Moreover, for at least 2 h prior to testing participants were required to refrain from caffeine-intake and smoking.

All subjects and their caretakers provided written informed consent to participate in the study. In the informed consent, permission is asked to add the participant's de-linked data to the brain database, and to use their de-linked data for the specified and other scientific investigations. The study was approved by the Western Sydney Area Health Service Human Research Ethics Committee.

Intelligence

Spot the Real Word Test. This test is a computerized adaptation of the Spot the Word Test (Baddeley, Emslie & Nimmo-Smith, 1993). The estimated IQ derived from this test correlates highly with full scale IQ, as assessed by the WAIS-III (r = 0.76; Paul et al., (2005)). On each of the 60 trials, a real word is presented simultaneously with a nonsense word. Participants were required to select the real word. The estimated IQ is derived from the total correct score.

Neuropsychological tests

The cognitive tests were part of the IntegNeuro battery, a fully computerized and standardized neuropsychological battery that is presented on a touch-screen computer. The IntegNeuro battery consists of 12 tests that tap five domains of cognitive functions: sensori-

motor functions, attention and working memory, executive function, learning and memory, and language skills (for more details, see: Clark et al., (2006); Paul et al., (2005); Williams et al., (2005)). Test-retest reliability and convergent and divergent validity of the IntegNeuro battery have been reported (Paul et al., 2005; Williams et al., 2005). Moreover, it has recently been demonstrated that the IntegNeuro battery could distinguish patients with ADHD from control participants with relatively high sensitivity and specificity (Williams et al., 2010b).

Standardized visual and auditory task instructions were presented. Each test was preceded by a practice trial. The test trials were presented only if participants passed the practice trial accurately. The present paper presents and discusses EEG data and the results of 6 cognitive tests covering the sensori-motor, attention/memory, and language domains. Since details of the neuropsychological tasks of the IntegNeuro battery have been extensively described previously (Clark et al., 2006; Paul et al., 2005), here only the most important details are reported.

Sensori-motor functions were assessed by the Choice Reaction Time test. Dependent variable is the mean reaction time across trials (i.e., mean choice reaction time: Choice RT).

The Digit span task (forward and backward version) and Span of Visual Memory task (forward and backward version) were used to tap verbal and visuo-spatial short-term memory (forward version) and verbal and visuo-spatial working memory (backward version), respectively. Dependent variables are the maximum number of digits and maximum number of squares correctly recalled.

The Continuous performance test (CPT) and a Go/Nogo paradigm were used to tap attention, as reflected in mean reaction time to correct target/go-stimuli.

Finally, language skills (verbal fluency) were assessed by the Word Generation task in which the total number of correct words generated across three letters was the variable of interest.

Electrophysiological recordings

EEG and EOG activity were recorded using a Quickcap (NuAmps) with 26 electrodes according to the 10-20 electrode international system. Data were referenced to averaged mastoids with the ground electrode placed at Fpz. Horizontal electrooculogram (HEOG) was recorded from electrodes placed lateral to the outer canthi of both eyes and vertical electrooculogram (VEOG) from electrodes attached above and below the left eye. Electrode impedance was kept below 5 kOhm. The sampling rate was 500 Hz and the data were filtered online with a 100 Hz low-pass filter (40dB attenuation).

Procedure

Participants were placed in a sound-attenuated testing room and asked to sit quietly for 4 min, 2 min with their eyes open and 2 min with their eyes closed during which baseline EEG

was recorded. Afterwards, participants completed the IntegNeuro battery in front of the touch-screen computer in approximately 50 min. Details of the procedure have been published (Gordon, Cooper, Rennie, Hermens & Williams, 2005; Paul et al., 2005).

EEG analyses

Since EEG data from one boy with ADHD were not recorded at all electrode sites of interest (i.e., Fz, F3, F4, Cz, C3, C4, Pz, P3, P4), he was excluded from the EEG analyses.

EEG data during the eyes open and eyes closed resting condition were processed and analyzed separately using BrainVision Analyzer software (www.brainproducts.com). EEG data were filtered using a band-pass filter of 0.5-100 Hz and a notch filter of 50 Hz. The sampling-rate was changed to 256 Hz. The continuous EEG data were segmented into 2-s epochs, separately for the eyes-open and eyes-closed condition. Epochs were rejected from further analyses if data exceeded 100 µV and ocular artifact correction was conducted according to the Gratton et al. (1983) algorithm. The average number of EEG epochs used for the FFT analyses was 57.3 (SD = 9.6) for the eyes-open and 57.6 (SD = 9.0) for the eyes-closed condition in the ADHD group and 57.8 (SD = 5.9) for the eyes-open and 56.3 (SD = 6.8) for the eyes-closed condition in the control group. EEG data were Fourier transformed (Hanning window length of 20%) and subsequently ln-transformed (Gasser, Bächer & Möcks, 1982).

First, mean theta and beta power were calculated using fixed frequency bands (4-7.5 Hz for theta and 12.5-25 Hz for beta). Additionally, since alpha peak frequency and consequently also EEG frequency bands vary as a function of age (Klimesch, 1999; Niedermeyer & Da Silva, 2004) and may differ between individuals (Arns et al., 2008), separately for each participant, the average power values of the different frequency bands were also calculated using individual alpha peak frequency as anchor point (Doppelmayr, Klimesch, Pachinger & Ripper, 1998). First, the frequency was assessed at which alpha power was maximum within 5-15 Hz at the parietal and occipital electrodes (Pz, P3, P4, Oz, O1, O2) in the eyes closed condition. Second, EEG data in the eyes open resting condition were subtracted from the EEG data in the eyes closed resting condition to find the frequency (within 5-15 Hz) at which alpha power was most attenuated by opening of the eyes (Posthuma, Neale, Boomsma & de Geus, 2001). When peak frequencies derived from the two methods and different electrode sites did not differ more than 0.5 Hz, the mean peak frequency at which alpha power was most attenuated by opening of the eyes across the parietal and occipital electrodes was used as individual alpha peak frequency (IAF). For peak frequencies occurring at the boundaries of the search window and for peak frequencies, which differed between electrode sites and the two methods, visual inspection of the EEG data was conducted to determine the true individual alpha peak frequency.

Three boys with ADHD did not show clear alpha peak frequencies and were excluded from the analysis of the individual frequency bands. For 2 boys with ADHD and 1 control boy, who did not show alpha attenuation after opening the eyes, but did show a clear alpha peak, individual alpha peak frequencies were assessed using the EEG data in the eyes closed resting condition. Further, for 2 ADHD boys and 2 control boys, who showed only alpha attenuation at occipital electrode sites and not at parietal sites, mean individual alpha peak

frequencies were calculated from the difference power spectrum (eyes closed minus eyes open) across occipital electrode sites. The bandwidth for the theta, alpha, and beta bands were defined using IAF as anchor point: 0.4*IAF – 0.6*IAF, 0.6*IAF – 0.8*IAF, 0.8*IAF – IAF, IAF – 1.2*IAF, 1.2*IAF – 25 Hz for theta, lower 1-alpha, lower-2-alpha, upper alpha, and beta, respectively (Doppelmayr et al., 1998).

For both fixed frequency and individualized frequency bands, average power spectra were calculated at frontal (Fz, F3, F4), central (Cz, C3, C4) and parietal (Pz, P3, P4) sites. Separately for each electrode, theta/beta power ratio was calculated by dividing the power of the slower frequency band by the power of the faster frequency band.

Statistical analyses

Since the behavioral data were not normally distributed, Mann-Whitney U tests were conducted for each dependent variable with group as between-subjects factor (ADHD vs. matched controls) to examine differences between boys with and without ADHD on cognitive performance in several domains.

Group differences with regard to mean IAF were tested by an one-way analysis of covariance (ANCOVA) with group as between-subjects factor and age as covariate. Separately for theta and beta power and theta/beta ratio, ln-transformed EEG data were analyzed with repeated measures ANCOVAs with resting-state condition (eyes open vs. eyes closed), area (frontal: Fz, F3, F4 vs. central Cz, C3, C4 vs. parietal Pz, P3, P4), and laterality (left vs. midline vs. right) as within-subjects factors, group (ADHD vs. controls) as between subjects factor, and age as covariate. The alpha level of significance was set at 0.05 two-tailed. Only significant (interaction with) group effects were reported.

Furthermore, partial correlation coefficients were calculated between behavioral variables and ln-transformed EEG data (mean power across electrodes for frontal, central, and parietal areas) with age as covariate, to explore the relation between resting-state brain oscillations and cognitive performance. 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. Note that the Bonferroni adjusted alpha-level of significance would be .00020.

Results

Behavioral data

Table 1 presents performance data for the ADHD and the control group. Boys with ADHD recalled significantly less number of squares in the span of visual memory task as compared to healthy control children, $Z = -2.58$, $p = .010$ (3.6 ± 2.0 and 4.6 ± 1.7, respectively). No significant differences between boys with and without ADHD were found for number of digits recalled in the digit span task, number of correct words generated in the word generation task or for mean reaction time in the choice reaction time task, CPT, and Go/No-Go task.

Table 1: *Behavioral data for the ADHD and control group*

	Digit span F	Digit span B	Span of VM	Verbal fluency	choice RT	Go/No-Go RT	CPT RT
ADHD	4.5 (2.1)	3.0 (1.9)	3.7 (2.1))	8.4 (3.6)	918.3 (393.8)	308.7 (75.6)	614.9 (164.7)
Control group	5.2 (1.2)	3.1 (1.9)	4.6 (1.7)	9.5 (3.8)	885.3 (293.5)	294.4 (43.6)	573.5 (138.1)

Note. Standard deviation (SD) is provided in parentheses. Digit span F = digit span forward; digit span B = digit span backward; VM = visuo-spatial memory; RT = reaction time; CPT = continuous performance test.

Ln-transformed electropsychophysiological (EEG) data

Mean individual alpha peak frequency did not differ significantly between the ADHD and control group (IAF = 9.42±0.8 and IAF = 9.47±0.8 for the ADHD and control group, respectively).

Repeated-measures ANCOVAs for theta and beta power, and theta/beta power ratio, as assessed with fixed frequency bands, revealed no significant main effects of group. A significant area X laterality X condition X group effect was found for theta/beta ratio, $F(4,376) = 2.56$, $p = .038$. As illustrated in Figure 1, boys with ADHD had higher theta/beta ratios power than control boys in both resting conditions and at all electrode sites. Post-hoc ANCOVAs per condition and electrode site, with group as between-subjects factor and age as covariate, revealed significant group effects in the eyes closed resting condition at Fz, F3, Cz, Pz, and P4 (p-values of .030, .057, .041, .055, .035; not corrected for multiple comparisons).

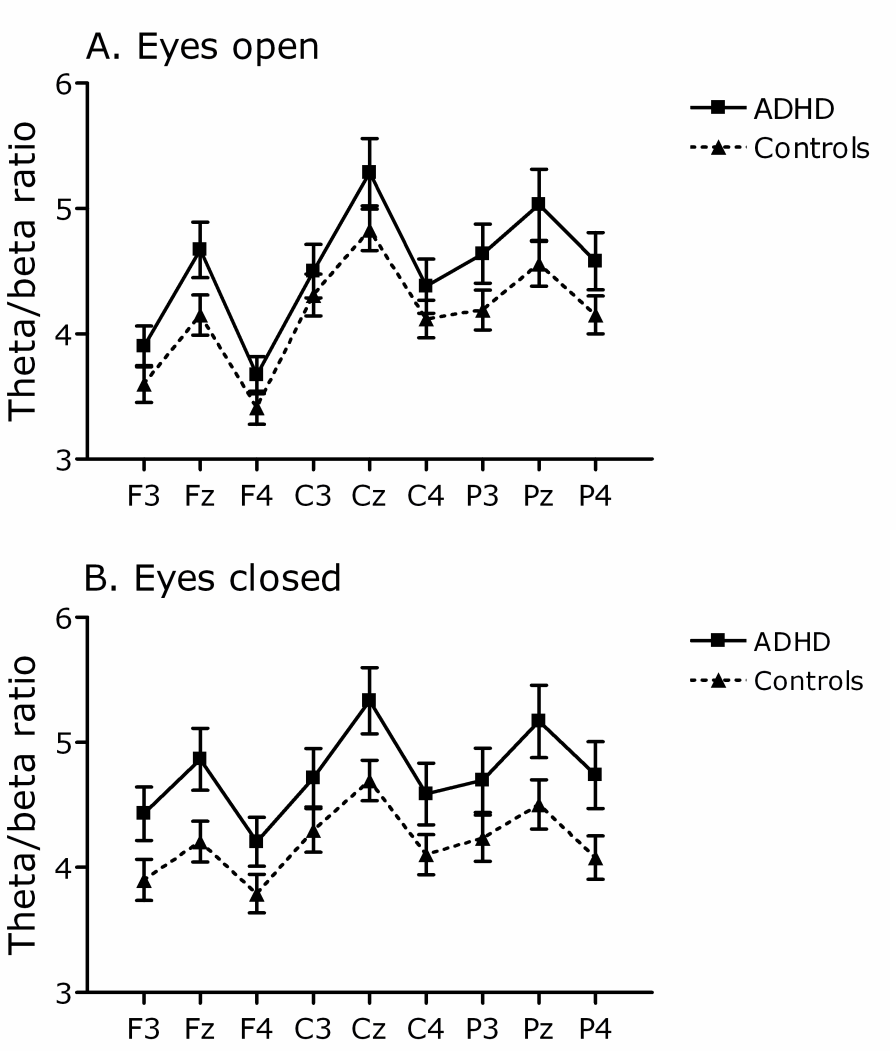


Figure 1: *Theta/beta ratio, derived from fixed frequency band analyses for the ADHD and control group at each electrode, separately for the eyes open (A) and eyes closed condition (B).*

Using the individualized frequency bands based on the IAF, repeated-measures ANCOVAs for theta (3.8±0.3 − 5.7±0.5 Hz) and beta power (11.4±0.9 − 25 Hz), and theta/beta power ratio, revealed no significant main effects of group or interaction effects with group (see the data for theta/beta ratio in Figure 2).

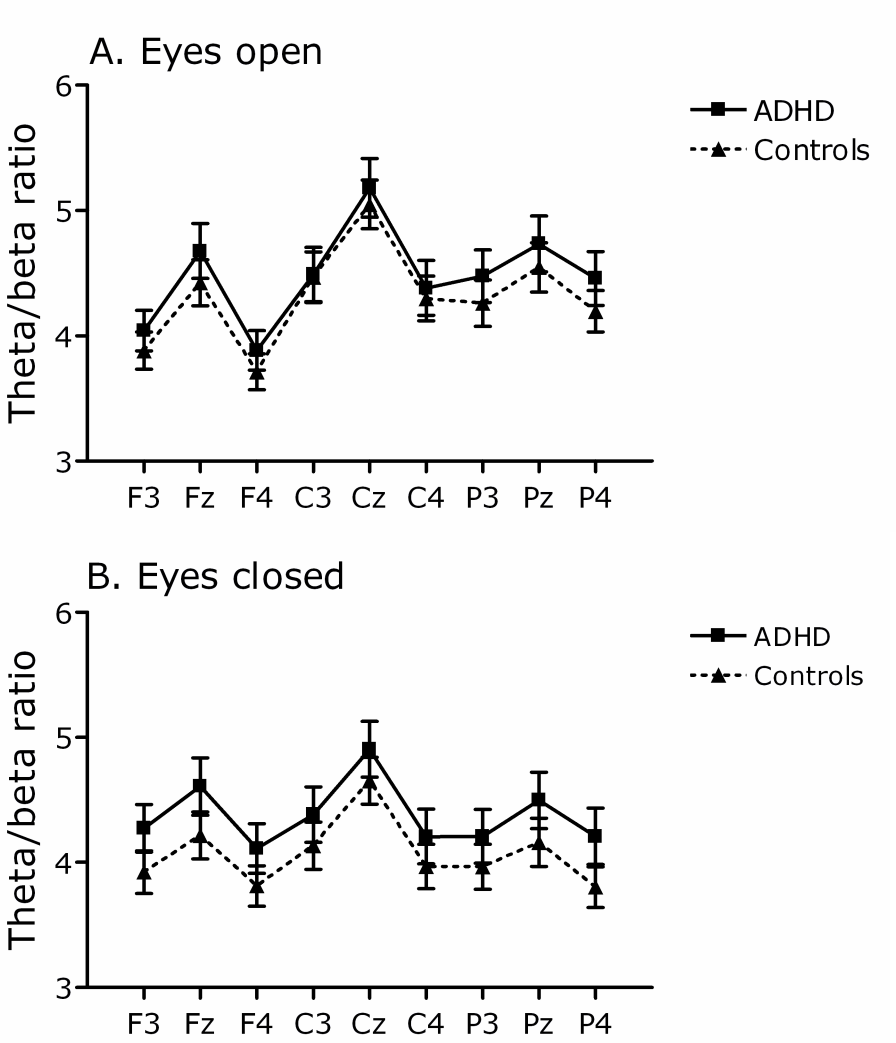


Figure 2: *Theta/beta ratio, derived from individual frequency band analyses for the ADHD and control group at each electrode, separately for the eyes open (A) and eyes closed condition (B).*

Relation between behavioral and ln-transformed EEG data

Partial correlation coefficients between behavioral performance and EEG power (based on individual frequency bands) for the whole sample were relatively small and after controlling for age, only 2 correlations were found to be significant at the alpha-level of 0.01 (see Table 1). Impaired performance on the Go/NoGo task was significantly correlated with increased lower-1 alpha power (5.7±0.5 Hz − 7.5±0.6 Hz) in the eyes closed resting condition at central sites, r = 0.294, p = .005, and parietal sites, r = 0.306, p = .003.

Table 1: Partial correlation coefficients for the relation between behavioral performance and EEG data (individual frequency bands), controlled for age, for the whole sample.

Condition	Freq band	Area	Digit span F	Digit span B	Span of VM	Verbal fluency	choice RT	Go/No-Go RT	CPT RT
Eyes open	theta	frontal	.036	.003	.082	-.025	-.149	-.020	-.123
		central	.093	.033	.049	.022	-.070	.046	-.053
		parietal	.064	.016	.061	-.001	-.092	.080	-.078
	alpha1	frontal	-.039	-.108	.165	.043	-.111	.130	-.085
		central	-.041	-.089	.095	.037	-.080	.178	-.062
		parietal	-.071	-.037	.048	.023	-.105	.191	-.069
	alpha2	frontal	.178	-.036	.214*	.114	-.079	.078	-.005
		central	.130	-.037	.145	.055	-.035	.080	.005
		parietal	.060	-.073	.099	.040	-.001	.149	.036
	upalpha	frontal	.215*	-.163	.241*	.231*	-.015	-.072	-.131
		central	.184	-.145	.151	.167	.026	-.098	-.129
		parietal	.135	-.206	.170	.192	.005	.029	-.030
	beta	frontal	.185	-.024	.185	.171	-.023	-.134	-.142
		central	.180	-.019	.181	.199	.004	-.085	-.112
		parietal	.146	-.062	.172	.195	-.041	-.063	-.144
	thebe	frontal	-.205	.011	-.140	-.177	-.088	.016	.027
		central	-.135	.076	-.109	-.158	-.064	.038	.055
		parietal	-.136	.081	-.100	-.177	-.038	.067	.066
Eyes closed	theta	frontal	-.012	-.062	.109	-.026	-.123	.047	-.083
		central	-.022	-.087	.075	.010	-.023	.148	-.032
		parietal	-.061	-.122	.082	.008	-.015	.245*	-.016
	alpha1	frontal	-.107	-.104	.194	.073	-.045	.222*	-.048
		central	-.138	-.101	.146	.053	-.033	.294**	-.041
		parietal	-.149	-.088	.069	.026	-.024	.306**	-.013
	alpha2	frontal	.096	-.138	.197	.087	-.009	.190	.001
		central	.053	-.152	.154	.026	-.019	.170	-.038
		parietal	-.045	-.175	.091	-.008	.062	.197	-.025
	upalpha	frontal	.154	-.246*	.217*	.143	-.002	.004	-.121
		central	.141	-.218*	.149	.082	-.018	-.047	-.160
		parietal	.021	-.265*	.117	.052	-.023	.089	-.129
	beta	frontal	.188	-.073	.188	.187	-.038	-.130	-.132
		central	.174	-.077	.188	.173	-.020	-.072	-.095
		parietal	.112	-.135	.139	.160	-.059	-.011	-.101
	thebe	frontal	-.251*	.056	-.097	-.209*	-.023	.076	.071
		central	-.224*	.072	-.094	-.163	.000	.087	.058
		parietal	-.200	.068	-.042	-.144	.049	.125	.056

Note: * = p < .05 (2-tailed); ** = p < .01 (2-tailed). Freq band = frequency band; Digit span F = digit span forward; digit span B = digit span backward; VM = visuo-spatial memory; RT = reaction time; CPT = continuous performance test; thebe = theta/beta ratio.

Discussion

The first goal of the present study was to test the hypothesis that at least two different EEG subtypes in ADHD, a subgroup with true frontal slow EEG (i.e., enhanced theta activity) and a subgroup with slow alpha peak frequency contribute to increased 'theta' power, and thus theta/beta power ratio, in ADHD (Arns et al., 2008). In other words, it was investigated whether the robust finding of increased theta activity and increased theta/beta ratio in children with ADHD relative to control children could be replicated, even after controlling for individuals with slow alpha peak frequencies. Consistent with our hypothesis, we replicated increased theta/beta ratio in boys with ADHD using fixed frequency bands to calculate EEG power, but this group effect attenuated when theta and beta power were calculated based on individual frequency bands. This result suggests that previous findings of increased theta power and increased theta/beta ratio in ADHD may be partially due to a subgroup of patients showing slow alpha peak frequencies instead of enhanced theta activity. Without correcting for individual alpha peak frequency, it is not possible to disentangle these neurophysiologically different EEG subtypes. Since only boys were included in the present study, the results cannot be generalized to girls. Although differences in theta power between ADHD and control participants appear to be smaller in females than males (Clarke et al., 2001a; Hermens, Kohn, Clarke, Gordon & Williams, 2005), there are no indications for a higher prevalence of slow alpha peak frequency in females or males. Therefore, the present results may also be expected in a group of girls.

Although the ADHD children in the present study showed increased theta activity, decreased beta activity, and increased theta/beta ratio relative to control participants (based on fixed frequency bands), group differences were only significant regarding theta/beta ratio. Increased theta/beta ratio has already been demonstrated to be the most robust finding in ADHD (effect size of 3.08; Snyder & Hall, (2006)). Possible explanations for the small differences in the present study may be the great heterogeneity of ADHD (i.e., different DSM-IV subtypes) and/or the heterogeneity of age within the sample (6-18 years). These factors may have increased interindividual variability and canceled out between-group differences. Although it is important to note that recent findings question whether the ADHD subtypes are really distinct and unrelated disorders (Baeyens, Roeyers & Walle, 2006; Todd et al., 2008). A second explanation for the small differences may be the length of EEG recording. Whereas a majority of studies recorded approximately 20 min (Clarke, personal communication), the present study only recorded 2 minutes of EEG. The differences between ADHD and control children in EEG activity during rest may increase with resting time. Several distinct stages of brain activity (i.e., vigilance stages) occur over time and it has been demonstrated that children with ADHD fluctuate more between stages (Sander, Arns, Olbrich & Hegerl, 2010). Therefore, longer EEG recordings may distinguish better between ADHD and control participants. Finally, note that not all studies have found clear differences with regard to increased theta and increased theta/beta ratio between ADHD and control groups (Loo et al., 2009; Swartwood, Swartwood, Lubar & Timmermann, 2003).

The second objective of the present study was to yield more insight into the functional role of EEG oscillations during a resting state. The relationship was examined between brain oscillations (corrected for individual alpha peak frequency) at rest and cognitive

performance. Correlation coefficients were small and after controlling for age, most correlations coefficients were not significant. Only increased power in the lower-1 alpha frequency band (at central and parietal sites in eyes closed condition) correlated with impaired attention in the Go/Nogo task. These findings are not in line with the hypothesis of Klimesch (Klimesch, Freunberger & Sauseng, 2009) that increased alpha power at rest predicts decreased event-related power, which is related to better performance. Assuming alpha activity at rest reflects a state of arousal (Barry et al., 2007), it may be speculated that increased arousal (i.e., low levels of alpha power) at rest is associated with better performance. However, note that the association was only significant for the eyes closed resting condition at central and parietal sites and not present for attention, as assessed by the CPT. Moreover, when applying Bonferroni corrections for multiple tests the associations were not significant anymore. In sum, so far, no straightforward and consistent relations have been found between EEG activity in a resting human and their cognitive performance on a variety of tasks. The inconsistent findings with regard to the relation between single frequency bands and cognitive functions dispute the view that the level of cortical activity at rest predicts or is strongly related to specific cognitive processes. So, the presence or absence of specific single frequency bands by itself cannot be regarded as an indication of impaired or improved cognitive function, but it should rather be investigated in relation to the task at hand (Sauseng et al., 2010). It has already been suggested that the phase of the oscillation is also important. For example, neuronal oscillations tend to entrain (phase-lock) to the rhythm of an attended stimulus sequence (Lakatos, Karmos, Mehta, Ulbert & Schroeder, 2008). So, the question remains whether EEG activity at rest is related or even predicts task-induced changes in EEG activity. More research is needed to unravel the relation between resting-state neuronal oscillations, task-induced neuronal oscillations, and cognitive task performance.

One possible explanation for the inconsistent findings with regard to the relation between EEG activity and cognitive performance is the idea that not specific brain oscillations, but rather the profile of the whole power spectrum of an individual is related to cognition. Recently, Arns et al. (2008) demonstrated that the EEG subtypes, as defined by Johnstone et al. (2005), are present in ADHD patients, but also within the normal population. Moreover, different EEG subtypes responded different to medication (Arns et al., 2008). Thus, the relation between EEG subtypes and cognition may be more evident than the relation between specific brain oscillations and cognition, as was investigated in the present study.

Conclusions

The deviant pattern of increased theta activity and increased theta/beta ratio in ADHD appears to largely depend on a subgroup of children with ADHD who have slow alpha peak frequencies rather than increased theta activity. Therefore, the often-reported theta/beta ratio in ADHD can be considered a non-specific measure combining several distinct neurophysiological sub-groups, which also respond differentially to medication (Arns et al., 2008). Further studies should replicate this finding in larger samples and investigate whether these two subgroups also differ clinically and neuropsychologically. Furthermore, the present results suggest that EEG activity in a resting human does not have a clear association with cognitive processes. Future research might address the relation between resting-state and task-induced neuronal oscillations, and subsequent behavioral

performance, also in larger samples. Furthermore, looking at different EEG subtypes rather than specific frequency bands may elucidate a more clear relationship between brain oscillations and cognitive deficits.

Acknowledgments

The authors gratefully acknowledge the support of the BrainGain Smart Mix Programme of the National Initiative Brain & Cognition. Further, we acknowledge the support of the Brain Resource International Database (under the auspices of Brain Resource - www.brainresource.com) for use of normative and clinical data. We also thank the individuals who gave their time to participate in the database. Access to the database for scientific purposes is administered independently via the scientific network (BRAINnet; www.brainnet.net), which is coordinated independently of the commercial operations of Brain Resource.

Chapter 5

Efficacy of neurofeedback treatment in ADHD: The effects on inattention, impulsivity and hyperactivity: A meta-analysis.

Arns, M., de Ridder, S., Strehl, U., Breteler, M., & Coenen, A. (2009). Efficacy of neurofeedback treatment in ADHD: The effects on inattention, impulsivity and hyperactivity: A meta-analysis. *Clinical EEG and Neuroscience*, *40*(3), 180-9.

Abstract

Since the first reports of neurofeedback treatment in ADHD in 1976 many studies have been carried out investigating the effects of neurofeedback on different symptoms of ADHD such as inattention, impulsivity and hyperactivity. This technique is also used by many practitioners, but the question as to the evidence-based level of this treatment is still unclear. In this study selected research on neurofeedback treatment for ADHD was collected and a meta-analysis was performed.

Both prospective controlled studies and studies employing a pre- and post-design found large effect sizes (ES) for neurofeedback on impulsivity and inattention and a medium ES for hyperactivity. Randomized studies demonstrated a lower ES for hyperactivity suggesting that hyperactivity is probably most sensitive to non-specific treatment factors.

Due to the inclusion of some very recent and sound methodological studies in this meta-analysis potential confounding factors such as small studies, lack of randomization in previous studies and a lack of adequate control groups have been addressed and the clinical effects of neurofeedback in the treatment of ADHD can be regarded as clinically meaningful. Three randomized studies have employed a semi-active control group, which can be regarded as a credible sham control providing an equal level of cognitive training and client-therapist interaction. Therefore, in line with the AAPB and ISNR guidelines for rating clinical efficacy, we conclude that neurofeedback treatment for ADHD can be considered 'Efficacious and Specific' (Level 5) with a large ES for inattention and impulsivity and a medium ES for hyperactivity.

Introduction

In 1976 Lubar and Shouse (1976) were the first to report on EEG and behavioral changes in a hyperkinetic child after training the Sensorimotor EEG rhythm (SMR: 12-14 Hz). The rationale behind using SMR training in hyperkinetic syndrome lays in the fact that the most characteristic behavioral correlate of this rhythm is immobility (Chase & Harper, 1971; Howe & Sterman, 1972), a reduction in muscular tension accompanying SMR training (Chase & Harper, 1971) and excessive SMR production in quadriplegics and paraplegics (Sterman, Macdonald & Stone, 1974) suggesting that enhancing this rhythm through operant conditioning should decrease the hyperkinetic complaints. Employing a within subject ABA design, Shouse and Lubar also showed that hyperactive symptoms decreased when SMR was enhanced and hyperactive symptoms increased when SMR was inhibited (Shouse & Lubar, 1979). Several variations of this training protocol have been developed and tested over the years such as enhancing beta and inhibiting theta, enhancing SMR and inhibiting beta etc. For a detailed explanation of these different protocols also see Monastra et al. (2005).

In 2004, Heinrich (Heinrich, Gevensleben, Freisleder, Moll & Rothenberger, 2004) were the first to report positive results after Slow Cortical Potential (SCP) neurofeedback in the treatment of ADHD. SCP neurofeedback is different from the above-mentioned approaches in that changes in the polarity of the EEG are rewarded (i.e. positivity vs. negativity in the EEG) and a discrete reward scheme is used. Interestingly both the SCP neurofeedback and SMR neurofeedback approaches have been successfully used in treating epilepsy as well (for an overview also see Egner & Sterman (2006) and are suggested to both regulate cortical excitability (Egner & Sterman, 2006; Kleinnijenhuis, Arns, Spronk, Breteler & Duysens, 2008). Several studies have compared theta-beta training and SCP training both within-subject (Gevensleben et al., 2009) and between-subjects (Leins et al., 2007) and both neurofeedback approaches show comparable effects on the different aspects of ADHD such as inattention, hyperactivity and impulsivity. Furthermore, SMR training also leads to concurrent positivity (For an overview of SMR-SCP interrelations also see Kleinnijenhuis et al. (2008)) further suggesting both approaches modulate activity in the same underlying neurophysiological network.

The initial findings by Lubar and Shouse (1976) and Heinrich et al. (2004) have stimulated a considerable amount of research into the treatment of ADHD with EEG Biofeedback or neurofeedback. Many clinicians are currently using this therapy in their clinical practice. Therefore, the question concerning the evidence-based level of neurofeedback therapy for ADHD and its significance in the treatment of ADHD arises.

The Guidelines for Evaluation of Clinical Efficacy of Psychophysiological Interventions (La Vaque et al., 2002) jointly accepted by the International Society for Neurofeedback and Research (ISNR) and the Association for Applied Psychophysiology and Biofeedback (AAPB) and similar to those from the American Psychological Association (APA) specify five types of classifications ranging from “Not empirically supported” to “Efficacious and specific”. These levels have been defined as follows:

Level 1: Not empirically supported. This classification is assigned to those treatments that have only been described and supported by anecdotal reports and/or case studies in non-peer reviewed journals.

Level 2: Possibly efficacious. This classification is considered appropriate for those treatments that have been investigated in at least one study that had sufficient statistical power, well identified outcome measures, but lacked randomized assignment to a control condition internal to the study.

Level 3: Probably efficacious. Treatment approaches that have been evaluated and shown to produce beneficial effects in multiple observational studies, clinical studies, wait list control studies, and within-subject and between-subject replication studies merit this classification.

Level 4: Efficacious. In order to be considered "efficacious," a treatment must meet the following criteria:

(a) In a comparison with a no-treatment control group, alternative treatment group, or sham (placebo) control utilizing randomized assignment, the investigational treatment is shown to be statistically significantly superior to the control condition or the investigational treatment is equivalent to a treatment of established efficacy in a study with sufficient power to detect moderate differences;

(b) The studies have been conducted with a population treated for a specific problem, from whom inclusion criteria are delineated in a reliable, operationally defined manner;

(c) The study used valid and clearly specified outcome measures related to the problem being treated;

(d) The data are subjected to appropriated data analysis;

(e) The diagnostic and treatment variables and procedures are clearly defined in a manner that permits replication of the study by independent researchers, and

(f) The superiority or equivalence of the investigational treatment have been shown

in at least two independent studies"

Level 5: Efficacious and Specific. To meet the criteria for this classification, the treatment needs to be demonstrated to be statistically superior to a credible sham therapy, pill, or bona fide treatment in at least two independent studies.

Monastra et al. (2005) critically reviewed the literature and applied the above-mentioned guidelines. It was concluded that neurofeedback treatment for ADHD could be considered as 'Level 3: probably efficacious'. However, in that same year Loo and Barkley (2005)

published a review article where they concluded that *"…the promise of EEG Biofeedback as a legitimate treatment cannot be fulfilled without studies that are scientifically rigorous."* (Loo & Barkley, 2005) (page 73). The main concerns they raised were the lack of well controlled, randomized studies, the small group sizes and the lack of proof that the EEG Feedback is solely responsible for the clinical benefit and not non-specific factors such as the additional time spent with a therapist or 'cognitive training'. In 2006, Holtmann and Stadtler (2006) concluded that EEG Biofeedback has gained promising empirical support in recent years, but there is still a strong need for more empirically and methodologically sound evaluation studies. Given these different conclusions based on the same literature, a more quantitative approach might be warranted to establish the evidence-based level of neurofeedback treatment in ADHD also including some more recent studies addressing some of the concerns raised.

To date no quantitative meta-analysis has been done on this topic. A meta-analysis provides a powerful approach to integrate many studies and investigate the overall effect across studies. Such an analysis could address some of the issues raised and test the effect size – and hence clinical relevance – of these methods in a quantitative manner. Since ADHD is characterized by persistent symptoms of inattention, impulsivity and/or hyperactivity (DSM-IV, 1994) in this meta-analysis we will investigate the effects of neurofeedback and stimulant medication on the core symptoms of ADHD: Hyperactivity, inattention and impulsivity.

Method

Study selection

The literature was searched for studies investigating neurofeedback or EEG Biofeedback in ADHD children. For this purpose the comprehensive neurofeedback bibliography compiled by Hammond (Hammond, 2008) served as the first basis. Furthermore, a search in PubMed was performed using combinations of the following keywords: 'neurofeedback' or 'EEG Biofeedback' or 'neurotherapy' or 'SCP' or 'Slow Cortical Potentials' and 'ADHD' or 'ADD' or 'Attention Deficit Hyperactivity Disorder' or 'Attention Deficit Disorder'. Furthermore, several authors were contacted who had presented neurofeedback studies in ADHD on conferences (ISNR and Society for Applied Neuroscience (SAN)) during the last 2 years to obtain potential studies that are currently in press.

All these publications were obtained and screened for inclusion criteria. The reference lists of the articles were also crosschecked for any missing studies.

In order to guarantee sufficient scientific rigidity papers had to be published in a peer-reviewed scientific journal or be part of a PhD thesis.

The designs had to comply with the following criteria:

Treated subjects should have a primary diagnosis of ADHD/ADD.

1) Controlled between subject design studies who have used a passive (waiting list) or active (stimulant medication; biofeedback; cognitive training) control groups either randomized or not; or 2) Prospective within subject design studies or 3) Retrospective within subject design studies with a large enough sample to provide a reliable representation of daily practice (N>500).

The neurofeedback treatment was provided in a standardized manner, and no more than two treatment protocols were used.

Standardized pre- and post-assessment means and Standard Deviations (SD's) for at least 1 of the following domains had to be available: Hyperactivity, Inattentiveness or CPT commission errors. When the means and SD's from a given study were not available, they were requested from the authors. Not all authors responded or were still able to retrieve this information, and if there was not sufficient information available the study was excluded from the meta-analysis.

Study grouping

In neurofeedback training several treatment protocols are used, such as SMR enhancement combined with Theta Suppression, Beta enhancement with Theta suppression, and the training of Slow Cortical Potentials (SCP). Most studies use central areas (Cz, C3, C4) as a training site and only few studies included Frontal sites (Fz, FCz). To remain in line with the majority of the literature on EEG frequency bands, for this meta-analysis we classified both SMR/Theta and Beta/Theta training as Beta/Theta training, since the SMR frequency band (12-15 Hz) is part of the Beta-1 frequency spectrum. Furthermore, as explained in the introduction both SCP and theta/beta neurofeedback show comparable effects on the different aspects of ADHD such as inattention, hyperactivity and impulsivity. Therefore, in the current meta-analysis both SCP and theta-beta neurofeedback protocols are investigated in the same analysis. The results from this meta-analysis will be reviewed post-hoc for differential effects of the different training protocols.

Data collection

The following pre- and post-assessment measures were collected from the included studies:

Hyperactivity: Assessed with a DSM rating scale such as Conners (CPRS-R); ADDES-Home, BASC, SNAP, FBB-HKS (parents) or DSM-IV Rating Scale (Lauth & Schlottke).

Inattention: Assessed with an inattention rating scale such as FBB-HKS, Conners (CPRS-R, BASC, ADDES-Home, SNAP/Iowa-Conners) or DSM-IV Rating Scale (Lauth & Schlottke).

Impulsivity: Commission errors on a CPT such as a TOVA, IVA (auditory prudence measure) or Go-NoGo test.

These measures were used as treatment endpoints.

Meta-Analysis

In a meta-analysis, Effect Sizes (ES) are calculated based on the pre-treatment and post-treatment averages and standard deviations taken from the studies included in the meta-analysis. This results in an ES with a 95% confidence interval per study. An ES is a scale free statistic, thus allowing comparison of scores on various instruments. Based on multiple studies a Grand Mean ES is calculated with a 95% confidence interval which provides the weighted ES for al studies which can be considered the true ES for the whole population. ES for the different studies are often plotted in a forest plot providing a graphical overview of all results. The ES is regarded as a measure of 'clinical relevance' in that the higher an ES the higher the clinical relevance.

In this study, two effect sizes were calculated. First, for the controlled between subject design studies the effect size of the neurofeedback group as compared to the control group were calculated. These data were used to compare the outcome after neurofeedback therapy with a control condition. Since some studies have used an active control group (Stimulant medication) or a semi-active control group (attention training (Gevensleben et al., 2009; Holtmann et al., 2009), EMG Biofeedback (Bakhshayesh, 2007) or group-therapy (Drechsler et al., 2007)) the within-subject effect sizes were also calculated and plotted for all ADHD children treated with neurofeedback from both the controlled and the within subject designs.

Effect sizes (ES) were calculated with Hedges' D using the pooled pre-test SD 29, 30 and the pre-post treatment differences for the outcome measures of the controlled studies. For the within-subject analysis the pre- and post-treatment means and SD's were used to calculate the ES. The Grand Mean Effect Size, 95% confidence intervals, Qt (heterogeneity of effect sizes) and Fail-safe number (Rosenthal's method: $\alpha<0.05$) were calculated using MetaWin version 2.1 31. The fail-safe number is the number of studies, indicating how many unpublished null-findings are needed in order to render an effect non-significant.

When the total heterogeneity of a sample (Qt) was significant – indicating that the variance among effect sizes is greater than expected by sampling error – studies were omitted from the meta-analysis one-by-one and the study contributing most to the significance of the Qt value was excluded from further analysis for that variable until the Qt value was no longer significant. This was done for a maximum of 3 iterations. If more than 3 studies needed to be excluded in order to obtain a non-significant Qt value, then other explanatory variables for the effects have to be assumed (Rosenberg, Adams & Gurevitch, 2000). In such a case the results for that variable will not be interpreted further.

Post-Hoc Analysis

Post-hoc analyses were carried out to check for potential differences in methodological approaches and quality of studies. The effect sizes were submitted to a one-way ANOVA to analyze the following variables:

Neurofeedback protocol: SMR/Beta/Theta vs. Beta/Theta vs. SCP protocols as well as SCP protocols vs. all Beta/Theta protocols.

Time: Studies before 2006 and studies after 2006 were compared to check for differences in ES in newer studies.

Studies employing randomization vs. non-randomized studies. Since the a-priori expectation is that randomized studies will have lower ES, we considered a p-value of below 0.1 as significant (one-tailed significance) thus using a strict criterion for this dimension.

Medication: Studies carried out in medicated subjects vs. studies carried out in unmedicated subjects.

Finally, the Pearson correlation coefficient was established between the average number of sessions and the effect size. Since it is expected from learning theory that more sessions will lead to better clinical effects a one-tailed test was performed.

Results

Fifteen studies met all criteria and were included in the meta-analysis. One randomized controlled trial (RCT) from Linden (Linden, Habib & Radojevic, 1996) and one prospective study (Lubar, Swartwood, Swartwood & O'Donnell, 1995) were excluded from the meta-analysis since no SD's were available for those studies. Two double-blind placebo controlled studies by DeBeus (DeBeus, Ball, DeBeus & Harrington, 2004) and Picard (Picard, 2006; Zaidel & Barnea, 2006) and one controlled study by Fine, Goldman & Sandford (1994) were excluded since they were not published and no means and SD's were available.

All studies investigated the effect of neurofeedback in children. An overview of all included studies can be found in Table 1. For all controlled studies there was a total of 476 subjects included in the meta analysis and for the pre- / post-design studies there was a total of 718 subjects included in the meta-analysis. Dropout rates were only reported in 5 studies (Bakhshayesh, 2007; Fuchs, Birbaumer, Lutzenberger, Gruzelier & Kaiser, 2003; Gevensleben et al., 2009; Rossiter, 2004; Strehl et al., 2006) and are therefore not included in table 1. Most reported dropout rates were around 10% for most studies for both treatment and control groups.

Prospective controlled studies

Note that there were two types of controlled studies; studies with a passive or semi-active control group such as a waiting list control group, EMG biofeedback and cognitive training and studies using an active control group such as stimulant medication ('gold standard' treatment for ADHD). These studies have been analyzed separately. Figure 1 shows the results of the meta-analysis for both the studies with a passive control group (black) and an active control group (grey). A positive effect size denotes a decrease in symptoms for that measure. For impulsivity the ES for the neurofeedback vs. stimulant medication group is close to 0; suggesting that neurofeedback has similar effects as compared to stimulant

medication. Furthermore, note the large grand mean ES for inattention (ES=0.81) and impulsivity (ES=0.69) for neurofeedback compared to a control group.

For hyperactivity and inattention there were not enough data available for a valid comparison between methylphenidate and neurofeedback.

Inattention
The test for heterogeneity was significant (Qt=43.47, p=0.0000; mean effect size: 0.9903) meaning that the variance among the effect sizes was greater than expected by sampling error. It was found that the study from Monastra et al. (Monastra, Monastra & George, 2002) (ES=2.22) and Holtmann et al. (2009) (ES=-0.39) contributed most to the significant Qt and were hence excluded from the analysis.

The mean effect size for inattention was 0.8097 (95% confidence interval (CI) 0.39—1.23; Total N=201). The test for heterogeneity was not significant (Qt=3.31, p=0.51). The fail safe number of studies was 52.1, indicating that at least 52 unpublished null-findings are needed in order to render the effect of neurofeedback on attention non-significant.

Hyperactivity
The test for heterogeneity was significant (Qt=16.45, p=0.01153; mean effect size: 0.6583). It was found that the study from Monastra et al. (2002) (ES=1.36) contributed most to the significant Qt and was hence excluded from the analysis.

The mean effect size for hyperactivity was 0.3962 (95% CI 0.05—0.75; Total N=235. The test for heterogeneity was not significant (Qt=2.83, p=0.726). The fail-safe number of studies was 15.4.

Impulsivity
Neurofeedback vs. Control Group
The mean effect size for impulsivity was 0.6862 (95% CI 0.34—1.03; Total N=241). The test for heterogeneity was not significant (Qt=2.63, p=0.757). The fail-safe number of studies was 37.7.

Neurofeedback vs. Methylphenidate
The mean effect size for impulsivity was -0.0393 (95% CI -0.45—0.37; Total N=240). The test for heterogeneity was not significant (Qt=0.26, p=0.967. The fail-safe number of studies was 0.

Table 1

This table shows an overview of all studies used in the meta-analysis. The study numbers correspond to the same numbers in the figures and the references. A total of 476 subjects were included based on prospective controlled studies and 718 subjects for studies employing a pre- post-test design.

Study	Country	Conditions		n	Age	Measure	Instrument	NF Site	Treatment	Mean # Ses.	Notes
PROSPECTIVE CONTROLLED STUDIES											
40) Rossiter & La Vaque 1995	USA	Stimulant control group	ADHD: Control:	23 23	12,9 12,9	Hyperactivity Impulsivity Inattention	BASC TOVA BASC	Cz or FCz-CPz	Beta/Theta 5/23 Medicated	20	
33) Monastra et al. 2002	USA	Control group	ADHD: Control:	51 49	10 10	Hyperactivity Impulsivity Inattention	ADDES TOVA ADDES	CPz and Cz	Beta/Theta Medicated	43	Only included subjects with increased theta/beta ratio Less cortical slowing
27) Fuchs et al. 2003	USA	Stimulant control group	ADHD: Control:	22 11	9,8 9,6	Impulsivity	TOVA	C3 or C4	Beta/Theta Unmedicated	36	
7) Heinrich et al. 2004	DE	Waiting list control	ADHD: Control:	13 9	11,1 10,5	Hyperactivity Impulsivity Inattention	FBB-HKS CPT FBB-HKS	Cz	SCP 8/13 Medicated	25	↑CNV ERP
28) Rossiter 2004	USA	Stimulant control group	ADHD: Control:	31 31	16,6 16,7	Hyperactivity Impulsivity Inattention	BASC TOVA BASC	C3 or C8	Beta/Theta 6/31 Medicated	50	
35) Levesque et al. 2006	CA	RCT Waiting list control	ADHD: Control:	15 5	10,2 10,2	Hyperactivity Impulsivity Inattention	CPRS-R IVA CPRS-R	Cz	Beta/Theta Unmedicated	40	fMRI showed activation of the right ACcd, left caudate and left substantia nigra during Counting Stroop test
29) Bakhshayesh, 2007	DE	RCT Control group EMG Biofeedback	ADHD: Control:	18 17	9,61 9,06	Hyperactivity Impulsivity Inattention	FBB-HKS CPT Commissions FBB-HKS	FCz-CPz	Beta/Theta 4/18 Medicated	30	
18) Drechsler, 2007	CH	Group therapy control group	ADHD: Control:	17 13	10,5 11,2	Hyperactivity Impulsivity Inattention	FBB-HKS TAP: Go-NoGo FBB-HKS	Cz	SCP 6/17 Medicated	30	Doehnert (2008): Post-QEEG: Theta decreased at Oz
10) Gevensleben et al. 2009	DE	RCT Attention training control group	ADHD: Control:	59 35	9,1 9,4	Hyperactivity Inattention	FBB-HKS FBB-HKS	Cz	SCP and Beta/Theta Unmedicated	36	
17) Holtmann et al. 2009	DE	RCT Captain's Log control group	ADHD: Control:	20 14	10,3 10,2	Hyperactivity Impulsivity Inattention	FBB-HKS Go-NoGo FBB-HKS	Cz	Beta/Theta 27/34 Medicated	20	Normalization of Frontal No-Go N2 ERP
			Total N:	476							
PROSPECTIVE PRE- / POST-DESIGN STUDIES											
31) Kropotov et al. 2005	Russia	Pre-/post-design	ADHD:	18	11,4	Hyperactivity Impulsivity Inattention	SNAP-4 Go-NoGo SNAP-4	C3-Fz or C4-Pz	Beta (C3) SMR (C4) Unmedicated	17	Normalization of ERPs for good-performers
32) Xiong et al. 2005	China	Pre-/post-design	ADHD:	60	>6	Omissions	IVA	?	Beta/Theta Unmedicated	40	
30) Strehl et al. 2006	DE	Pre-/post-design Randomized to SCP or Beta/Theta	ADHD:	23	9,3	Hyperactivity Impulsivity Inattention	DSM-IV RS TAP: Go-NoGo DSM-IV RS	Cz	SCP 5/23 Medicated	30	
11) Leins et al. 2007	DE	Pre-/post-design Randomized to SCP or Beta/Theta	ADHD:	19	9,2	Hyperactivity Impulsivity Inattention	DSM-IV RS TAP: Go-NoGo DSM-IV RS	C3f and C4f	Beta/Theta 1/19 Medicated	30	
RETROSPECTIVE PRE-/POST-DESIGN STUDY											
34) Kaiser & Othmer, 2000	USA	Multisite naturalistic pre-/postdesign	ADHD:	530*	17,3	Impulsivity	TOVA	C3, C4	Beta/Theta Unmedicated		
			Total N:	718							

SCP = Slow Cortical Potentials; SMR = Sensorimotor EEG Rhythm; RCT = Randomized Controlled Trial; DSM-IV RS = DSM-IV Rating Scale (Lauth & Schlottke). * The original Kaiser & Othmer sample consisted of 1089 subjects, however Means and SDs were only available for N=530 (Kaiser, personal communication.)

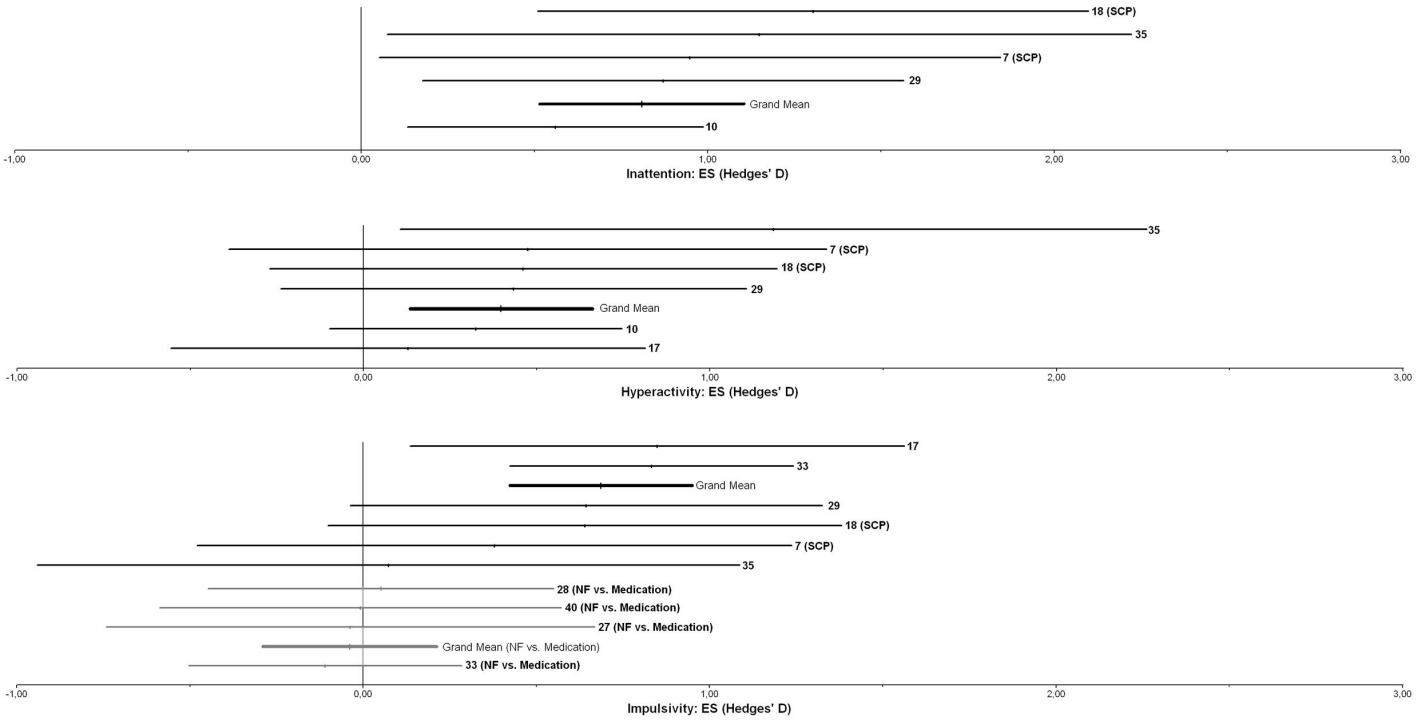


Figure 1: *This graph shows the forest plots for the controlled studies with the ES and their 95% confidence intervals for controlled studies (Black = Neurofeedback vs. Control group; Grey = Neurofeedback vs. Stimulant medication group; SCP neurofeedback studies indicated by 'SCP'). The black bars are the Grand Mean ES for inattention, hyperactivity and impulsivity with the forest plot for impulsivity showing both the ES for neurofeedback compared to control groups (top grand mean) and neurofeedback compared to stimulant medication (bottom grand mean). A positive Effect Size denotes a larger decrease in symptoms for the neurofeedback group as compared to the control group. It can be clearly seen from this figure that most studies had positive ES with Grand Mean ES medium to large and significantly different from zero. Also note that the Grand Mean ES for the comparison of neurofeedback with stimulant medication is almost 0 for impulsivity, indicating that these treatments have similar effects.*

Within-subject effects

In figure 2 the within-subject effect sizes are shown for all studies included in the meta-analysis. Note the high Grand Mean ES for all 3 domains. The study by Strehl et al. (2006) and Leins et al. (2007) showed relatively low ES for hyperactivity and inattention. This is probably caused by the DSM-IV based questionnaire they used which only employs categorical answers (yes/no) whereas all other studies used scales that employed dimensional scales.

Inattention

The test for heterogeneity was significant (Qt=26.07, p=0.006; mean effect size: 1.1126). It was found that the Monastra et al. (2002) (ES=1.45)) study contributed most to the significant Qt. This study combined a Comprehensive Clinical Care plan with neurofeedback which might partly explain this finding. Furthermore, this study selected subjects based on an increased theta/beta ratio and hence might not have been a representative ADHD group.

This selection might have led to inclusion of a sub-group of ADHD patients, which are good responders to neurofeedback, hence explaining the large ES.

The mean effect size for inattention after excluding this study was 1.0238 (95% CI 0.84—1.21; Total N=324). The test for heterogeneity was not significant (Qt=16.26, p=0.093) meaning that the variance among the effect sizes was not greater than expected by sampling error. The fail-safe number of studies was 508.6.

Hyperactivity

The mean effect size for hyperactivity was 0.7082 (95% CI 0.54—0.87; Total N=375). The test for heterogeneity was not significant (Qt=13.57, p=0.258) meaning that the variance among the effect sizes was greater than expected by sampling error. The fail-safe number of studies was 320.3.

Impulsivity

The test for heterogeneity was significant (Qt=24.93, p=0.015; mean effect size: 0.7487). It was found that the Kaiser & Othmer study (Kaiser & Othmer, 2000) (ES=0.63) contributed most to the significant Qt. This was also the only naturalistic study; hence the effect size was calculated excluding this study.

The mean effect size for impulsivity was 0.9394 (95% CI 0.76—1.12; Total N=338). The test for heterogeneity was not significant (Qt=16.15, p=0.135) meaning that the variance among the effect sizes was not greater than expected by sampling error. The fail-safe number of studies was 511.7.

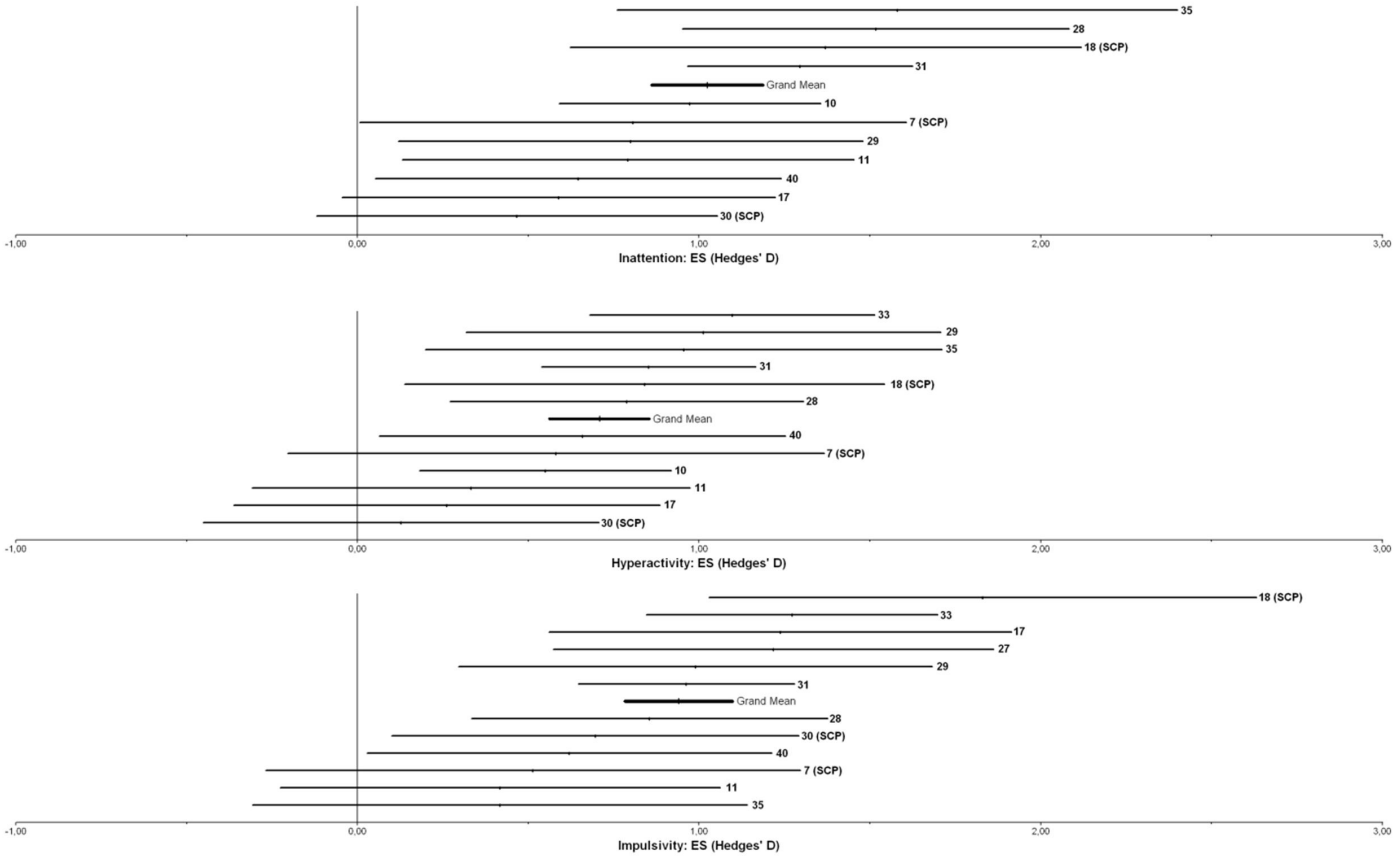


Figure 2: *This graph shows the forest plots for the within-subject ES for inattention (ES= 1.02), hyperactivity (ES=0.71) and impulsivity (ES=0.94). The SCP studies are indicated by 'SCP', the other studies are the Theta/Beta studies and the black bar represents the Grand Mean ES. All ES are shown with their 95% confidence intervals and numbers correspond to the studies in table 1. It can be clearly seen that all studies show positive ES and most are significant from 0 given their 95% confidence intervals.*

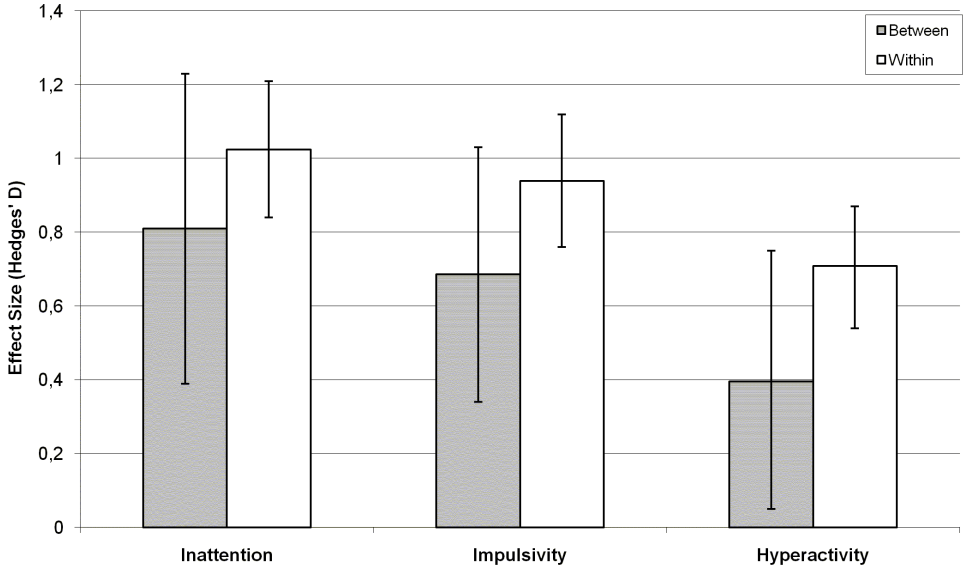


Figure 3: *This figure shows the grand mean ES for the controlled studies compared to the within-subject effect sizes for all studies for all 3-core ADHD symptoms. Note that the ES for the controlled studies are slightly smaller, which could be due to the fact that many controlled studies used a 'semi-active' control group. Furthermore, given the 95% confidence intervals the ES for inattention, hyperactivity and impulsivity are significant for both comparisons.*

Post-hoc analysis

Post-hoc analysis did not reveal any differences in effect size between studies 1) employing SMR/Theta, Beta/Theta, SMR/Beta/Theta and SCP neurofeedback protocols. Also no differences were found between SCP studies on the one hand and all Beta/Theta studies on the other hand and no effect was found for 2) Time. It can also be seen from the Forest plots that there is no clear relation between ES and time, since the studies are numbered in chronological order. No significant differences were found between studies carried out in medicated vs. unmedicated subjects. For this purpose the ES for studies with no medicated subjects (Fuchs et al., 2003; Gevensleben et al., 2009; Kaiser & Othmer, 2000; Kropotov et al., 2005; Lévesque, Beauregard & Mensour, 2006; Xiong, Shi & Xu, 2005) were compared against the other studies. Most studies only included a minority of medicated subjects. In total 113 subjects treated with neurofeedback were on medication from a total of 973 subjects (12%).

For randomization there was a significant effect for the hyperactivity scale only (p=.080; F=3.716; df=1, 11), demonstrating that the ES for randomized studies was lower (ES=0.54) as compared to nonrandomized studies (ES=0.80). For inattention and impulsivity there were no differences.

There was a significant correlation between the average number of sessions in studies and improvement of inattention (p=0.04; r=.550) but not for impulsivity and hyperactivity, meaning that better effects on inattention are achieved with more sessions, also see figure 4 below.

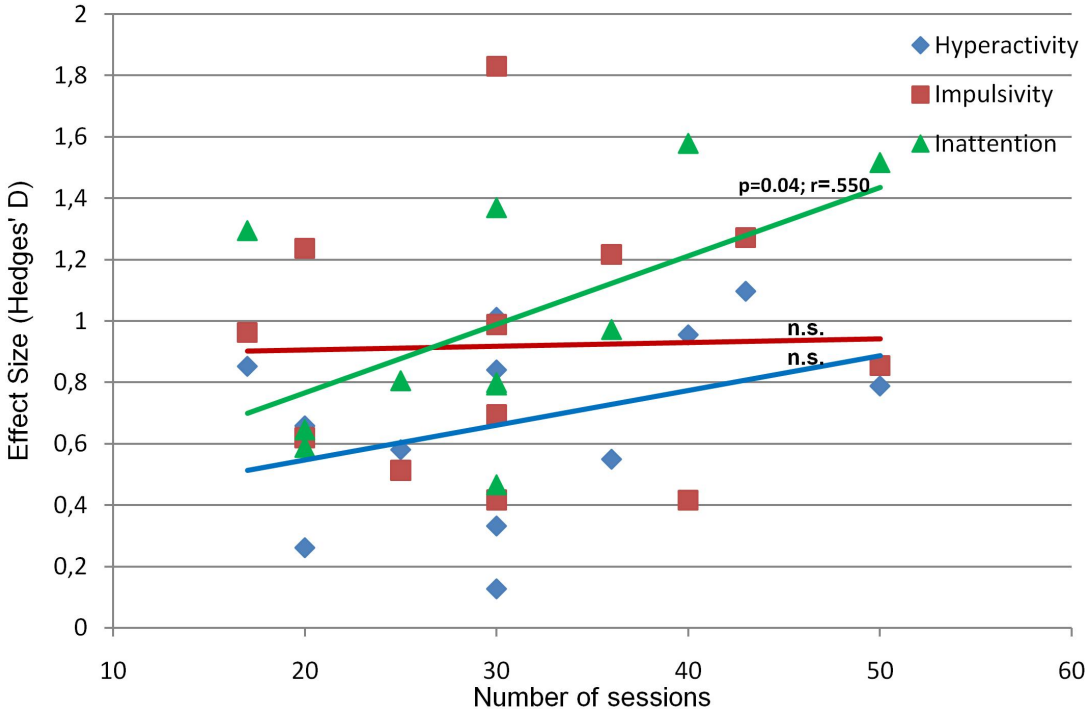


Figure 4: *This figure shows the correlation between number of sessions (horizontal) and the ES (vertical) for the different studies. This figure shows the association for inattention (which was significant) and that there is an effect of a larger number of sessions.*

Discussion

This study investigated the effects of neurofeedback therapy on core symptoms of ADHD using a meta-analytic approach. Fifteen studies were found fulfilling our criteria, with a total of 1194 subjects and the majority of studies conducted in Germany (6 studies) and the USA (5 studies). Four studies employed randomized allocation of subjects and 3 studies compared neurofeedback with stimulant medication (the current 'gold standard' in the treatment of ADHD). The study by Bakhshayesh (2007) was a PhD thesis, however this manuscript has also been submitted for publication in an international journal (Bakhshayesh, personal communication).

From the controlled studies in the meta-analysis it was evident that neurofeedback had large effect sizes (Cohen, 1992) on inattention and impulsivity and a medium ES for hyperactivity. Many of these controlled studies have used semi-active control groups such as cognitive training (Gevensleben et al., 2009; Holtmann et al., 2009) EMG Biofeedback (Bakhshayesh, 2007) or group-therapy (Drechsler et al., 2007). Since it is known that cognitive training for instance can improve ADHD symptoms such as inattention and hyperactivity/impulsivity (Klingberg et al., 2005; Toplak, Connors, Shuster, Knezevic & Parks, 2008) the within-subject ES were also calculated. These showed large effect sizes. They were significant for each of the core symptoms: Inattention, impulsivity and hyperactivity. For an overview of ES from controlled studies as well as those of within subject effects also see Figure 3.

From Figure 1 it can be clearly seen that the studies from Bakhshayesh (2007), Gevensleben et al (2009) and Holtmann et al. (2009) have the lowest ES for hyperactivity. These were exactly the 3 studies that all employed a semi-active control group in a randomized design. The fact that the ES for hyperactivity was significantly lower – though still a medium ES - for randomized studies suggests that hyperactivity is probably most sensitive to non-specific treatment factors. Future studies should use randomization in order to provide evidence for treatment effects on hyperactivity.

Interestingly, post-hoc analyses did not reveal any differences between the different neurofeedback approaches used such as theta/beta, SMR theta and SCP neurofeedback nor a differential efficacy for the 3 domains. Given Lubar's initial rationale to use SMR training in hyperkinetic syndrome we expected a higher ES for hyperactivity in SMR/theta studies. This was not the case. This lends further support to the fact that these approaches modulate activity in the same underlying neurophysiological network. However, further research is needed to investigate this issue. There also were no differences between neurofeedback studies in medicated vs. unmedicated subjects. Only 12% of all subjects in this meta-analysis were on medication. Although it was not possible to separate the effects within the studies, these results tend to suggest that the effects of neurofeedback are similar for medicated and unmedicated subjects. Further research on the impact of medication on neurofeedback is also needed.

There are several issues when interpreting meta-analytical data. For instance the selection of studies and relevant variables is directly related to the quality of the outcome of the meta-analysis. Furthermore, there is the possibility of publication bias causing a higher ES due to unpublished results of null findings also referred to as the 'file drawer problem'

(Rosenberg et al., 2000). The fail-safe numbers in relation to the number of included studies were rather high in this study. The fail-safe number is the number of non-significant unpublished studies to be added to the meta-analysis to change the results of the meta-analysis from significant to not significant. The fail-safe number for controlled studies was 15 for hyperactivity, 52 for inattention and 37 for impulsivity. The fail-safe number for within-subject studies was 320 for hyperactivity and more than 500 for inattention and impulsivity. It seems rather unlikely that such numbers of studies with null-findings exist and have not been published.

This 'file-drawer problem' was further addressed by the a-priori selection of treatment end-points and requesting additional (unpublished) data from authors if required. Most studies reported many results, such as rating scale data for inattention and impulsivity and a range of neuropsychological tests. For this meta-analysis we specifically defined the measures to be included for the 3 domains a priori, such as rating scale data for hyperactivity and inattention and commission errors on a CPT test as a measure of impulsivity. Since most authors will focus their papers mostly on the significant findings of their study, our approach aimed at minimizing the risk of over-estimating the effect sizes. In many cases (such as: Heinrich et al., (2004), Lévesque et al., (2006), Strehl et al., (2006), Leins et al., (2007)) we requested the means and SD's for the commission errors and/or rating scale data which in some cases were not even significant for that study.

In the past several criticisms have been raised about studies investigating the efficacy of neurofeedback in the treatment of ADHD for instance by Loo and Barkley (2005) and Holtmann and Stadtler (2006) as regards to small sample sizes, lack of adequate control group, no randomization, disregard of long term outcome. Below we will address these critical issues in the light of the many recently conducted studies.

Randomization

In this meta-analysis support was found for the need of randomized trials, given the fact that ES were significantly smaller for randomized trials for hyperactivity scales, but not for inattention and impulsivity. The average effect size for randomized studies was still medium (ES=0.54). Furthermore, in this meta-analysis the results of 6 randomized studies have been incorporated, with all showing medium to high effect sizes for inattention and impulsivity and low to high effect sizes for hyperactivity. Indeed randomization is required in order to conduct reliable studies, but it can be concluded that randomized studies so far still show large effect sizes for inattention and impulsivity.

Sample-size

The largest studies to date are the studies by Monastra et al. (2002) (N=100), Gevensleben et al. (2009) (N=94) and Kaiser & Othmer (2000) (original study N=1089; data available in this meta-analysis N=530; Kaiser, personal communication). The results from the Monastra study (2002) need to be interpreted with caution since this study was excluded from most analysis since it contributed most to the heterogeneity of effect sizes (Qt). This is probably related to the fact that subjects in that study besides neurofeedback and Ritalin also received a Comprehensive Clinical Care program, leading to higher ES as compared to the

other studies. Furthermore, the Monastra study (2002) only included subjects with an increased theta/beta ratio, thereby potentially selecting those subjects who could benefit most from neurofeedback treatment. The subjects in that study might therefore not have been representative of the general ADHD population, which might have led to the observed high ES. The study by Gevensleben et al. (2009) is the most methodologically sound study to date. It included randomization, a large sample size and a multi-center approach. This study showed a medium ES for hyperactivity (ES=0.55) and a large ES for inattention (ES=0.97). Finally, the Kaiser & Othmer study (2000) is the largest study to date. For impulsivity the ES was medium (ES=0.63), but this value was excluded from the analysis since this study contributed most to the heterogeneity of effect sizes. This can probably be explained by the fact that this study was a naturalistic study and was methodologically the least controlled study included in the meta-analysis. However, this medium ES of a large uncontrolled naturalistic study does further demonstrate the ecological validity of neurofeedback in clinical practice.

Finally, the current meta-analysis also addresses the issue of small-sample size by combining all studies into a meta-analysis, thereby further addressing the sample size concern.

Adequate control groups

In the past it has been suggested by many authors that a potential explanation of the effects of neurofeedback could stem from 'cognitive training' since children are engaging in a feedback task for often 30-50 sessions. Furthermore, it has been suggested that the time spent with a therapist could be an explanation for the treatment effects. Such concerns could be addressed by double-blind controlled studies.

Given the difficulty of conducting a double-blind placebo controlled study in neurofeedback, which is likely to be associated with high drop-out rates in the control group (Orlandi & Greco, 2005) several groups have still addressed these concerns. For instance, Gevensleben et al. (2009) and Holtmann et al. (2009) have used control groups who were intensively and equally trained on an attention demanding task (computerized cognitive training) to control for these unspecific effects. Furthermore, Drechsler et al (2007) used a control group undergoing group-therapy and Bakhshayesh (2007) used an EMG Biofeedback group as a control group. In all these studies neurofeedback in comparison to this semi-active control group still had medium to large ES for inattention and impulsivity, and small to medium ES for hyperactivity. Especially the control groups used by Gevensleben et al. (2009), Holtmann et al. (2009) and Bakhshayesh (2007) can be considered a credible sham control, with even 'active' properties expected to show improvements on symptoms such as working memory, inattention and hyperactivity/impulsivity (Klingberg et al., 2005; Toplak et al., 2008).

None of the studies comparing neurofeedback with stimulant medication used random assignment. Participants self-selected the treatment of their preference. This may bias these results, however self selection potentially maximizes the effects of expectancy in both groups. Failure to find a significant difference between treatments in small unrandomized trials (possibly a type 2 error) does not prove that neurofeedback is as good as stimulant medication. More studies using randomization and larger sample sizes are needed to

investigate further how neurofeedback compares to stimulant medication in the treatment of ADHD.

Publication in unsubscribed journals

Many studies in the past have only been published in neurofeedback specific journals such as the Journal of Neurotherapy (which is not indexed by Medline) and Applied Psychophysiology and Biofeedback. As can be seen from the studies in Table 1 most of the recent studies have been published in journals with higher impact factors, which are indexed in Medline such as Biological Psychiatry, Neuroscience Letters and Pediatrics.

Long term effects

Long-term effects could not be addressed in this meta analysis. However, several studies did report follow-up results. Heinrich et al. (2004) performed 3 months follow-up for the SCP group and found all measures improving further (Heinrich, personal communication: Unpublished results). For the study of Strehl and colleagues 6 months follow-up scores in impulsivity, inattention and hyperactivity were shown to improve even further as compared to the end of treatment (Leins et al., 2007; Strehl et al., 2006). A 2-year follow-up for this study (Gani, Birbaumer & Strehl, 2008) showed that all improvements in behavior and attention turned out to be stable. Test results for attention and some of the parents' ratings once more improved significantly. In addition, EEG-self regulation skills turned out to be still preserved, indicating that these children were still able to successfully regulate their brain activity.

Taken together, it can be concluded that the clinical effects of neurofeedback are stable and might even improve further with time. This, in contrast to stimulant medication where it is known that when the medication is stopped often the initial complaints will come back again and recent evidence showing that temporary treatment with stimulant medication is not likely to improve long-term outcomes (Molina et al., 2009).

Pre- and post-QEEG differences

Finally, it is often stated that studies do not - or fail to report pre- and post-QEEG differences since the EEG is the basis of treatment in neurofeedback (for example see: Loo & Barkley, (2005)). However, this is not a credible reason to criticize the clinical efficacy of neurofeedback or any other treatment. The primary question is 'does it work?', and a secondary question which is not addressed in this paper is 'how does it work?'. Other clinical trials into psychoactive medication or other neuromodulation techniques also do not demonstrate this. For example, a study investigating pre- and post QEEG and ERP (Event Related Potential) data after 20 sessions of rapid Transcranial Magnetic Stimulation (rTMS) in depressed patients also failed to find any pre- and post-QEEG differences, but did find localized changes in ERP's (Spronk, Arns, Bootsma, van Ruth & Fitzgerald, 2008). rTMS treatment is also based on the assumption of frontal-asymmetry, often reported in EEG studies as well (Baehr, Rosenfeld & Baehr, 2001; Baehr, Rosenfeld, Baehr & Earnest, 1998).

Interestingly, several studies did find a normalization of ERP's as a result of neurofeedback (Heinrich et al., 2004; Holtmann et al., 2009; Kropotov et al., 2005) as can be seen in table 1 suggesting that rather task-related EEG (or ERPs) but not passive Eyes Open and Eyes Closed EEG should be further investigated. In our opinion, passive EEG such as Eyes Open and Eyes Closed EEG should be seen as a stable trait marker or Phenotype (Arns et al., 2008; Johnstone et al., 2005) and should hence not be considered a valid treatment end-point, whereas disorder specific behavioral questionnaires and/or event related EEG or ERPs should be the primary treatment end-points.

Conclusion

Due to the inclusion of some very recent and sound methodological studies in this meta-analysis many potential confounding factors have been addressed and the clinical effects of neurofeedback in the treatment of ADHD can be regarded as clinically meaningful with large effect sizes for inattention and impulsivity and a medium ES for hyperactivity.

The three randomized controlled trials from Bakhshayesh (2007), Gevensleben et al. (2009) and Holtmann et al. (2009) have shown neurofeedback to be superior to a (semi-active) control group. The semi-active control group in these studies can be regarded as a credible sham control providing an equal level of cognitive training and client-therapist interaction. Therefore, in line with the guidelines for rating clinical efficacy, we conclude that neurofeedback treatment for ADHD can be considered 'Efficacious and Specific' (level 5) with a high ES for inattention and impulsivity and a medium ES for hyperactivity.

Acknowledgement

We wish to acknowledge the following people for providing us with additional information for the meta-analysis: Hartmut Heinrich, Petra Studer, Jochen Kaiser, David Kaiser, Michael Linden, Johanne Lévesque, Martin Holtmann, Ulrike Leins, Domenic Greco, André Achim, Geneviève Moreau and Ali Reza Bakhshayesh. We also wish to acknowledge the support of Desiree Spronk in the preparation of this manuscript.

Chapter 6

The effects of QEEG-*informed* neurofeedback in ADHD: An open-label pilot study.

Arns, M., Drinkenburg, W.H.I.M. & Kenemans, J.L. (submitted) The effects of QEEG-*informed* neurofeedback in ADHD: An Open-label pilot study. *Applied Psychophysioloy and Biofeedback.*

Abstract

Background: In ADHD several EEG biomarkers have been described before, with relevance to treatment outcome to stimulant medication. This pilot-study aimed at personalizing neurofeedback treatment to these specific sub-groups to investigate if such an approach leads to improved clinical outcomes. Furthermore, pre- and post-treatment EEG and ERP changes were investigated to also investigate the neurophysiological effects of neurofeedback.

Methods: Twenty-one patients with ADHD were treated with QEEG-informed neurofeedback and post-treatment effects on inattention (ATT), hyperactivity/impulsivity (HI) and comorbid depressive symptoms were investigated as well as pre- to post-treatment changes in EEG and ERP variables for a sub-group of patients treated with SMR neurofeedback.

Results: There was a significant improvement for both ATT, HI and comorbid depressive complaints after QEEG-informed neurofeedback. The ES for ATT was 1.78 and for HI was 1.22. Furthermore, anterior individual alpha peak frequency (iAPF) demonstrated a strong relation to improvement on comorbid depressive complaints. Pre- and post-treatment effects for the SMR neurofeedback group exhibited increased N200 and P300 amplitudes and decreased SMR EEG power post-treatment.

Conclusions: This pilot study is the first study demonstrating that it is possible to select neurofeedback protocols based on individual EEG biomarkers and suggests this results in improved treatment outcome specifically for ATT, however these results should be replicated in further controlled studies. A slow anterior iAPF at baseline predicts poor treatment response on comorbid depressive complaints in line with studies in depression. The effects of SMR neurofeedback resulted in specific ERP and EEG changes. The effect of SMR neurofeedback is speculated to be the result of improved sleep, resolving sleep onset insomnia in ADHD subsequently resulting in improved vigilance regulation and concomitant behavioral improvements.

Introduction

The development of personalized medicine in psychiatry has received increased interest, with a quest for biomarkers that can be used to predict treatment outcome to specific therapies. Stratification of patient subgroups is one of the basic approaches to personalized medicine. This can be achieved for example by measures of brain function such as the EEG. In ADHD it has been reported that ADHD patients with excess frontal theta EEG power (Arns, Gunkelman, Breteler, & Spronk, 2008; Clarke, Barry, McCarthy, Selikowitz, & Croft, 2002; Satterfield, Lesser, & Podosin, 1971) and excess frontal alpha EEG power (Arns et al., 2008; Chabot, Orgill, Crawford, Harris, & Serfontein, 1999) are more likely to respond to stimulant medication. Furthermore, a low-voltage EEG occurs more often in ADHD as compared to controls Arns et al. (2008). Conceptually, stratification in these 3 'sub-groups' has been interpreted as sub-groups of ADHD patients exhibiting a lower and more instable vigilance regulation, while the ADHD symptoms are explained by so-called 'vigilance auto-stabilization behavior' (Hegerl, Himmerich, Engmann, & Hensch, 2010; Sander, Arns, Olbrich, & Hegerl, 2010). This, in turn would be consistent with the efficacy of stimulant medication in these sub-groups.

Another reported neurophysiological sub-group is composed of patients showing an excess beta or beta spindling (Arns et al., 2008; Chabot & Serfontein, 1996; Clarke, Barry, McCarthy, & Selikowitz, 2001) who were reported to respond to stimulant medication by Clarke and co-workers (Clarke et al., 2003) whereas Arns and co-workers (2008) reported a lack of a significant improvement on impulsivity and inattention (ATT) after stimulant medication. Finally, ADHD patients with a slowed individual Alpha Peak Frequency (iAPF) do not respond to stimulant medication (Arns et al., 2008) which presumably characterizes a non-specific trait of non-response to various treatments because deviations in this measure have also been found in non-responders (NR) to antidepressants (Ulrich, Renfordt, Zeller, & Frick, 1984) and repetitive transcranial magnetic stimulation (rTMS) in depression (Arns, Spronk, & Fitzgerald, 2010; Conca et al., 2000).

Classical conditioning of the EEG has been shown as early as in 1935 (Durup & Fessard, 1935) and Jasper and Shagass demonstrated that conditioning of the alpha-blocking response demonstrated all of the Pavlovian types of conditioned responses (Jasper & Shagass, 1941a). In a subsequent study the first demonstration of voluntary control of the alpha-blocking response based on classical conditioning principles was demonstrated (Jasper & Shagass, 1941b) which laid the foundation for techniques we currently know as Brain Computer Interfaces (BCI) and neurofeedback. The clinical applications of these techniques were not discovered until the beginning of the 1960's by Kamiya and Sterman (For review see: Kamiya, 2011; Sterman, LoPresti, & Fairchild, 2010). The first clinical application of neurofeedback in ADHD was not reported until 1976 (Lubar & Shouse, 1976).

Recently a meta-analysis on the effects of neurofeedback in the treatment of ADHD has been published in which it was concluded that neurofeedback resulted in large and clinically relevant effect sizes (ES) for ATT and impulsivity and a low to medium ES for hyperactivity (Arns et al., 2009). Furthermore, several studies have demonstrated that the effects of neurofeedback are maintained over 6 months follow-up (Gevensleben et al., 2010; Leins et al., 2007; Strehl et al., 2006). However, several recent studies employing placebo controlled

designs failed to find a difference between neurofeedback and sham-neurofeedback consisting of a non-contingent feedback control condition (Lansbergen, van Dongen-Boomsma, Buitelaar, & Slaats-Willemse, 2011; Perreau-Linck, Lessard, Levesque, & Beauregard, 2010). Although both comprised small sample sizes (Perreau-Linck et al., (2010): N=4 and Lansbergen et al. (2011): N=8) and had methodological limitations such as the use of auto-tresholding and unconventional QEEG based protocols (Lansbergen et al., 2011) these studies warrant more research into the specificity of neurofeedback in ADHD.

In a pioneering study by Monastra et al. (2002) only ADHD patients with a deviating theta/beta ratio were selected and treated with theta/beta neurofeedback, which resulted in a substantial ES of 1.8 on ATT, which for that reason was excluded from the meta-analysis by Arns et al. (2009). Therefore, in this study we aimed to personalize the neurofeedback protocol based on the individual EEG pattern – as described above - to investigate if such an approach leads to better clinical results as compared to Arns et al. (2009). Additionally we expect that patients with a slow iAPF will be NR to neurofeedback. Furthermore, pre- and post-treatment EEG and ERP changes will be investigated to investigate if neurofeedback results in any neurophysiological changes suggestive of a neurophysiological normalization, which is assumed to be the rationale behind neurofeedback.

Methods

Participants

This study is an open-label pilot study. All files from patients seen in our clinic (Brainclinics, Nijmegen, The Netherlands) between August 12th 2008 and September 12th 2010 were screened. Patients were screened for ADHD or ADD by a clinical psychologist using a structured interview (MINI Plus Dutch version 5.0.0, for adults or MINI KID for children) during intake. During intake, every 10th session and outtake a DSM-IV based self-report scale for ADHD symptoms (Kooij et al., 2005) was assessed. Mood disorders are very common in (adult) ADHD (38%: Kessler et al., 2006) hence the Becks depression Inventory (BDI) was also assessed when comorbid depressive complaints were present at screening. Only subjects with a primary diagnosis of ADHD/ADD were included in the study. Only results at pre-treatment, mid-treatment and at post-treatment will be reported. All patients signed an informed consent form before treatment was initiated.

Pre- and post-assessments: QEEG and ERP's

EEG and ERP recordings were performed using a standardized methodology, details of this procedure have been published elsewhere (Arns et al., 2008; Spronk, Arns, Bootsma, van Ruth, & Fitzgerald, 2008; Williams et al., 2005) and details of reliability, validity and across site-consistency of this EEG and ERP procedure have been published here (Clark et al., 2006; Paul et al., 2007; Williams et al., 2005).

QEEG informed neurofeedback protocols

The QEEG was used to establish the neurofeedback protocol by visual inspection of the raw EEG followed by inspection of the deviating Z-scores after comparison to the Brain Resource International Brain database. More details on this procedure for the use in ADHD have been published by Williams and coworkers (2010). The QEEG informed selection of neurofeedback protocols in line with the 4 ADHD subtypes presented in the introduction (Frontal Theta, Frontal Alpha, Low Voltage and Excess Beta) was based on the decision rules as outlined below. These subtypes and recommendations are in line with the EEG Phenotype approach (see: Johnstone, Gunkelman, & Lunt, 2005) for more details and background). For most clients two neurofeedback protocols were used throughout the treatment, with the goal to use at least one of the well-established protocols (SMR/Theta or Theta/Beta) and one additional protocol based on other QEEG findings and symptoms. The locations for C3 and C4 for the SMR protocol were established using TMS to localize the area where a visual response of the musculus abductor pollicis (thumb movement) was observed, in order to also personalize the neurofeedback location to be exactly localized above the sensori-motor strip.

The following decision rules were used to obtain QEEG-informed neurofeedback protocols:

1) Frontocentral Theta/(beta) protocol: If excess fronto-central theta was observed then the midline site (Fz, FCz or Cz) where this activity was maximal was chosen and the exact theta frequency band was determined from the QEEG report by inspecting the Z-scores for single hertz bins in the theta frequency range. In these patients hence a theta/beta protocol was used with an additional reward on beta (15-20 Hz). When there was beta-excess, only theta would be downtrained and no beta reward was used. When theta was normal but beta was decreased only beta was rewarded.
2) Frontocentral alpha protocol: If there was excess fronto-central alpha (especially during eyes open) then the midline site where this activity was maximal was chosen and next this activity was downtrained. If there was no excess beta activity or beta spindles then a beta reward was also used.
3) Beta-downtraining protocol: If excess beta or beta spindles were present then the site where this activity was maximal (Z-score) was identified and selected as training site. The exact training frequency was established from the QEEG single Hz bin Z-scores and this frequency was specifically downtrained. No further inhibits or rewards were used.
4) A Low-Voltage EEG: If this type of EEG was observed, then an 'SMR protocol' was used (either rewarding SMR spindles with a 0.25 s. duration, or SMR/theta at C3/C4). When there was also a lack of alpha power during eyes closed, alpha uptraining during Eyes Closed at Pz (Alpha-uptraining protocol) was added, as suggested by Johnstone and coworkers (2005).
5) If there were no clear QEEG deviations and/or if sleep problems were a main complaint, then an 'SMR protocol' was used (the side was chosen based on the location where the 12-15 Hz activity was lowest).

In all protocols EMG inhibits were employed whereby the EMG (55-100 Hz) had to be kept below 5-10 µV. An overview of all protocols used in this study is depicted in table 2.

Neurofeedback Treatment

Treatment was carried out by a masters level psychologist specialized in neurofeedback, supervised by the first author. Sessions took place 2-3 times a week, for 20-30 minutes provided in 5 minute blocks separated by a 2 minutes pause. The wireless Brainquiry PET 4.0 (Brainquiry B.V.) and BioExplorer software (CyberEvolution, Inc.) were used to provide visual feedback (bargraphs or neuropuzzles) and auditory feedback. Tresholds were set to achieve a 75-80% reward per training contingency. For discrete SMR training the threshold was aimed at providing 1 minute reward during a 5 minute period, or adjusted consequently.

Data analysis

Clinical outcome

All patients treated have been included in the analysis, including patients who dropped out or who did not respond to treatment.

ADHD patients were classified into the following groups based on outtake data:

- Responder (R): At least a 50% reduction on one or both subscales of the ADHD self-report rating scale (ATT or Hyperactivity/Impulsivity (HI)) at outtake.
- Drop-out (DO): When a patient did not take more than 20 sessions and could not be classified a responder. A last observation carried forward (LOCF) procedure was used to handle these data in that the last available scores (at session 10) were used as 'outtake'.
- Non-responder (NR): A patient not meeting criteria for being a 'responder' who finished more than 20 sessions of neurofeedback.

EEG and ERP variables

The employed method used for calculation of the iAPF has been published before (Doppelmayr, Klimesch, Pachinger, & Ripper, 1998; Lansbergen, Arns, van Dongen-Boomsma, Spronk, & Buitelaar, 2011) but in summary consisted of EOG correction of eyes open (EO) and eyes closed (EC) EEG data (Gratton, Coles, & Donchin, 1983); filtering (1-40 Hz), segmentation in 8 sec. epochs and manual de-artifacting using Brain Vision Analyzer 2.0 (BVA). The FFT power spectrum (6-13 Hz for children and 7-13 Hz for adults) from EO was deducted from the FFT power spectrum from and the maximum (representative of maximum alpha suppression) was established at P3, Pz, P4, O1, Oz or O2. Furthermore, the average iAPF at anterior sites (F3, Fz and F4) was scored at the frequency with maximum alpha suppression. Data from the SMR (12-15 Hz), Alpha (8-12 Hz) and Beta band (15-20 Hz) were extracted using an FFT for pre- and post-treatment EEG's for EO and EC.

Conventional ERP averages were calculated at Pz. The peaks (amplitude and latency) of the N100, P200, N200 and P300 for the target waveforms of the ERP component were identified (relative to a pre-stimulus baseline average of -300 to 0 ms).

Statistical analysis

A repeated measures ANOVA with factor time (3 levels, pre-; mid-; and post-treatment) and between factor Child-Adult was used to investigate the effects on ATT and HI. One-way ANOVA's were used to investigate whether there were any baseline differences between R and NR on ATT, HI, BDI scores and iAPF and posterior and anterior iAPF were correlated with ATT, HI and BDI.

Pre- and post-treatment differences on ERP components were assessed using a repeated measures ANOVA with factor time (pre- and post-treatment) and for EEG power (alpha, SMR and Beta) using a repeated measures ANOVA with factor time (pre- and post-treatment) and a factor site (9 channels: FC3, FCz, FC4, C3, Cz, C4, CP3, CPz and CP4) and the within subject factor condition (Eyes Open or Eyes Closed).

The within group ES for the neurofeedback effects were calculated using MetaWin 2.1 and these were plotted against the effect sizes from the meta-analysis obtained for the whole meta-analysis (Arns et al., 2009) and the ES for Monastra et al. (2002).

Results

Clinical Outcome

Table 1 shows the sample characteristics and the neurofeedback protocols used. Note that 1/3th of the sample consisted of children and 2/3th consisted of adults with ADHD/ADD, and approximately half of the sample was diagnosed with ADD (N=11) and the other half with ADHD (N=10). Six patients were medicated with methylphenidate, one with dextro-amphetamine, one with citalopram and one with risperidon.

General response rate was 76% (16/21), with 3 patients classified as a NR (14%) and 2 as a DO (10%). See figure 1 and figure 3 for an overview of the results. Figure 1 demonstrates the effects on ATT and HI, whereas figure 3 shows the effects on the BDI reflective of comorbid depressive symptoms. For figure 3 only data from 12 subjects were available, since they initially presented with elevated depression scores whereas the remaining 9 subjects did not.

Table 1: *Sample characteristics and neurofeedback protocols used in the present study.*

Sample characteristics	
Age	29,95 (SD: 16,19) years
Gender	8 female / 13 male
Children / Adults	7 children / 14 adults
Medicated	9 / 21
ADD / ADHD	11 / 10
Number of sessions	33.62 (SD: 16.09)
Neurofeedback protocols:	
SMR protocol	15/21
Theta/(beta) protocol	6/21
Beta-downtraining protocol	7/21
Frontal Alpha protocol	3/21
Alpha-uptraining protocol	6/21

The analysis only revealed highly significant effects of time (ATT: p=.000; F=16.377; DF=2, 18; HI: p=.001; F=10.795; DF=2, 18; BDI: p=.003; F=14.517; DF=2, 7) but no significant ATT X Child-Adult or impulsivity X Child-Adult interactions, suggesting the effects of neurofeedback were similar for children and adults. Also see figure 1 for the scores on ATT and HI over time. There were no differences between R and NR on ATT, HI and BDI at baseline.

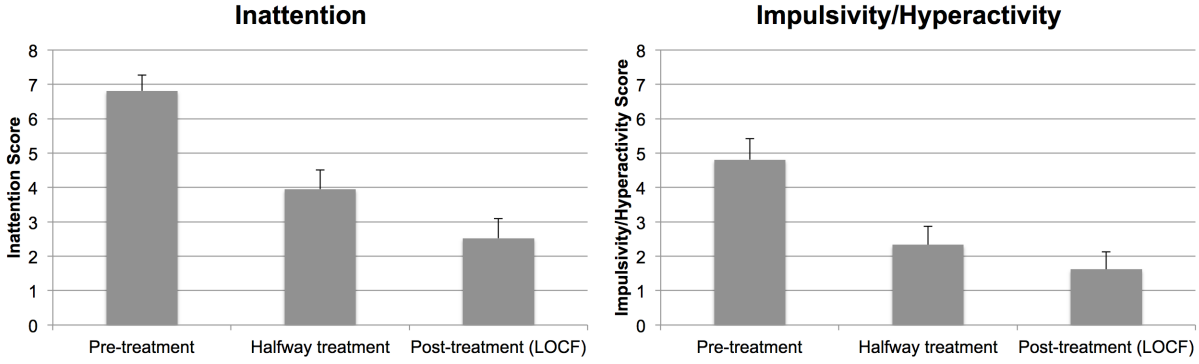


Figure 1: *Clinical effects over time for the total group of ADHD/ADD patients at pre-treatment, halfway treatment and post-treatment (averages plus SEM) for ATT and HI. All time effects were highly significant (p≤.001)*

Figure 2 below shows that the within subject ES from the current study for ATT was 1.78 and for HI was 1.22, compared to the within subject ES obtained from the meta-analysis (Arns et al., 2009) and the Monastra et al. (2002) study

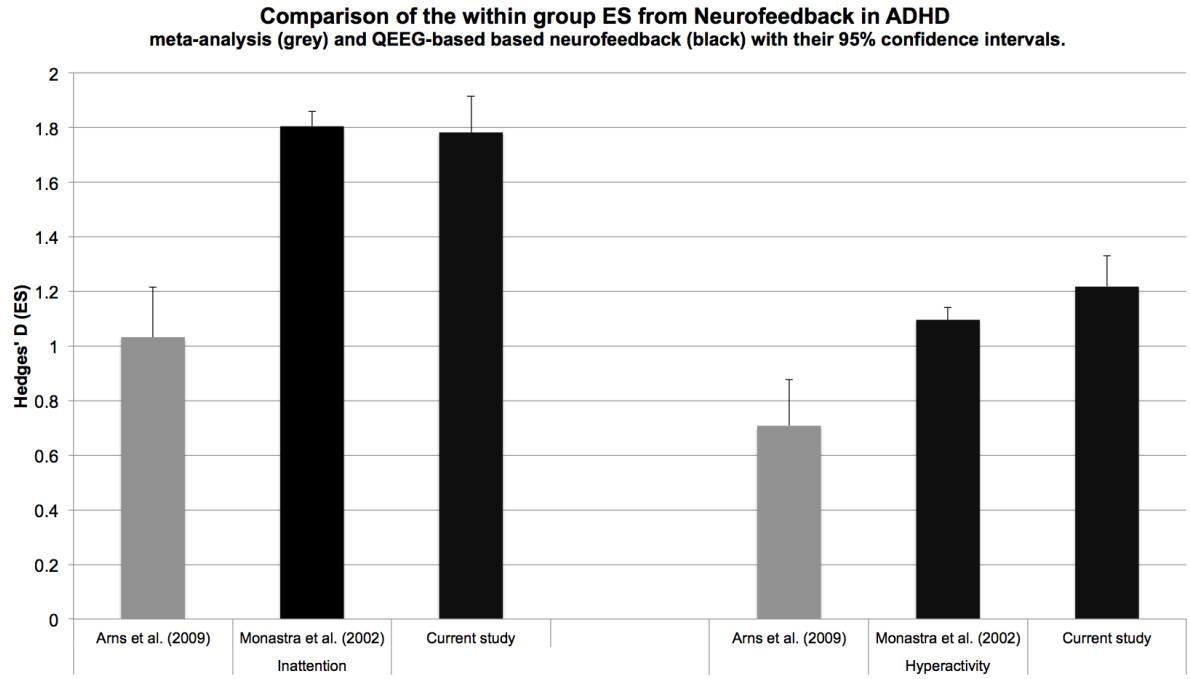


Figure 2: *ES for the different studies mentioned in the introduction and the ES obtained from the current study, with on the left ES for ATT and on the right ES for hyperactivity. Note that ES for hyperactivity for this study was based on a combined HI scale.*

iAPF

Two subjects exhibited a low-voltage EEG that did not allow calculation of a reliable iAPF. Therefore, BDI data were available for 12 patients (who at baseline demonstrated an increased BDI score) and for 10 patients a correlation with the iAPF could be established. Furthermore, 2 ADD subjects had a score of 0 on HI hence no percentage change scores for HI was available for these 2 subjects.

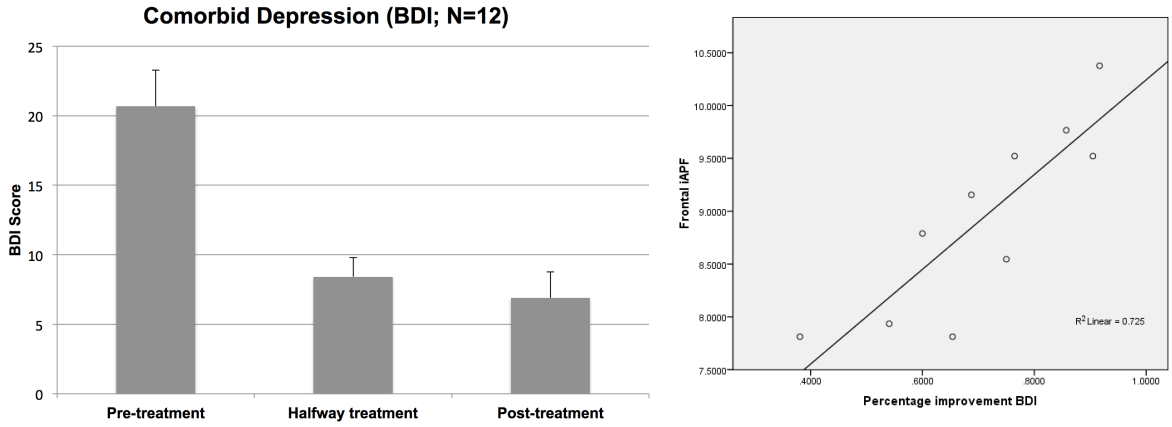


Figure 3: *Improvement on comorbid depressive symptoms for the patients across time (time effects: p=.003; Left) and the highly significant correlation between the frontal iAPF and the percentage improvement in BDI scores (p=.002; r=.851; Right).*

No correlation between the posterior iAPF and a) percentage improvement on ADHD ATT (p=.934; r=-.015; df=17), b) HI (p=.610; r=-.110; df=15) and anterior iAPF and a) percentage improvement on ATT (p=.771; r=.053; df=17) and b) HI (p=.127; r=-.326; df=15) were found. Furthermore, 1-way ANOVA demonstrated no differences between R and NR on posterior iAPF (p=.836; F=.044; DF=1, 15) and anterior iAPF (p=.669; F=.190; DF=1, 15), lending no support to the finding that NR displayed lower iAPF's.

A highly significant correlation was found between the anterior iAPF and the percentage improvement on the BDI (p=.002; r=.851, DF=10) suggesting that patients with a slow iAPF improved much less on comorbid depressive complaints. Note that there were no significant correlations between the improvements on the BDI and improvements on ATT and HI hence this could not explain the clinical improvements. Figure 3 depicts the improvement over time on the BDI scores and also the correlation between baseline anterior iAPF and improvement on the BDI after neurofeedback.

Pre- and post-treatment effects of neurofeedback on QEEG and ERP's.

Pre-treatment and post-treatment data for EEG and ERP's were available for six R treated with SMR neurofeedback.

There were no time effects neither for N100 and P200 amplitudes and latencies, nor for the N200 and P300 latency (all P>.18). There was a significant time effect for N200 amplitude (p=.014; F=13.861; DF=1, 5) and P300 amplitude (p=.004; F=24.190; DF=1, 5). In figure 4 the oddball ERP at Pz can be seen, demonstrating that there was a clear increase in N200 and P300 amplitude after neurofeedback treatment.

The repeated measures ANOVA for SMR power demonstrated a highly significant effect of time (p=.009; F=10.254; DF=1, 10) and site (p=.033; F=12.010; DF=8, 3). There were no significant Time X Condition, Site X Condition, Time X Site or Time X Site X Condition interactions and there was no main effect of condition. For alpha power and beta power there were neither significant main effects nor significant interactions. In figure 5 these data are depicted and as can be seen SMR power was significantly *decreased* post treatment. This figure further demonstrates the specificity of the effect for the SMR band only and not in the neighboring frequency bands alpha and beta.

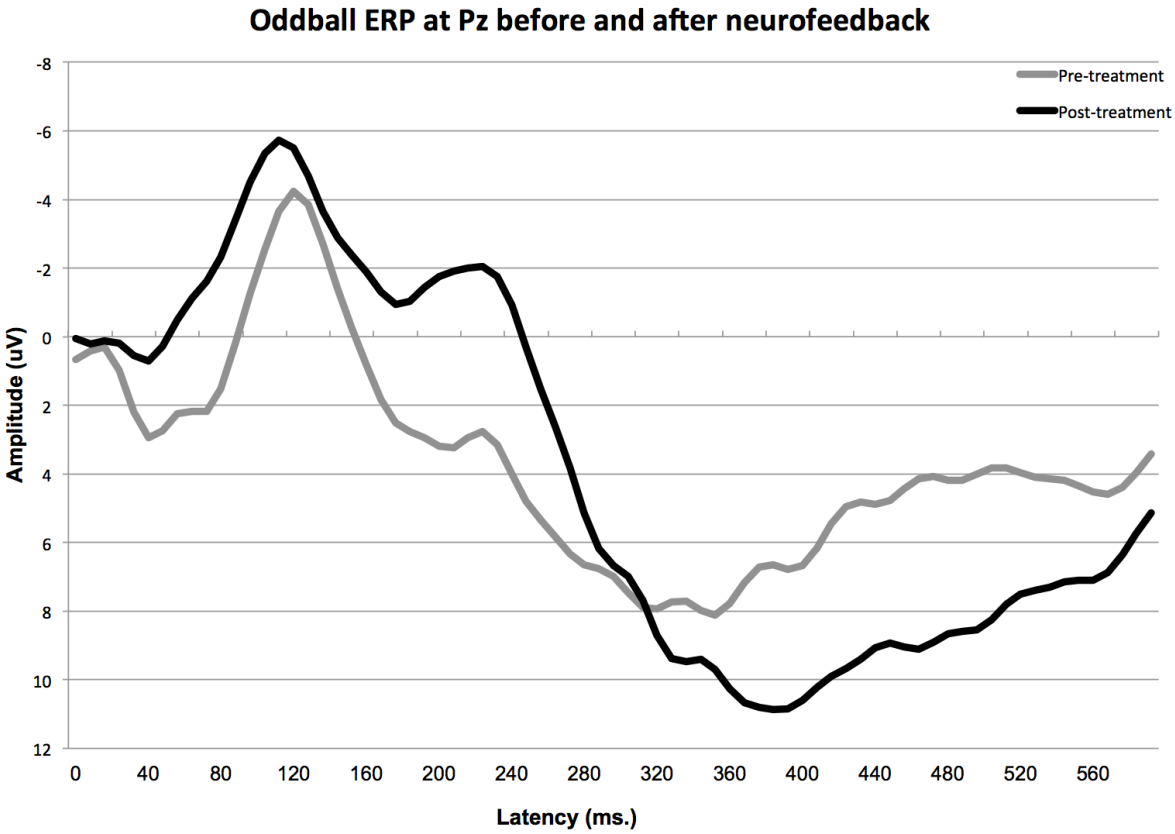


Figure 4: *Oddball ERP at Pz before and after treatment for a sub-group of patients who have all been treated with SMR neurofeedback. Note the clear increased N200 and P300 amplitudes after treatment.*

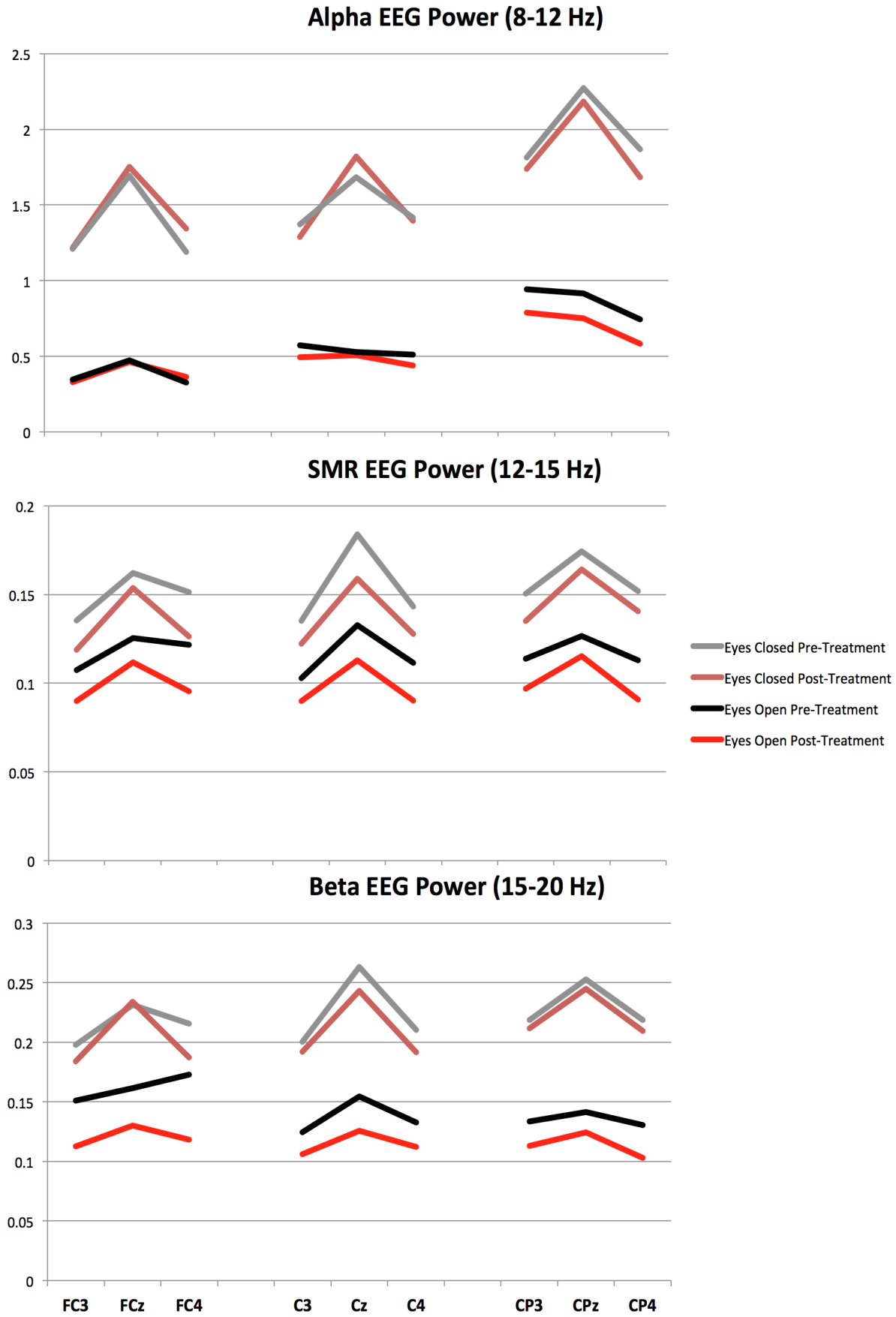


Figure 5: *Pre- to post-treatment changes in EEG power for SMR Power – which was trained using neurofeedback – and the neighboring frequency bands alpha and beta. Note the specific decrease in SMR power from pre- to post-treatment for both Eyes Open and Eyes Closed EEG, which is specific for only the SMR frequency band.*

Discussion

This pilot-study is the first study to investigate in a systematic way the effects of QEEG-informed neurofeedback in ADHD. It was found that neurofeedback resulted in significant improvements on ATT, HI and comorbid depressive complaints and the response rate was 76%. The ES obtained in this study were identical to the ES reported by Monastra et al. (2002) for ATT and were almost double the ES reported in the meta-analysis (Arns et al., 2009). In comparison, a recently conducted meta-analysis on the effects of stimulant medication in ADHD found an ES of 0.84 for Ritalin on ATT (Faraone & Buitelaar, 2009). Therefore, these results suggest that personalizing the treatment to the individual QEEG improves clinical outcomes, most clearly for ATT. Regarding the effects on HI it is difficult to draw conclusions. Arns et al. (2009) already pointed out that the effects of neurofeedback on hyperactivity are to a large part due to non-specific treatment effects. In this study we only had a combined measure of HI making a direct comparison difficult and possibly explaining the slightly larger ES as compared to the other studies (see figure 2).

We did not find a clear relationship between a slow iAPF and treatment outcome on ADHD relevant measures as hypothesized. However, we did find that a slow anterior iAPF at baseline was associated with a smaller decrease of comorbid depressive complaints as measured on the BDI in agreement with the depression literature (tricyclic antidepressants: Ulrich et al., (1984), rTMS: Arns et al., (2010); Conca et al., (2000)) supporting the notion that a slow anterior iAPF at baseline is related to worse treatment outcome on depressive complaints. In this study only few patients had an iAPF of 8 Hz or lower, whereas in Arns et al. (2008; 2010) this group was larger. Hence, in this sample the representation of slow iAPF's might have been too low to find a clear relationship between a slow iAPF and treatment outcome on ADHD rating scales. Therefore the conclusion that neurofeedback can be considered an effective treatment for those patients with a slow iAPF and who do not respond to stimulant medication is unjustified at this moment. More research with larger samples is required to further investigate this issue.

Pre- to post-treatment effects

In a sub-group of R who all underwent an SMR protocol we were able to demonstrate specific pre- to post-treatment improvements such as increased N200 and P300 amplitude and specific effects only related to the SMR EEG frequency band. The N200 has been related to stimulus discrimination (Näätänen & Picton, 1986) and the P300 to attention and memory updating (for review see: Kenemans & Kähkönen, 2011) and both have been found to be reduced in ADHD (for review see: Barry, Johnstone, & Clarke, 2003). Therefore, the finding of increased N200 and P300 amplitude suggests a normalization in underlying neural circuitry related to stimulus discrimination and attention/memory updating. Normalization of ERP components in ADHD as a result of neurofeedback has been reported by several other authors as well (Heinrich, Gevensleben, Freisleder, Moll, & Rothenberger, 2004; Kropotov et al., 2005; Wangler et al., 2011), therefore this finding provides further support of the specificity of SMR neurofeedback in this sub-group of patients.

Regarding post-treatment EEG changes, patients exhibited *decreased* SMR power post-treatment whereas the neurofeedback aimed at *increasing* this frequency band. The observed effects in the EEG were specific to the narrow SMR frequency band of 12-15 Hz and were not found in the neighboring alpha and beta frequency bands, which suggests the effects are specific to the frequency band trained (see figure 5).

Similar findings were observed in an earlier study by Pineda et al. (2008). They observed that children with autism demonstrated impaired mu-suppression when observing movement. In their double-blind neurofeedback study they rewarded mu rhythm (10-13 Hz) and found that mu-suppression was significantly *improved* after treatment. So by uptraining this frequency they found that children were better able to suppress that frequency. This finding hints at the notion that SMR neurofeedback serves as a procedure to teach people voluntary control over specific EEG frequencies, rather then structurally upregulate this EEG activity. This would be more in line with the Slow Cortical Potential neurofeedback (SCP) approach where children with ADHD learn to self-regulate their SCP towards both positivity and negativity (Heinrich et al., 2004; Strehl et al., 2006). In an earlier BCI study in which we compared SCP and SMR as a means of achieving voluntary control, we also demonstrated that healthy volunteers are able to self regulate SMR in a comparable way as subjects can self-regulate their SCP's. In this study subjects had to randomly enhance or suppress their SMR relative to baseline, and 30% gained control by SMR suppression whereas 40% gained by control by SMR enhancement (Kleinnijenhuis, Arns, Spronk, Breteler, & Duysens, 2008) demonstrating that subjects develop individual strategies to achieve control.

SMR neurofeedback has been demonstrated to improve sleep in patients with primary insomnia (Cortoos, De Valck, Arns, Breteler, & Cluydts, 2010) and in healthy volunteers (Hoedlmoser et al., 2008) and to result in enhanced sleep spindle density *during sleep* (Hoedlmoser et al., 2008; Sterman, Howe, & Macdonald, 1970). Several studies have reported a high incidence (73-78%) of sleep onset insomnia in ADHD characterized by a delayed endogenous circadian phase (Van Veen, Kooij, Boonstra, Gordijn, & Van Someren, 2010; Van der Heijden, Smits, Van Someren, & Gunning, 2005). When this sub-group is treated with melatonin to normalize the circadian phase, clear normalizations of sleep-onset insomnia are observed (Hoebert, van der Heijden, van Geijlswijk & Smits, 2009; Van der Heijden, Smits, Van Someren, Ridderinkhof & Gunning, 2007) followed by improvements in behavior after sustained treatment with melatonin (Hoebert et al., 2009). Therefore, it could be hypothesized that the effects of SMR neurofeedback result in improvements of sleep-onset insomnia and subsequent vigilance stabilization (Hegerl et al., 2010; Sander et al., 2010) thereby explaining the improvements of ADHD symptoms. The reduced SMR EEG power we found could therefore reflect not so much a specific treatment effect, but rather a self-regulation capability. However, future studies should further investigate this with larger samples and by also recording polysomnographic EEG prospectively to further quantify sleep spindle density and relate those to improvements in ADHD symptomatology.

Limitations

This pilot-study lacked a (double-blind) control group hence it cannot be ruled out that the effects were due to non-specific treatment effects as pointed out in previous studies (Lansbergen et al., 2011; Perreau-Linck et al., 2010). Furthermore, in contrast to most other

studies, in this study neurofeedback was carried out as 'treatment as usual' and often patients had to pay out-of-pocket to cover the costs of neurofeedback. This might have potentially led to the higher ES as well.

Finally, calculating an ES based on pilot study data is not as reliable as calculating these on large RCT's (Kraemer, Mintz, Noda, Tinklenberg, & Yesavage, 2006), hence caution should be taken in interpreting the ES reported in this study. The reported ES in figure 2 only provides a rough indication of the effects and an RCT is required to further substantiate this ES for QEEG informed neurofeedback.

Summary

This pilot-study provides support for the possibility to personalize neurofeedback treatment to the individual QEEG using a limited set of decision rules whereby most patients are still treated with one of the well investigated neurofeedback protocols (SMR/Theta or Theta/Beta neurofeedback), resulting in high response rates and a relatively high ES on ATT. Furthermore, specific neurophysiological improvements (increased N200 and P300 ERP amplitudes and decreased SMR) were obtained in a sub-group of patients who were treated with SMR neurofeedback. Future studies employing randomized double-blind placebo controlled designs and larger sample sizes are required to replicate these findings. The decision rules employed in this study could be easily used for designing a study employing more objective means of QEEG-based protocol selection.

Supplementary table 2:

Table 2: *This table shows the neurofeedback protocols received by the different patients. Note that ID 1 received alpha downtraining at Pz (Eyes Open) since alpha was most specifically increased at that site. All other patients received standard versions of the protocols as outlined above.*

ID	Frontocentral T/(b)	Frontocentral Alpha/(b)	Beta downtraining	SMR Protocol)	Alpha Uptraining
1		Pz (EO)		1	
2			1	1	1
3				1	1
4			1	1	
5		1		1	
6				1	1
7	1			1	
8			1	1	
9	1		1		
10			1		
11				1	1
12		1			
13	1			1	
14		1		1	
15	1			1	
16	1		1		
17	1			1	
18	1			1	
19			1		
20	1				1
21				1	1

Acknowledgements

We want to acknowledge the helpful suggestions on a first version from Hartmut Heinrich, Dianne Winkelmolen and the swift responses from Michelle Wang in providing us with some of the data. Furthermore, we would like to acknowledge Sabine de Ridder for carrying out the neurofeedback sessions and Hanneke Friesen, Desiree Spronk and Niels Veth for further support in data collection and acquisition of QEEG and neuropsychology data.

Part 2

Prediction of treatment response in depression

Chapter 7

An investigation of EEG, genetic and cognitive markers of treatment response to antidepressant medication in patients with major depressive disorder: A pilot study

Spronk, D., Arns, M., Barnett, K. J., Cooper, N. J., & Gordon, E. (2011). An investigation of EEG, genetic and cognitive markers of treatment response to antidepressant medication in patients with major depressive disorder: A pilot study. *Journal of Affective Disorders* , *128*, 41-48.

Abstract

The aim of this study was to investigate if biomarkers in QEEG, genetic and neuropsychological measures are suitable for the prediction of antidepressant treatment outcome in depression. Twenty-five patients diagnosed with Major Depressive Disorder were assessed twice, pre-treatment and at 8 week follow-up, on a variety of QEEG and neuropsychological tasks. Additionally, cheek swab samples were collected to assess genetic predictors of treatment outcome. The primary outcome measure was the absolute decrease on the HAM-D rating scale. Regression models were built in order to investigate which markers contribute most to the decrease in absolute HAM-D scores. Patients who had a better clinical outcome were characterized by a decrease in the amplitude of the Auditory Oddball N1 at baseline. The 'Met/Met' variant of the COMT gene was the best genetic predictor of treatment outcome. Impaired Verbal Memory performance was the best cognitive predictor. Raised frontal Theta power was the best EEG predictor of change in HAM-D scores. A tentative integrative model showed that a combination of N1 amplitude at Pz and Verbal Memory performance accounted for the largest part of the explained variance. These markers may serve as new biomarkers suitable for the prediction of antidepressant treatment outcome.

Introduction

Antidepressant medication is the first line of treatment for major depressive disorder (MDD). However, given the multifactorial nature of depression (Millan, 2006), not all patients will benefit from the same treatment. Identification of subgroups of patients based on objective biomarkers, may contribute to a more effective treatment prescription (antidepressant medication or other antidepressant treatments). It has been argued that the use of a combination of cognitive indicators, psychophysiology and genetics may be more reliable than clinical markers and have more potential in establishing treatment predictors (Bruder et al., 1999; Kemp et al., 2008). To date, various predictors have been proposed, but the results are both limited and heterogeneous. In addition, none of the findings have resulted in clinically meaningful applications. There is a need to continue to search for objective biomarkers and combination of markers, in order to proceed to a faster and more efficacious treatment of depression.

In quantitative EEG (QEEG) research, various pre-treatment differences in QEEG measures have been reported to be associated with improved antidepressant treatment outcomes such as lower pre-treatment Theta power (Knott et al., 1996); decreased theta cordance 48 hours to 2 weeks after start of medication (Bares et al., 2008; Bares et al., 2007; Cook et al., 2002), decreased Beta power, slower Beta frequencies, greater interhemispheric Beta coherences (SSRI's: Knott et al., (2000)), greater Alpha power (Bruder et al., 2008), increased theta in the rostral anterior cingulate (Pizzagalli et al., 2001) and greater Alpha power over the right hemisphere (Bruder et al., 2001; 2008). In contrast, increased Theta and Delta power have been associated with poor treatment response (Knott et al., 2000). Event-related potential (ERP) research has shown a clear relation between the loudness dependence of the auditory evoked potential (LDAEP) to serotonergic treatment outcome (Juckel et al., 2007; Mulert et al., 2007; Paige, Fitzpatrick, Kline, Balogh & Hendricks, 1994; Paige, Hendricks, Fitzpatrick, Balogh & Burke, 1995) where a stronger LDAEP has been associated with a better response to SSRIs. Other ERP measures related to favorable treatment outcome are smaller P300 amplitudes in a perceptual asymmetry task (Bruder et al., 2001; Bruder et al., 1995) and a prolonged P300 latency in an auditory evoked potential (Kalayam & Alexopoulos, 1999). Neuropsychological studies find that in general better cognitive performance is predictive of better treatment response to antidepressants (executive functioning: Bogner et al., (2007); Dunkin et al., (2000); Gorlyn et al., (2008); Kalayam & Alexopoulos, (1999)), working memory (Gorlyn et al., 2008) and psychomotor functioning (Kalayam & Alexopoulos, 1999; Taylor et al., 2006). However some have reported that relatively worse performance was associated with better response (Herrera-Guzmán et al., 2008). Finally from a genetic perspective, the genetic polymorphisms from the brain-derived neurotrophic factor (BDNF), catechol-O-methyltransferase (COMT) and 5-HT (serotonin) related polymorphisms are currently the most interesting candidates in antidepressant treatment prediction (Arias et al., 2006; Baune et al., 2008; Benedetti, Colombo, Pirovano, Marino & Smeraldi, 2009; Chen, Dowlatshahi, MacQueen, Wang & Young, 2001; Choi, Kang, Lim, Oh & Lee, 2006; Domschke et al., 2009; Peters et al., 2009; Tsai, Cheng, Yu, Chen & Hong, 2003; Tsai et al., 2009). Results to date have not been consistent; various combinations of carriers resulting in different associations with antidepressant treatment outcome.

The above studies propose various biomarkers in several modalities in the prediction of antidepressant treatment outcome. None of the biomarkers in each of these modalities have shown to be robust and specific enough to be used in current practice. Also, previously obtained potential biomarkers have been investigated in isolation. To the best of our knowledge, to date there have not been any studies that have taken an integrative approach by analysing neuropsychological, psychophysiological and genetic data simultaneously. The goal of the present exploratory study was to investigate various regression models in each of the modalities described above and in addition to provide a tentative integrative model by combining biomarkers in each of the individual investigated fields.

Methods

Participants

From a cohort of 128 patients with a diagnosis of major depressive disorder who received only a single pre-treatment assessment, thirty-one patients were recruited for a follow-up assessment and included in this study. Of the group of 31 patients, data from 25 patients could be analyzed (excess EEG artifact resulted in too many missing values for 6 of the participants). Participants were recruited by collaborating clinicians and community advertisements. Diagnoses were made by trained research assistants using the Mini-International Neuropsychiatric Interview (MINI). Patients were also assessed using the Hamilton Depression Rating Scale (HAM-D, Hamilton 1960; Williams, 1988). Inclusion criteria were age 18-65 and scoring negative for a drug screen. Exclusion criteria included a blow to the head that resulted in unconsciousness, blood borne illness, substance abuse or dependence for greater than 1 year and severe impediment to vision, hearing or hand movement. Participants were also excluded if depressive symptoms were due to somatic disorder or medication, or they had somatic disorders likely to interfere with gene expression patterns, abnormal thyroid function and a history of substance abuse or dependence for greater than 1 year. All were medication-free at the time of enrollment and the pre-treatment assessments for at least 5 half lives of any previous antidepressant medication. All participants provided written informed consent prior to their inclusion in the study. The study was reviewed and approved by the Sydney West Area Health Service and the University of Sydney Human Research Ethics Committees.

Experimental design and procedures

This study was based on an open-label non-randomized design. Patients who were willing to participate first visited their general practitioner and a psychiatrist in order to assess if they met the inclusion criteria. Choice of treatment was decided by their own-treating physician, who remained responsible for dosing and any changes in medication during the study (see Table 1 for demographics and assigned antidepressant treatment). Patients were assessed twice during the study using clinical, neuropsychological and QEEG assessments. A DNA cheek swab sample was collected from each participant at the time of the screening session.

EEG recordings were performed using a standardized methodology, details published elsewhere (Arns, Gunkelman, Breteler & Spronk, 2008; Gordon et al., 2005; Spronk et al., 2008; Williams et al., 2005). For the purpose of this study EEG power measures from 'eyes open' and 'eyes closed' resting states, as well as the N1, P2, N2 and P3 latencies and amplitudes from the Auditory Oddball and the Continuous Performance Test were analyzed. Details on the standardized cognition test battery IntegNeuro has also been published elsewhere (Clark et al., 2006; Gordon et al., 2005; Williams et al., 2005). For the purpose of this study measures from each cognitive domain, memory, verbal fluency, working memory capacity, response speed, sustained attention and executive functioning, were included in the cognitive model.

Data analysis

EEG and ERP analysis: Average power spectra were computed for the eyes open and eyes closed paradigms using Fast Fourier Transformation (FFT). The resulting power spectra were then averaged for each electrode position in each of the two paradigms over the following frequency bands: Alpha (8-13 Hz), Beta (14.5-30 Hz), Theta (4-7.5 Hz) and Delta (1.5-3.5 Hz). Data was square-root transformed to approximate the normal distributional assumptions required by parametric statistical methods. For ERP analysis single-trial epochs to target and background stimuli from the Auditory Oddball and Continuous Performance Test (n-back) paradigms were filtered with a low-pass Tukey (cosine taper) filter function. These epochs were then averaged to form conventional ERPs. The amplitude and latency of the N1, P2, N2 and P3 ERP components were identified for the 'target' trials. Key sites for the frequency bands as well as the ERPs were; Fz, Cz, and Pz.

Genetic analysis: DNA was extracted from cheek swab samples, for the purpose of this analysis two genetic polymorphisms BDNF and COMT were analyzed. Due to the small sample size, we decided grouping the homozygote genotype with the lowest prevalence together with the heterozygote genotype. For the COMT polymorphisms the number of Val/Val homozygotes was the smallest (n=4) so we grouped Val carriers (Val/Val n=4, and Val/Met n= 15) and Met/Met homozygotes (n=6). For the BDNF, the Met/Met had the lowest prevalence and we therefore grouped the Met carriers (Val/Met (n=10) and Met/MET (n = 1)) and the Val/Val homozygote group Val/Val (n= 15).

Statistical analyses

Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS, version 17). In order to identify predictors for treatment outcome, several multiple regression models were generated. In each linear regression model, the absolute change in HAM-D between week 8 and baseline was taken as the dependent variable. Because of the small sample size, the data of all participants was taken together regardless of the medication they were treated with. A post-hoc inspection was carried out to confirm that variables entered into the regression models did not behave differently between the medication types. Prior to analysis the data was screened for quality and outliers. In case participants showed consisting missing values for a specific type of assessment, indicating that the assessment was omitted for these subjects, these subjects were left out for

generation of the specific regression model as happened for the oddball paradigm. All other missing values were pairwise excluded. Five different models based on QEEG, Oddball ERPs, the Continuous-Performance-Test ERPs, cognition and genetic outcomes were generated. In addition, an explorative analyses on the significant predictor variables from the domains was performed in order to propose a tentative integrative model.

The relationship between HAM-D and potential predictor variables was inspected by means of scatter plots and correlation analysis, in order to identify foci for statistical analysis. Subsequently, hierarchical linear regression models per domain were generated with change in HAM-D score between week 8 and the pre-treatment assessment taken as outcome measure. Since baseline severity is a known predictor in treatment outcome (Marie-Mitchell, Leuchter, Chou, James Gauderman & Azen, 2004), the pre-treatment HAM-D score was hence entered as a covariate as a first step in each of the models. The significant variables from the correlation analysis were entered into the second block of the regression model. A tentative integrative model was generated by entering each of the significant prediction variables from the other models into one regression model. Again pre-treatment HAM-D score was first entered and subsequently the significant variables from the other models were entered in the second block. Missing values for the predictor variables were replaced by using the 'norm' package in 'R', based on Schafer's (Schafer, 1997) method (http://www.r-project.org/). All variables were entered by means of the 'forced entry' method. For all analysis the following model parameters were reported; the regression beta coefficient (B), the standard error of the regression coefficient (SE), the t-statistic (t-value) and the significance level (p-value). In addition for each of the model the R2 was given, which provides the percentage of the total variability which can be accounted for by the predictors in the model. Since we were only interested in the contribution of potential new predictors in treatment outcome only values of the newly entered variable in the second step were provided. This study was an exploratory study used to generate specific hypotheses for future studies. A liberal statistical approach was taken and no corrections for multiple comparisons were made.

Results

Demographics

The demographic and clinical characteristics of the sample are shown in Table 1.

Table 1: demographics and clinical characteristics

Variable	Mean (S.D.)
Age	42.8 (14.2)
Male/Female	7/18
Years of education	14.2 (3.1)
HAM-D-17 baseline	20.2
HAM-D-17 week 8	11.2
SSRI/SNRI/TCA	14/8/2*

*Study medication was missing for 1 participant

Linear Regression models

Cognitive measures

We performed a linear regression analysis with measures from the following cognitive domains: memory recall, memory recognition, digit span, sustained attention, word generation, switching of attention, response speed, time estimation and executive functioning. From the cognitive variables investigated, only the total memory score loaded significant into the model (B (SE) = .337 (.138), t-value = 2.442, p-value = .024, R2 = .263). The higher the pre-treatment memory performance, the greater decrease in depressive symptoms (see Figure 1). Based on the beta coefficient, for every additional 3 words remembered across 4 trials of the verbal memory task HAM-D score decreased by 1 point.

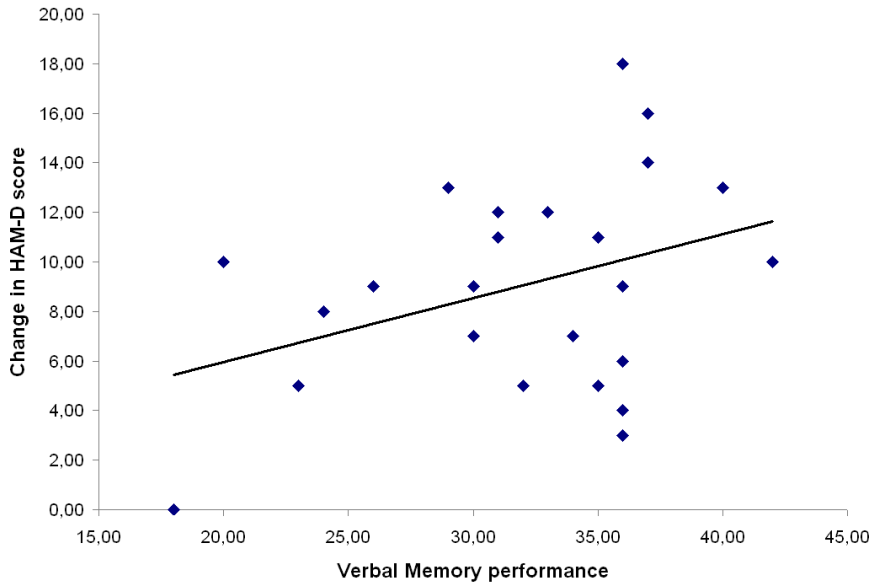


Figure 1: Scatterplot between absolute decrease in HAM-D after treatment with antidepressant medication and Verbal memory performance

ERP measures

Regression models were created separately for ERPs from the Auditory Oddball and Continuous Performance Test (n-back) paradigms. The N1 amplitude at Pz was a significant predictor in the ERP model (B(SE) = -1.428 (.522), t-value = -2.735, p-value = .015, R2 = .369). A larger N1 amplitude was associated with a bigger decrease on the HAM-D (see Figure 2). Based on the beta coefficient, for every increase in 0.7 microvolts of the N100 amplitude, HAM-D score decreased by 1 point. None of the ERPs obtained from the Continuous Performance Test (n-back) contributed significantly to the model.

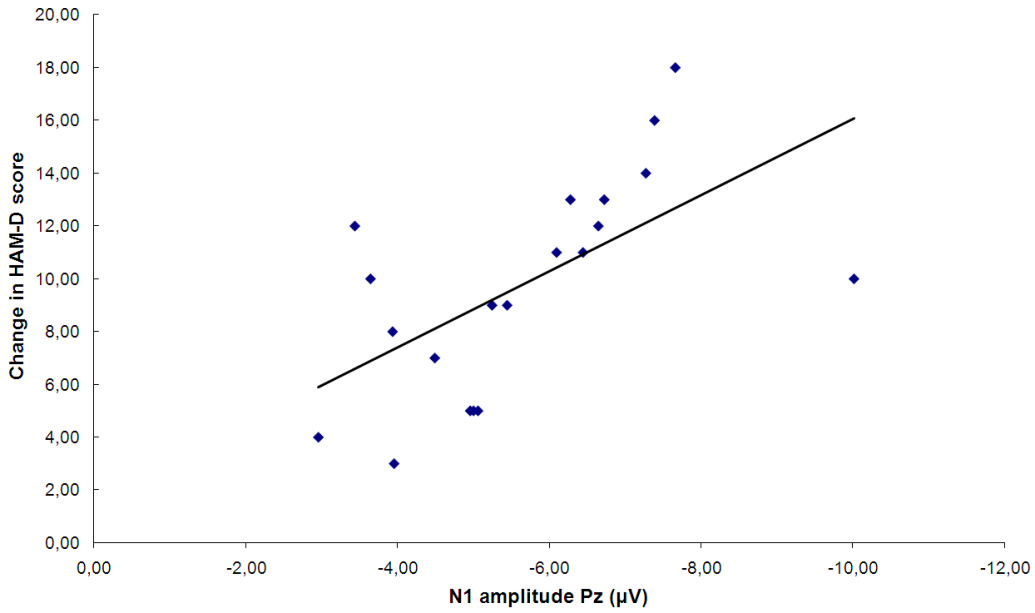


Figure 2: Scatterplot between absolute decrease in HAM-D after treatment with antidepressant medication and pre-treatment N1 amplitude as measured in an Auditory Oddball task.

EEG power measures

For the EEG power measures only frontal Theta activity as measured from Fz in eyes closed resting state entered the model significantly (B (SE) = 2.549 (1.158), t-value = 2.201, p-value = .039, R2 = .236). As can be seen in Figure 3; higher absolute Theta power at the pre-treatment assessment indicates higher decrease in depressive symptoms in response to antidepressant treatment. Based on the beta coefficient, for every increase in 0.4 microvolts2 of theta power, HAM-D score decreased by 1 point.

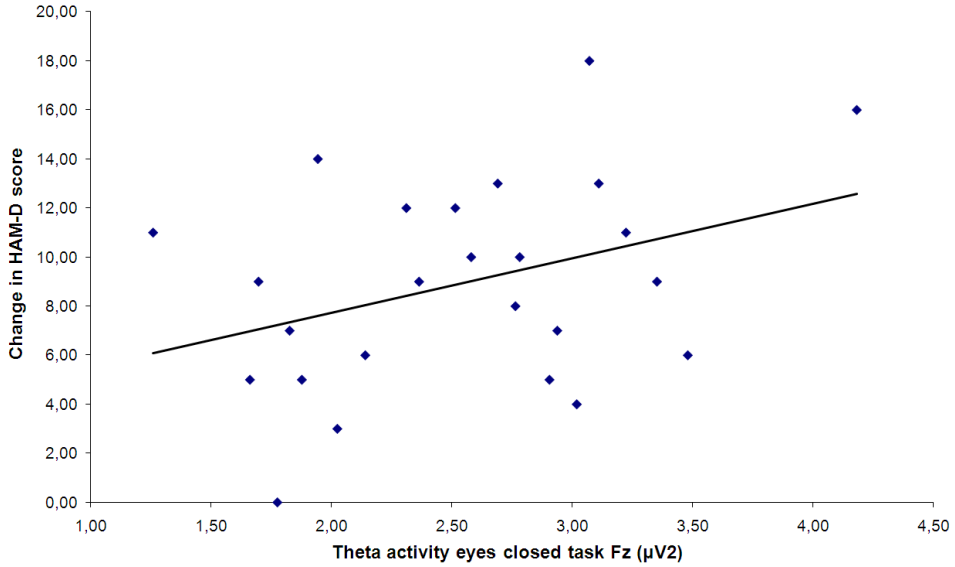


Figure 3: Scatterplot between absolute decrease in HAM-D after treatment with antidepressant medication and pre-treatment absolute Theta power measure during the rest EEG eyes closed task.

Genetics

Of the two genes investigated, the COMT polymorphisms significantly entered the model (B(SE) = 5.051 (1.778), t-value = 2.841, p-value = .009, R2 = .318). The presence of the SNPs in the 'MET group' were identified as a positive predictor for treatment outcome and were associated with the highest decrease in HAM-D score (Figure 4). Based on the beta coefficient the MET group decreased their HAM-D scores by 5 points more than the VAL group.

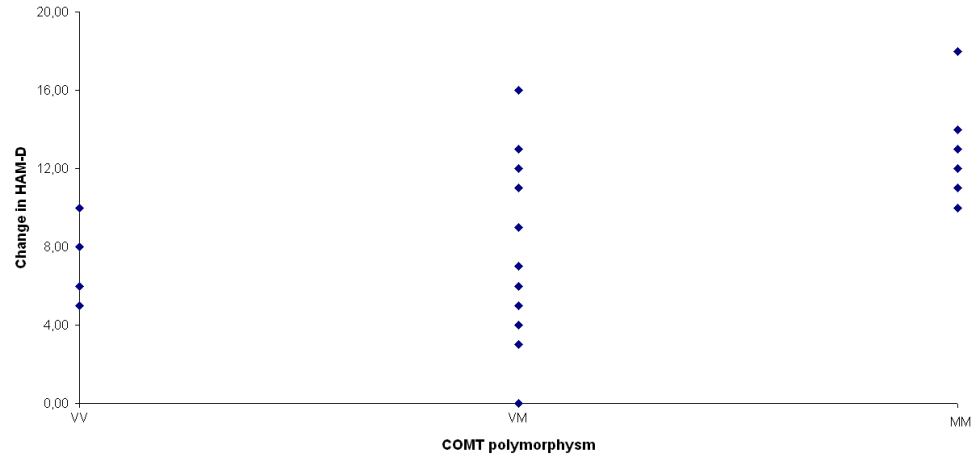


Figure 4: Individual COMT genetic variants against change in HAM-D score.

Integrative model

A tentative integrative model was generated based on the significant predictor variables from each of the regression models discussed above. Of the four variables entered (total memory, N1 amplitude Pz, frontal Theta and COMT), the combination of N1 amplitude Pz and the total memory score revealed the highest percentage explained variance (R2= 60,2%). See Table 2 and regression equation below.

Decrease in HAM-D = -5.53 + -.179*baseline HAM-D score + -1.58*N1 amplitude Pz + .30* Verbal Memory Performance

Table 2: model parameters Integrative model

Variable	B (SE.)	T-statistic	p-value
HAM-D session 1	-.179 (.181)	-.988	.334
N1 Amplitude Pz	-1.581 (.381)	-4.145	.001
Verbal Memory performance	.300 (.100)	2,994	.007

Discussion

The main objective of this exploratory analysis was to generate hypotheses about potential predictors of improved mood over time in patients with MDD treated with antidepressant medication. Using an exploratory approach we developed several regression models in which various pre-treatment neuropsychological, psychophysiological and genetic variables were incorporated. Of the individual domain models, the ERP and genetic models explained slightly more of the variance compared to the neuropsychological and QEEG models, but all four models had R2 near 30%. The integrative model showed that a combination of N1 amplitude at Pz (ERPs) and verbal memory performance (cognition) resulted in the largest percentage explained variance. This result shows the utility of combining measures from different domains as the integrative model (R2 = 60.2%) showed almost no overlap (roughly 3% of variance) between the comprising predictors - as the sum of variances explained in the separate models is only 63.2%. Baseline HAM-D score was entered as a covariate but was non-significant ($p>.05$) and did not contribute meaningfully to the predictive power of the integrative model.

Pre-treatment memory scores positively predicted the decrease in depressive symptoms. This finding contributes to a growing number of studies that show that better cognitive functioning pre-treatment is associated with better treatment outcome. There is a potential modulatory influence of a reduced motivation, associated with depression severity, rather than memory per se. However, since the post-hoc correlation analyses in this sample showed no significant relation between to memory performance and depression severity, the likelihood of a potential modulating effect of motivation is small. To date, the exact cognitive domains which could act as suitable predictors remain elusive. Previous studies have proposed working memory (Gorlyn et al., 2008), executive functioning (Bogner et al., 2007; Dunkin et al., 2000; Gorlyn et al., 2008; Kalayam & Alexopoulos, 1999), and indices of psychomotor functioning (Kalayam & Alexopoulos, 1999; Taylor et al., 2006) as predictors. A range of cognitive abnormalities has been found in depression itself including information speed, memory, attention and executive functioning and psychomotor deficits (Porter, Gallagher, Thompson & Young, 2003; Weiland-Fiedler et al., 2004). But as the findings of the present study suggest, some of these factors are not suitable for the prediction of antidepressant treatment outcome and verbal memory performance seems most promising.

We also investigated the EEG power measures (Alpha, Beta, Theta and Delta) in relation to treatment outcome. Theta power measures at Fz loaded as a significant predictor, a finding that has been reported in previous studies (Knott et al., 1996). However, our finding was in the opposite direction i.e. higher pre-treatment Theta power was predictive of a higher decrease in depressive symptoms. Differences in findings could result from differences in

study medication and design. In addition to Theta power measures, Theta cordance seems the most replicated EEG power measure related to treatment outcome. Cordance is usually measured between 48 hours to 2 weeks after start of medication (Cook & Leuchter, 2001; Cook et al., 2002; Leuchter et al., 1994) and therefore these results could not be tested in this study. Nevertheless Theta activity derived measures remain a biomarker of interest. It has been suggested that higher Theta activity at baseline could be interpreted as an electrophysiological manifestation of higher activation within the anterior cingulate (Pizzagalli et al., 2001). To date, the exact mechanism remains elusive but research is being directed to gain more knowledge about the involvement of frontal brain regions and recovery from depression.

To the authors' knowledge, there have been no studies reporting the use of ERPs from Auditory Oddball and Continuous Performance Tests (n-back) as predictors for treatment response to antidepressants. The ERP prediction model in this study could hence be regarded as the most explorative domain investigated. The parietal oddball N1 amplitude turned out to attribute significantly to the ERP regression model. Danos et al. (1994) demonstrated that patients who benefitted most from a night of sleep deprivation had a reduced N1 amplitude, which is in line with our finding. To the authors' knowledge, this is the only previous reported study on the relation of antidepressant treatment outcome in relation to the amplitude of the auditory N1 ERP. The investigated ERP parameters derived from a Continuous Performance Test (n-back), did not yield a significant contribution and might therefore not be the most suitable candidate in the future investigation of antidepressant treatment prediction. In contrast to our investigation of single ERP parameters, the majority of previous reports on antidepressant treatment outcome and ERPs, have focused on the LDAEP (Hegerl et al., 1998; Juckel et al., 2007; Mulert et al., 2007; Paige et al., 1994; Paige et al., 1995). The relation between the LDAEP and antidepressant treatment response is the most replicated and investigated ERP measure, and has shown to be in particular predictive in the treatment response to SSRI's. The battery did not contain the LDAEP task so no comparison to such studies was made.

Of the two genetic variants that were incorporated in the regression model, only the COMT 'Met/Met' group was found to be most strongly related to treatment outcome. This result is in accordance with studies on treatment outcome on SSRI (Benedetti et al., 2009; Tsai et al., 2009), light therapy and sleep deprivation (Benedetti et al., 2009). These studies all demonstrated a favorable association with treatment outcome for carriers of the Met/Met genotype. In contrast, others have found a negative effect of the Met COMT variant to antidepressant response to a TCA and SSRI (Arias et al., 2006; Szegedi et al., 2005). Inconsistencies between findings could be accounted for by differences in patient samples, study design, type of antidepressant medication that patients were treated with and statistical methods (Benedetti et al., 2009). It should be noted that of all genetic polymorphisms only COMT and BDNF have been explored and that there are more likely polymorphic candidates to explore (McMahon et al., 2006). More research into the contribution of the polymorphisms of the COMT variant and catecholaminergic actions on antidepressant treatment response is warranted to further unravel the contribution of this variant to antidepressant treatment outcome.

A highly explorative model was generated by combining all significant predictor variables from each model separately into one model; Verbal Memory performance, frontal Theta activity during Eyes Closed, COMT genetic marker and N1 amplitude measured from Pz. The combination of two biomarkers, N1 amplitude in oddball task at Pz and Verbal Memory performance was the best predictive model of all models performed. The EEG frequency and genetic marker did not yield an additional contribution to the integrative model and hence were not incorporated. Verbal Memory performance and N1 amplitude at Pz are both relatively easy to assess by means of an EEG oddball task and neuropsychological assessment, which is favorable for potential applicability of biomarkers in daily practice. Since these biomarkers must be replicated the results from the integrative model should be interpreted with caution.

The findings of this study should obviously be regarded as preliminary and thus are subject to a certain set of limitations. One of the biggest concerns and limitations of this study is the large number of measures tested without correction for multiple comparisons. It will be crucial to replicate these findings in a new study. Furthermore, the small sample size and the non-standardized dosage regimes and the heterogeneity of the prescribed medication (SNRI, SSRI, TCA) make it hard to draw definitive conclusions. From a post-hoc inspection of the data, the direction and contribution of the markers found in this study did not appear to substantially differentiate between the three medication types. It would be worthwhile to investigate this in a larger sample. A key feature of the current study is the incorporation a comprehensive set of psychophysiological/psychological variables. This made it possible to incorporate and investigate biomarkers that have not been associated with antidepressant treatment outcomes previously. The result is that new testable hypotheses were generated for replication in future studies. The naturalistic assignment to treatment was advantageous since it mimics treatment in the real world.

In conclusion, the results of the present study could be used to improve the prediction of treatment efficacy to antidepressant medication. One of the biggest challenges of biomarker studies is increasing their ecological validity in order to transfer results of studies to the clinical setting. The increasing interest from the pharmaceutical field and psychiatrists stimulates new research projects and holds promise for future development of biomarkers and personalized medicine in Psychiatry. An example is an international biomarker study aiming to include 2,016 MDD participants as well as 672 healthy controls (International Study to predict Optimized Treatment Response in Depression, iSPOT-D). This study is currently enrolling and recruiting patients. One of the ultimate goals of personalized medicine is the prediction of which therapy should be delivered to which patient. The search for neuropsychology, psychophysiological and genetic markers will make an invaluable contribution to this goal.

Acknowledgements

We note that Brain Resource and Johnson & Johnson (J&J) sponsored this study but that analysis and interpretation of data was unconstrained. DS is an employee of Brainclinics and has no declared conflict of interest. MA is director of Brainclinics and owns options in Brain Resource, which are a minimal percentage of the company's value. KJB and NC are employees of Brain Resource (http://www.brainresource.com) and own personal shares in Brain Resource although shares owned are less than 1% of the company value. EG is the CEO and has significant financial interest in the Brain Resource. The authors thank Patrick Hopkinson and Andrew Kemp for their contribution to the study. Furthermore, we like to thank two anonymous reviewers for their helpful comments.

Supplement 1

Based on the same dataset presented in this chapter the EEG Phenotypes were also characterized for 113 depressed patients and 121 matched healthy in the same manner as described in chapter 2 by the same raters (Martijn Arns and Jay Gunkelman), and ratings were performed blinded to diagnosis. These data have been published as part of a book chapter in (Arns et al., 2010a) and results will be provided below.

EEG Phenotypes in depression

Figure 1 shows the prevalence of the different EEG Phenotypes in depression and in matched normal controls, and no differences in prevalence of EEG phenotypes were present. One-Way ANOVA revealed no difference for age. Furthermore, there was a significant difference in Frontal alpha peak frequency (p=.025; F=5.089; DF=1, 214) between the depressed (9,62 Hz) and non-depressed groups (9,27 Hz), which was not different for Pz (p=.632; F=.231; DF=1, 225) indicating the depressed clients had a faster iAPF at frontal sites.

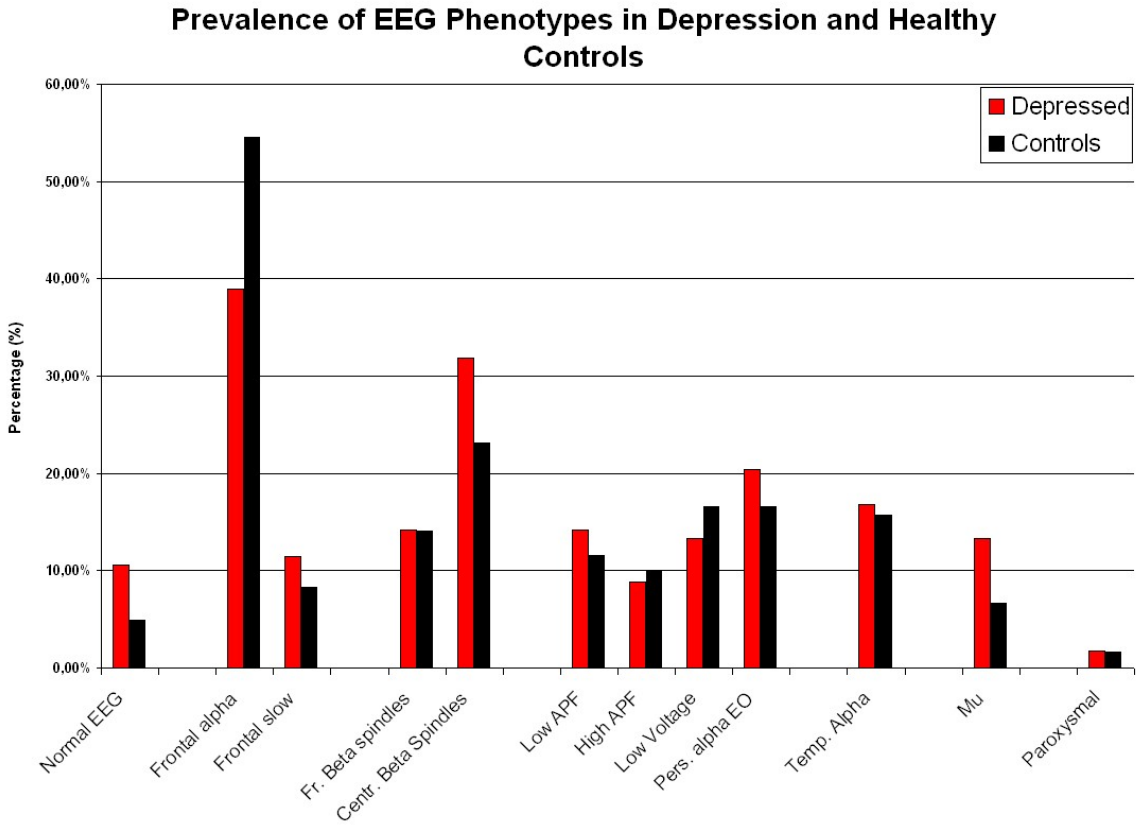


Figure 1: The occurrence of the different EEG Phenotypes for depression and matched control groups (black). Note the lower prevalence of frontal alpha and the higher prevalence of mu rhythm, which failed to reach significance. Also note that the Control group has similar prevalences of most of the EEG phenotypes.

For a sub-sample of 27 patients post-treatment HAM-D scores were available (these were identical to the subjects reported in this chapter). In figure 2 the EEG Phenotypes showing

the largest decrease in HAM-D scores related to antidepressant medication are shown with 3 measures of treatment response: average improvement on HAM-D as a percentage (blue), response (defined as > 50% improvement: dark grey) and partial response (defines as > 30% improvement; light grey). Although results have to be treated with caution due to very low subjects numbers per EEG Phenotype, these data suggest that the frontal alpha phenotype (a reasonably large sub-group of N=10) does not predict treatment outcome well judged on the overall improvement of 32% and response rate of 20% (in contrast to what would be expected based on work of for example Suffin & Emory, 1995).

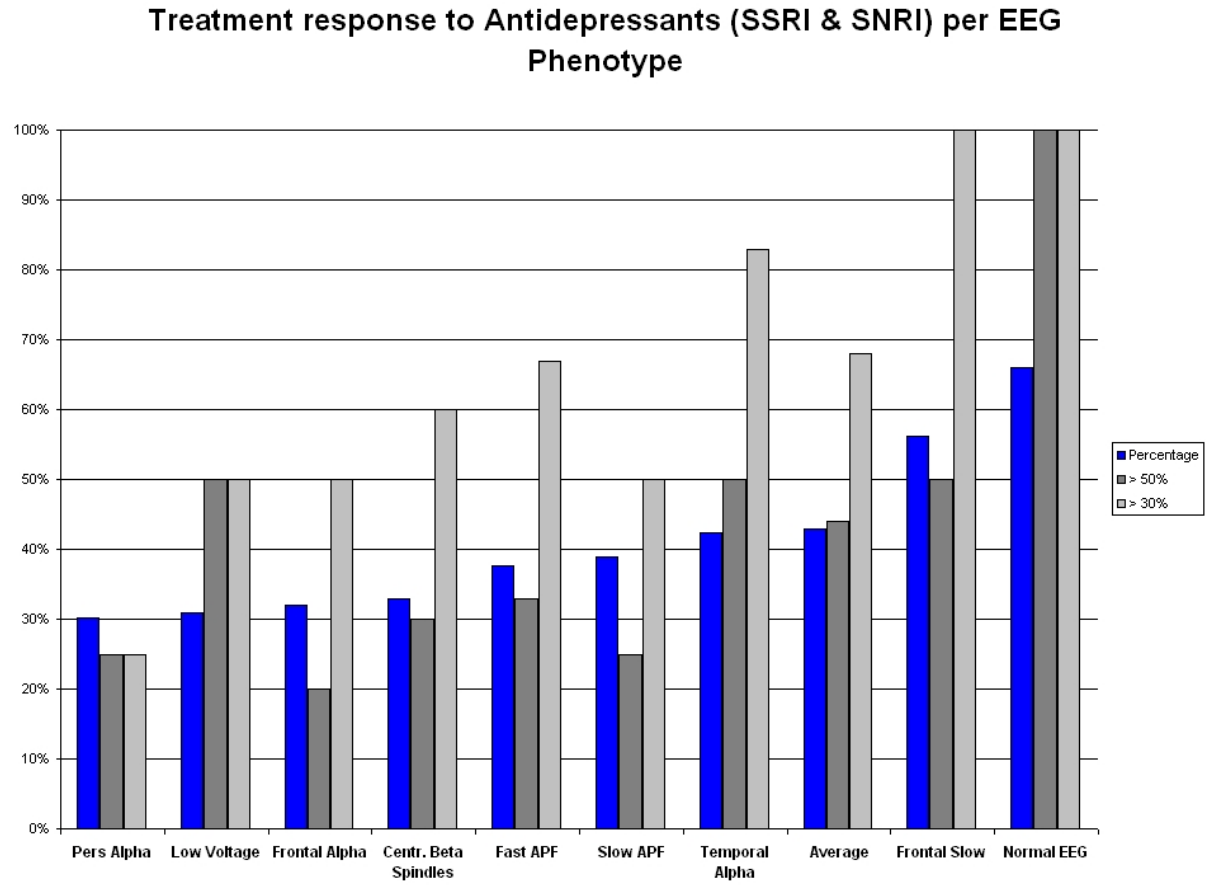


Figure 2: Improvement in HAM-D scores for patients with depression per EEG Phenotype (depression N=27). Note that these sub-groups all consist of very low subject numbers. The frontal alpha group contained 10 patients.

In comparison to the results obtained with this EEG phenotype approach in ADHD (see chapter 2) the results in depression were much less promising. This is due to the larger heterogeneity in EEG Phenotypes within depression (also see figure 1 with most EEG phenotypes having a prevalence of less than 20%) and hence the sample size was not sufficient to detect any significant differences. Therefore, for the studies in depression we have employed more integrative methods using data from multiple domains in this chapter and also in chapter 10.

Chapter 8

Repetitive Transcranial Magnetic Stimulation in Depression: Protocols, Mechanisms and New Developments

Spronk, D., Arns, M., & Fitzgerald, P. B. (2010). Repetitive transcranial magnetic stimulation in depression: Protocols, mechanisms and new developments. In *Neuromodulation and neurofeedback: Techniques and applications.* Elsevier.

Abstract

This book chapter introduces and explains protocols, mechanisms and new developments of transcranial magnetic stimulation (TMS) in the treatment of depression. Repetitive TMS protocols for depression can mainly be differentiated based on the stimulation location and frequency, but trains, sessions and inter train intervals are also parameters that can be manipulated. Various neuroimaging, neurochemical and genetic findings that shed light on potential antidepressant mechanisms are discussed. Furthermore, new developments in the field of engineering, in particular the development of the H-coil, and new protocols are reviewed. The chapter finishes with a discussion of the potential use of neurophysiological data in optimizing treatment by means of characterizing patient groups.

Introduction

TMS (transcranial magnetic stimulation) is a non-invasive neuromodulation technique. Nevertheless, it has a very direct influence on brain physiology. The basic principle of TMS is the application of short magnetic pulses over the scalp of a subject with the aim of inducing electrical currents in the neurons of the cortex. A typical TMS device consists of a stimulator that can generate a strong electrical current, and a coil in which the fluctuating electrical current generates magnetic pulses. If the magnetic pulses are delivered in the proximity of a conductive medium, e.g. the brain, a secondary current in the conductive material (e.g. neurons) is induced (Figure 1). In the practice of TMS, a subject is seated in a chair and an operator positions the coil above the scalp of the subject, tunes the stimulation parameters of the stimulator, and applies the TMS pulses.

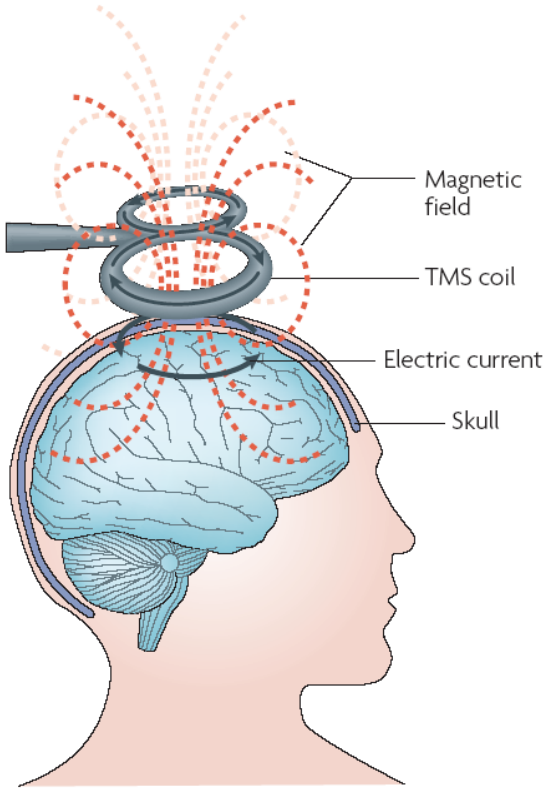


Figure 1: *Visual illustration of the induction of electrical currents in the brain (black arrows in brain) through the magnetic pulses (red/pink) applied by means of the coil (grey 8-shaped figure) positioned above the head. Figure taken and adapted from Ridding and Rothwell (Ridding & Rothwell, 2007).*

Anthony Barker and his colleagues at the University of Sheffield were the first to develop a TMS device, introducing a new neuromodulatory technique in neuroscience. The first application, demonstrated first by these researchers, was the induction of a motor evoked potential (e.g. activating the muscles abducting the thumb) by means of applying a TMS pulse over the motor cortex (Barker, Jalinous & Freeston, 1985).

Initially, TMS was used mainly in studies on motor conductivity through investigating the temporal aspects and amplitude of the evoked motor responses after stimulating the motor cortex. Continuing progress on the technical aspects of TMS devices soon made it possible to deliver multiple pulses within in a short time period, i.e. repetitive TMS (rTMS). With the development of rTMS, researchers were able to induce changes that outlasted the stimulation period (Pascual-Leone et al., 1999). This has led to a considerable extension of the possible applications of TMS. Currently, rTMS is used for an increasing variety of applications such as the study of pathophysiology of diseases, the investigation of the contribution of certain brain regions to particular cognitive functions and, most relevant for this chapter, the treatment of psychiatric diseases.

The potential of repetitive TMS in the treatment of psychiatric disorders was suggested for the first time relatively soon after the development of the first TMS device in 1985. In a study on motor conductivity, changes in mood in several normal volunteers who received single pulses over the motor cortex were described (Bickford, Guidi, Fortesque & Swenson, 1987). Following this initial observation, the technical progress and the increasing availability of TMS devices has led to the opportune investigation of rTMS in the treatment of depression. Apart from being the first investigated psychiatric application, it is also the most investigated psychiatric application in many centers all around the world. In addition, an rTMS device has been approved by the FDA in late 2008, and a growing number of private outpatient as well as hospitalized patients with depression are treated in clinical settings (approximately 150 US centers in the middle of 2010).

Major depression is a common disorder with millions of sufferers around the world and a lifetime prevalence of about 13% in men and 21% in women (Blazer, Kessler, McGonagle & Swartz, 1994)). The World Health Organization has predicted that depression will globally become the 2nd largest burden of disease by 2020, following cardiovascular conditions (Murray & Lopez, 1997). Individuals with depression experience a wide range of symptoms including a loss of interest or pleasure, feelings of sadness, guilt, low self-esteem, disturbances in sleep and appetite, poor concentration and suicidal ideations (DSM-IV, 1994). It is obvious that major depression has a disabling effect on daily activity, indicating that effective treatment is crucial. Treatment with antidepressant medication is the most common and first line treatment for many individuals. However, a significant percentage of patients do not sufficiently respond to antidepressant medication (Keller et al., 2000; Kirsch et al., 2008; Rush et al., 2006) and some of the patients proceed to electroconvulsive therapy (ECT). Despite some remarkable clinical results (Husain et al., 2004), ECT is a controversial and unpopular treatment option due to the required induction of a seizure and associated side-effects such as memory loss (Robertson and Pryor, 2006). Following initial positive results with depression, and due to its painless and non-invasive administration, rTMS has been proposed as a ‘better’ alternative to ECT (Paus & Barrett, 2004) or as an alternative for patients who may not be willing to undergo ECT, or for whom ECT may not be suitable. In order to compare efficacy of these treatments, rTMS and ECT have been jointly investigated in several studies (Eranti et al., 2007; Rosa et al., 2006). Of the several studies performed Eranti et al., (2007) observed a great advantage for ECT. However, others (Grunhaus, Schreiber, Dolberg, Polak & Dannon, 2003; Pridmore, Bruno, Turnier-Shea, Reid & Rybak, 2000; Rosa et al., 2006) found comparable efficacy rates for ECT and rTMS in the treatment of depression. Notably, studies that have reported an advantage

of ECT have compared an unlimited number of usually flexibly administered (unilateral or bilateral) ECT treatments to a fixed number of only one type of rTMS, potentially biasing the results of these studies. In addition, Eranti et al. (2007) included patients with psychotic depression whereas the other studies only involved non-psychotic depression (Pridmore et al., 2000), suggesting that rTMS might not be the best treatment option for the treatment of depression with psychotic features.

The early reports of rTMS as an antidepressant treatment modality consisted of pilot studies with a small number of subjects. In these early studies arbitrary stimulation parameters over various and non-specific brain regions were applied (Hoflich, Kasper, Hufnagel, Ruhrmann, Moller, 1993). A report by George et al. (1995) showed robust improvements in depressive symptoms in two out of six patients. This study marked the start of the serious pursuit of rTMS as a potential treatment option for depressed patients. Subsequently, a reasonably large number of open label as well as randomized sham-controlled studies were performed. Most studies found a moderately favorable treatment effect for rTMS using various designs (Avery et al., 2006; Fitzgerald et al., 2006; Fitzgerald et al., 2003; Garcia-Toro et al., 2001; Mogg et al., 2008; O'Reardon et al., 2007; Padberg et al., 1999; Rossini, Lucca, Zanardi, Magri & Smeraldi, 2005), which has recently been confirmed by several meta-analyses (Schutter, 2009a; Schutter, 2010). However, some researchers could not replicate these findings and found no differences between sham and active treatment conditions (Loo et al., 2003; Nahas, Kozel, Li, Anderson & George, 2003).

After 15 years of research, the general consensus is that rTMS treatment in depression has potential, but has not yet fully lived up to initial expectations. In large part this is due to limited understanding of the mechanisms underlying the clinical treatment effect. A substantial research effort, already in progress, may elucidate the mechanisms of the beneficial effects of rTMS in depressed patients. Hopefully, results of this effort will lead to continued improvements in treatment protocols, and provide patients with the best possible treatment of their depression.

In this chapter, a comprehensive overview of rTMS in the treatment of depression will be provided. In the first section various rTMS protocols will be reviewed in terms of the different stimulation parameters that are of interest. Subsequently, some potential physiological mechanisms that are associated with antidepressant outcome will be reviewed. In regard to this, we present an overview of rTMS-induced effects found in imaging studies, pharmacological studies and genetic studies. Finally, we will address new developments in the field.

Protocols

The behavioral effects of rTMS have been found to depend on the frequency, intensity and duration of stimulation (e.g. O'Reardon et al., 2007; Avery et al., 2006; Fitzgerald et al., 2006b; Padberg et al., 2002). The most important parameters that rTMS protocols in depression can be distinguished on are the stimulation frequency and the stimulation location. These will be discussed at length by reviewing literature that used diverse choices for these parameters. Some other relevant parameters (intensity, number of trains, inter train interval and number of sessions) will be briefly described. In Figure 2, some of the characteristics of an rTMS stimulation protocol are illustrated.

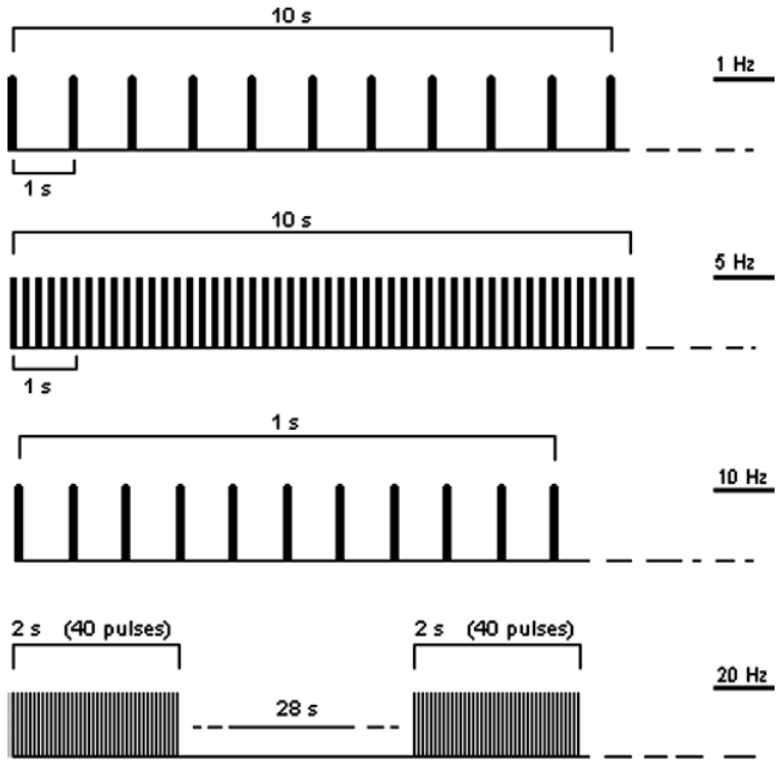


Figure 2: *Examples of 10 s of rTMS at 1 Hz (first trace) and at 5 Hz (second trace); 1 s of rTMS at 10 Hz and an example of 20 Hz application (trains of 2 s interleaved by a pause of 28 s). Figure taken and adapted from Rossi et al. (Rossi, Hallett, Rossini, Pascual-Leone & The Safety of TMS Consensus Group, 2009).*

Progress in the development of technical aspects of TMS devices and advancing insights have led to a continuing progression of experimental and innovative protocols. Some more recently developed protocols investigated in the treatment of depression, such as theta burst stimulation and deep TMS stimulation, and are discussed in the section 'new developments'.

Stimulation frequency

The stimulation frequency refers to the number of pulses delivered per second, as can be programmed on the TMS device. Examination of these rTMS studies in depression reveals that, at first glance, two types of studies can be discerned: studies performing high frequency (also referred to as fast) rTMS (HF-rTMS) and studies in which low frequency (also referred to as slow) rTMS (LF-rTMS) parameters are applied. HF-rTMS usually includes frequency parameters of 5Hz or above, whilst LF-rTMS incorporates stimulation frequencies of 1Hz or below. HF-rTMS is usually applied over the left prefrontal cortex, whilst LF-rTMS is mostly applied over the right prefrontal cortex (see 'stimulation location' for a more elaborate review). In addition to studies applying solely HF-rTMS or LF-rTMS, combined approaches have been proposed.

High frequency rTMS.

Most rTMS studies in depression to date have been performed by means of applying high-frequency stimulation (Avery et al., 2006; O'Reardon et al., 2007). To date HF-rTMS protocols have mostly used stimulation frequencies of 10 Hz (but this has varied from 5 to 20 Hz). In the largest study to date, O'Reardon et al. (2007) reported significantly better clinical results in an active rTMS group in comparison to the sham group, as measured by the Hamilton Rating Scale for Depression (HAM-D) scale and the Montgomery Asberg Depression Rating Scale (MADRS). This was a randomized study in which 301 medication-free patients were treated with 10 Hz stimulation frequency. In a recent non-industry sponsored trial, George and colleagues (2010) demonstrated that 10 Hz HF-rTMS yielded a remission rate of 14% in the active group as compared to 5% in the sham. The total number of intention to treat patients was 190, a group which was characterized by a highly treatment resistant depression. Apart from these large multi-center studies, numerous single site studies applying stimulation frequencies of 10 Hz have been performed. These have shown response (more than 50% decrease on the depression scale) rates between 30-50% (Avery et al. 2006; Garcia-Toro et al., 2001; Mogg et al., 2008; O'Reardon et al., 2007; Padberg et al., 1999; Rossini et al., 2005; George et al., 2010). Most of these studies have been performed in treatment resistant patients. A few trials which have applied frequencies of 5, 17, or 20 Hz have been reported (Fitzgerald et al., 2006; Luborzewski et al., 2007). In Fitzgerald's study (2006), patients who did not respond to a protocol with frequencies of 1 or 2 Hz (LF-rTMS see below) were assigned to either 5Hz or 10Hz HF-rTMS protocol. No significant differences in response to 5 or 10Hz were shown. In addition, Luborzewski and colleagues (Luborzewski et al., 2007) have shown beneficial treatment effects in patients who had received 10 sessions of 20Hz rTMS. Due to the limited number of studies no definitive conclusions can be drawn, but results suggest that 5, 17 or 20 Hz stimulation frequencies do at least have antidepressant effect. However, some reports have shown differential effects of different stimulation parameters, including a report of 9 Hz rTMS tending to be less beneficial than 10 Hz (Arns, 2010). To summarize, it is not yet known which exact frequencies appear to be the most beneficial in HF-rTMS, but 10 Hz rTMS has been investigated best and is often used.

Low frequency rTMS.

In addition to the HF-rTMS studies in the treatment of depression, several LF-rTMS studies have been performed (Fitzgerald et al., 2003; Januel et al., 2006; Klein et al., 1999). For example; Klein et al. (1999) showed in a large sham-controlled study that 1 Hz rTMS, in which 70 patients were randomly assigned to sham or active treatment, yielded a response rate of 49% in the active treatment as compared to 25% in the sham. This study also showed a significant larger improvement in depression scores in the active as compared to the sham group. In the largest controlled study on LF-rTMS in depression, 130 patients were initially assigned to a stimulation protocol of either 1 or 2 Hz (Fitzgerald et al., 2006). Of the 130 patients enrolled, approximately 51% could be classified as responders after 10 days of treatment. Interestingly the response rates between the 1 Hz and 2 Hz did not significantly differ. Although LF-rTMS is a more recently developed protocol and is less well studied, it appears to have beneficial effects comparable to HF-rTMS.

In order to systematically investigate if HF or LF-rTMS is more beneficial, protocols were directly compared (Fitzgerald et al., 2003; Fitzgerald, Hoy, Daskalakis & Kulkarni, 2009; Isenberg et al., 2005). In a double-blind, randomized, sham-controlled study, 60 treatment resistant patients were divided into three groups; one received HF-rTMS trains to the left prefrontal cortex at 10 Hz, the second group received five LF-rTMS trains at 1 Hz to the right prefrontal cortex and the third group received sham treatment. The clinical results showed that the groups treated with HF-rTMS and LF-rTMS had a similar reduction in depressive symptoms, and for both groups, treatment response was better than within the sham group (Fitzgerald et al., 2003). In another study with a similar aim, 27 subjects were assigned to either HF-rTMS (10Hz) or LF-rTMS (1Hz) rTMS. It was concluded that both treatment modalities appeared to be equally efficacious (Fitzgerald et al., 2009). Schutter (2010), based on a meta-analysis of all randomized controlled LF-rTMS studies in depression, suggested that LF-rTMS might even be more beneficial than HF-rTMS. However, direct comparisons of the effect sizes of HF and LF-rTMS did not show a statistically significant difference. More research with larger samples is required to confirm these findings and demonstrate if LF-rTMS and HF-rTMS are similarly efficacious, or if LF-rTMS is more efficacious than HF-rTMS. Aside from the comparison of clinical effects, it appears that LF-rTMS is better tolerated i.e. patients reported less headaches. It may also minimize the risk of inducing adverse events like seizures (Schutter, 2010).

Although the vast majority of studies have focused on low frequency stimulation applied to the right and high frequency stimulation applied to the left prefrontal cortex, it is to be noted that in a few studies parameters have varied from these traditional sites. Some have suggested that low frequency stimulation applied to the left may also have antidepressant effects, thus questioning the traditional model of laterality in depression.

Combined HF and LF-rTMS protocols.

These aforementioned studies demonstrate evidence that active HF-rTMS and LF-rTMS are more effective in the treatment of depression as compared to sham. However, HF-rTMS and LF-rTMS are not necessarily incompatible with each other. In recent years, add-on, bilateral -sequential and priming protocols have been postulated and investigated.

Add-on protocols concern the combination of one protocol with another protocol e.g. when patients do not respond to LF-rTMS after several sessions, they can proceed to HF-rTMS treatment. In the aforementioned study by Fitzgerald et al. (2006) in which LF-rTMS was investigated, non-responders to the low frequency protocol subsequently were treated with HF-rTMS. A subset of these LF-rTMS non-responders did respond to HF-rTMS. Hence, it is likely that different protocols act through different mechanisms and that different patient groups are susceptible to different approaches. It could also be argued that subjects in the add-on protocol received more sessions, and possibly needed longer to respond to treatment. Thus, the full extent of the increase in response rate might not solely be attributable to the change in stimulation frequency.

A second variant is the sequential stimulation protocol in which within one session both HF-rTMS and LF-rTMS are applied. This protocol was examined in a double-blind study that included 50 patients with depression. Half of the group received 1 Hz rTMS over the right prefrontal cortex, followed by HF-rTMS over the left prefrontal cortex in the same session, for a period of 4-6 weeks. The other half of the patients received sham stimulation in the same protocol. The higher response rates in the treatment group (44% vs. 8% in sham) suggested that a within-session LF/HF combination protocol might be more effective than applying either protocol alone (Fitzgerald, Huntsman, Gunewardene, Kulkarni & Daskalakis, 2006). However, this hypothesis could not be confirmed by a recent study by Pallanti et al. (Pallanti, Bernardi, Rollo, Antonini & Quercioli, 2010) in which a sequential combination protocol was compared with unilateral LF-rTMS and sham. Of the three groups, patients who were treated with the unilateral LF-rTMS protocol benefited most from treatment. The authors propose that these results, in contrast to the findings of Fitzgerald et al. (2006), suggest that a 'simple' unilateral protocol is the first treatment of choice. Nevertheless, the authors believe that it remains relevant to further explore combination protocols and compare them to traditional unilateral protocols.

A third option is the unilateral combination of high and low frequency stimulation in a protocol referred to as ‘priming’ stimulation. This involves the application of low intensity high-frequency trains (usually 6 Hz) followed by standard low frequency stimulation. Basic neurophysiological studies have shown that priming stimulation results in greater suppression of cortical excitability than low frequency stimulation applied alone (Iyer, Schleper & Wassermann, 2003). A single clinical study has compared such priming stimulation to 1 Hz TMS (both applied to the right side) and shown a greater clinical effect in the priming group compared to the sham group (Fitzgerald & Daskalakis, 2008).

Stimulation location

The dorsolateral prefrontal cortex (DLPFC) has been the primary area of interest for stimulation (see Figure 3). The motivation behind choosing this brain area stems from various imaging studies that indicated depression is associated with regional brain dysfunction in, among other regions, the DLPFC (Cummings, 1993). Other researchers have not only proposed an ‘underactivated’ L-DLPFC, but suggested an imbalance between frontal regions. For example, the ‘frontal asymmetry hypothesis’ of depression states that in depression there is an imbalance in left vs. right frontal brain activation (Henriques & Davidson, (1990), but also see the chapter in this book by Arns et al., 2010). In addition, of

all brain regions known to be related to the pathophysiology of depression (e.g., prefrontal, cingulate, parietal and temporal cortical regions, as well as parts of the striatum, thalamus and hypothalamus) the DLPFC is regarded as most accessible for treatment with rTMS (Wassermann & Lisanby, 2001). On the basis of such previous theories and findings, the supposedly 'activating'/ HF-rTMS protocols are applied over the left DLPFC and supposedly 'inhibiting'/LF-rTMS protocols are applied over the right DLPFC. The choice of the stimulation frequency is thus closely linked to the stimulation location.

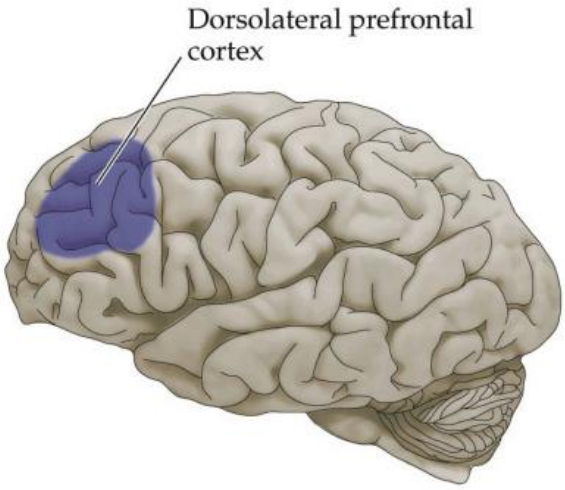


Figure 3: *Image of the location of the (left) Dorsolateral Prefrontal Cortex in the brain.*

In most studies, localizing the DLPFC has been performed by means of the '5cm rule'. The hand area of the primary motor cortex (M1) (which elicits a contralateral motor response of the thumb when stimulated), is taken as the detectable reference point. From there, the coil is moved 5 cm anteriorly, in a sagittal direction. Positioning the coil at that location during treatment is assumed to target the DLPFC. It can be argued that this literal "rule of thumb" has some flaws and may result in inconsistent results between sessions within subjects. Moreover, it may not target the DLPFC at all due to differences in head size and shape across individuals and—even more relevant—in the folding patterns of the cortex. In order to solve this problem, technical advances have enabled structural MRI based neuronavigation systems. In neuronavigation, an MRI of a patient's brain is acquired before treatment. A series of software co-registrations are made between real anatomical points on the head (which are fixed in location) and the corresponding anatomical points in a three-dimensional reconstruction of the patient's MRI scan. This allows one to establish the scalp point that corresponds to a location on the brain scan that becomes the proposed target for TMS treatment. A more complicated process can also allow the position and orientation of the coil relative to the corresponding brain region to be monitored in real time. In a study by Herwig et al. (Herwig, Padberg, Unger, Spitzer & Schönfeldt-Lecuona, 2001) the reliability of the '5 cm rule' was investigated by means of comparing the target area defined by the '5 cm rule', with the target defined by DLPFC neuronavigation. Of the total 22 subjects, the targets corresponded in only seven. In a similar study, it was found

that the true DLPFC was in general located more anteriorly to the site traditionally identified by the '5 cm rule' (Fitzgerald et al., 2009).

Together, these studies suggest that clinical efficacy may be improved by means of more precise targeting methods. This has been directly tested in one study with 52 patients who were randomized to stimulation localized by the '5 cm rule' or neuronavigation (Fitzgerald et al., 2009). Neuronavigationally targeted treatment resulted in a statistically significant greater response in depression scores than treatment targeted by the traditional method.

Despite the fact that the majority of the studies target the DLPFC, some authors have argued that it has never been experimentally proven that the DLPFC is the most effective target for rTMS treatment of depression. In addition, the pathophysiology of depression is certainly not limited to the DLPFC (Drevets, Price & Furey, 2008). Investigation of antidepressant effects of rTMS applied to other brain regions has therefore been explored (Schutter, 2009a; Schutter, Peper, Koppeschaar, Kahn & van Honk, 2005). Schutter and colleagues (Schutter, 2009a) applied 2 Hz rTMS at 90% of the motor threshold (see next section) to the right parietal cortex in a group of patients with depression for a period of 10 sessions. Their findings did not show statistically significant changes between the active and sham group. However, comparison of both groups on a partial response outcome (at least a 30% reduction in HAM-D score) showed a significantly higher response in the active rTMS group as compared to the sham group. This result suggests that targeting the right parietal cortex with 2Hz rTMS may have antidepressant properties, although the effects were not as strong as compared to frontal HF or LF-rTMS. Although these findings need to be replicated in larger studies, they are encouraging regarding searching for other cortical targets in the treatment of depression with rTMS.

Stimulation intensity, trains and sessions

For rTMS to be effective, the magnetic field has to induce currents in the neurons of the cortex. The intensity of the magnetic field that induces this current is referred to as the stimulation intensity. This is usually expressed as a percentage of the motor threshold (MT). The MT is usually determined prior to each session by applying the TMS coil over the 'thumb' area of the motor cortex. Single pulses are applied by stepwise variation of the output intensity of the device. The minimal output intensity which yields a motor response (moving of the thumb) in at least half of the applied trials is determined to be the MT. So if the intensity of a TMS protocol is 100% MT, then it is the same as the output intensity of the device which was determined to be MT. All other intensity values are reflected as a percentage of this MT, e.g. if the MT is at an output intensity of the device of 60%, than an intensity of 110% MT means that the output intensity is 66%. Although this determination of stimulation intensity may seem arbitrary, it takes individual differences in motor cortex excitability (and therefore excitability of other brain regions) into account. This contributes to a safer administration of TMS pulses to an individual. In depression protocols reported to date, the lowest stimulation intensity used was 80% MT (George et al., 1995) and the maximal intensity used was 120% MT (O'Reardon et al., 2007; Rumi et al., 2005). The majority of the depression protocols use stimulation intensities of 100% MT or 110% MT. In a study by Padberg et al. (2002), in which the relation between treatment efficacy and stimulation intensity was investigated, patients who were treated with a HF-rTMS (10Hz)

protocol at 100% MT showed a 30% decrease in depressive symptoms as measured by the HAM-D, as compared to a 15% decrease for patients who were treated with the same protocol but at 90% MT. This result, among others, suggests more beneficial outcomes for higher stimulation intensities. Therefore, more recent studies have used intensities of 110% and 120% MT (O'Reardon et al., 2007; Rumi et al., 2005), in contrast to earlier research where intensities between 80% and 100% MT were more common (George et al., 1997; Kimbrell et al., 1999).

In most rTMS protocols the stimulation is delivered in pulse trains (see Figure 2). That is, pulses are delivered in trains and are separated by certain time intervals: the inter train interval (ITI). This is done for two reasons. First, the effect of TMS pulses is cumulative in the brain (Hallett, 2007; Ridding & Rothwell, 2007; Rossi & Rossini, 2004), and this summation causes an increase of the likelihood of the induction of a seizure (the most serious potential side-effect associated with rTMS). In several reports, safety guidelines in which maximum recommended values of stimulus parameters like stimulus intensity, train duration, number of trains and ITI are provided for the safety of the patients (Rossi et al., 2009; Wassermann, 1998). Secondly, the repetitive release of strong electrical pulses causes heating of the electronics of the TMS device. The ITI between trains allows the device to partially cool down. Due to safety reasons for the subject and protection of the device, all devices are manufactured to automatically turn off as soon as a certain heat-limit has been reached. Newer TMS devices are designed with better cooling systems (e.g. air or fluid cooled coils), which reduce the likelihood of overheating. However, the overheating of the device is still possible when multiple sessions are performed within a short period, or if a highly demanding (e.g. high rate of pulse delivery) protocol is performed. Train durations in HF-rTMS protocols are usually between 2 and 10 seconds with an ITI between 20-60 seconds. In LF-rTMS protocols often, continuous stimulation is used.

In studies performed thus far, the number of sessions applied has been highly variable, ranging from 5 sessions (Manes et al., 2001; Miniussi et al., 2005) to up to or greater than 30 sessions (Fitzgerald et al., 2006; O'Reardon et al., 2007). However, to date, the majority of studies have involved a total of 10 sessions (for example, Fitzgerald et al., (2003); Garcia-Toro et al., (2001); Koerselman, Laman, van Duijn, van Duijn & Willems, (2004); Poulet et al., (2004)). Based on more recent studies, a general trend towards a greater number of sessions (>10) are associated with continuing improvement in depression scores (Fitzgerald et al., 2006; Rumi et al., 2005; Spronk & Arns, 2009). Schutter (2009a) suggested that similar to antidepressant medication, rTMS treatment may involve a delayed therapeutic onset. Investigation of the number of sessions optimally required is important for gaining information about the temporal course of the antidepressant effect.

The variety of protocols discussed above indicate that rTMS is an active field of research. Treatment outcome has been shown to vary with protocols, but some protocols have proven their efficacy. However, it has been argued that it is unlikely that the current combinations of stimulation parameters potentiate optimum clinical effects. It is likely that there is much room for improvement, and studies directly addressing the question of optimal stimulation parameters are urgently required. This statement is further supported by the finding that early rTMS depression protocols have shown less favorable results compared to relatively newer, more promising protocols (Gross, Nakamura, Pascual-Leone

& Fregni, 2007). Increasing knowledge about the mechanisms underlying treatment efficacy – the topic of the next section - may result in new protocols with closer to optimal treatment effects.

Mechanisms of rTMS treatment in depression

With rTMS the goal is to modulate brain activity, with a resultant reduction of depressive symptoms. Although clinical results appear promising, mechanisms explaining the symptomatic reduction are unknown. In order to optimize rTMS for therapeutic use, it is necessary to gain a better understanding of possible neurobiological mechanisms underlying the clinical response. This is currently a topic of active interdisciplinary research.

Knowledge of neurobiological mechanisms to date is derived from neuroimaging studies, studies on neurotransmitter and neuroendocrinologic systems and from gene expression research. Together, these efforts will hopefully explain the substrate of the antidepressant effects of rTMS. In the following paragraphs, studies in each of the fields mentioned above on rTMS-induced changes will be reviewed. The neurophysiology of rTMS at the neuronal level in general is outside the scope of this review. However, the interested reader is referred to an excellent review by Wasserman and colleagues on this topic (Wassermann, Epstein & Ziemann, 2008).

Neuroimaging

The combination of rTMS with neuroimaging research provides a unique opportunity to elucidate the underlying mechanisms of rTMS in the treatment of depression. Most imaging studies to date have used positron emission tomography (PET) or single-proton emission computed tomography (SPECT) to identify brain regions with altered blood flow or glucose metabolism as a result of rTMS. These modalities have lower temporal resolution compared to fMRI, and therefore not much is known about the time course of brain activation in response to rTMS. Recently however, some studies using near-infrared spectroscopy (NIRS) have been performed (Aoyama et al., 2009; Hanaoka, Aoyama, Kameyama, Fukuda & Mikuni, 2007; Kozel et al., 2009).

As discussed in the “Protocols” section, in most depression protocols rTMS is applied over the left or right DLPFC. Several neuroimaging studies have indeed demonstrated rTMS-induced changes within the DLPFC. HF-rTMS over the left DLPFC of depressed patients induces a local increase in regional cerebral blood flow (rCBF) as indicated by SPECT (Catafau et al., 2001; Kito, Fujita & Koga, 2008a; Speer et al., 2000) and fMRI BOLD response (Cardoso et al., 2008). In contrast, imaging studies of LF-rTMS over the right DLPFC showed a local decrease in rCBF (Loo et al., 2003; Speer et al., 2000). It should be noted however, that in an fMRI study (Fitzgerald et al., 2007) could not replicate the local decrease in BOLD response following LF-rTMS. Instead, a bilateral frontal reduction in BOLD response was observed.

In early studies using PET/SPECT it was shown that changes in brain activation induced by rTMS were not limited to the stimulated area (Paus et al., 1997). A single TMS pulse can lead to effects in more distal brain areas within the same network as the stimulated area (Siebner et al., 2009). In a similar vein, rTMS-induced changes in brain activity in depression may not necessarily be limited to the DLPFC; remote regions are often in good accordance with areas known to be associated with the pathophysiology of depression (reviewed in (Fitzgerald et al., 2006c). In support of this theory, imaging studies cited above have also found changes in blood flow in remote/subcortical brain regions following rTMS (Baeken et al., 2009; Loo et al., 2003; Speer et al., 2000). Other brain regions which have been reported to show a change in rCBF after HF-rTMS over the left DLPFC are the ventrolateral prefrontal cortex, right-dominant orbitofrontal cortex, the anterior cingulate, the left subgenual cingulate, the anterior insula, and the right putamen/pallidum (Kito et al., 2008a). Of clinical relevance, it was demonstrated that increases in rCBF in the L-DLPFC are related to significant improvement in clinical outcomes, and that increases in the R-DLPFC and subcortical regions mentioned above are negatively correlated with the change in depressive symptoms (Kito et al., 2008a).

One neuroimaging study has directly compared the effects of high frequency stimulation applied to the left side with low frequency stimulation applied to the right (Fitzgerald et al., 2007). This study, using fMRI recordings during a cognitive task, found that low frequency stimulation produced a bilateral reduction in neural activity whereas high frequency stimulation had the opposite effect. The direction of these effects was in keeping with traditional models of the effect of low and high frequency TMS. However, the fact that changes were produced bilaterally when both groups improved clinically to a similar degree, is not consistent with laterality models of depression, such as that proposed by Henriques and Davison (1990).

Event related potentials (ERPs), and especially late ERPs, are related to cognitive processes such as attention, stimulus evaluation and early visual detection. Similar to other psychiatric disorders, a reduced P300 amplitude is often observed in depression (Blackwood et al., 1987; Himani, Tandon & Bhatia, 1999). In a study by Möller et al. (Möller, Hjaltason, Ivarsson & Stefánsson, 2006) it was demonstrated that active TMS was associated with a significant increase in the P300 amplitude after 5 daily HF-rTMS sessions over the left DLPFC. In a study by our own group it was shown that using an auditory oddball paradigm, patients who were treated with HF-rTMS over left DLPFC showed localized changes on N1, P2, N2 and P300 amplitudes over left frontal areas, but not over the right frontal region. These results were interpreted as an increased positivity in the ERP, which was localized to the stimulated area only (Spronk et al., 2008).

These findings demonstrate specific and selective alterations induced by repeated rTMS, which are distinct from those induced by other antidepressant treatments. The rTMS induced effects on neuroanatomical functions are commensurate with some known abnormalities in depression, e.g. decreased rCBF and metabolism values (Baxter et al., 1989; Biver et al., 1994). Additionally, other research has shown similar changes in rCBF and metabolism relating to improvement of depression either after spontaneous recovery (Bench, Frackowiak & Dolan, 1995) or after treatment with antidepressant medication (Kennedy et al., 2001).

Neurochemical effects: Neurotransmitters and Neuroendocrinology

Apart from altering rCBF in stimulated regions and connected networks, rTMS also has an effect on the neuroendocrinologic (Post & Keck, 2001) and neurotransmitter systems (Ben-Shachar, Belmaker, Grisaru & Klein, 1997; Strafella, Paus, Barrett & Dagher, 2001). Many lines of research on antidepressant mechanisms have focused on monoaminergic neurotransmission, i.e. through dopamine, norepinephrine and serotonin. Depression is thought to be associated with deficiencies in monoaminergic neurotransmission, and antidepressant medication is thought to act through enhancement of monoamines. These three neurotransmitter systems have also been investigated in relation to rTMS treatment (Ben-Shachar et al., 1997; Keck et al., 2000), and most studies support a role for the dopaminergic system. By means of microdialysis techniques in animal models, it was demonstrated that HF-rTMS induced an increase in the release of dopamine in the hippocampus (Ben-Shachar et al., 1997; Keck et al., 2000; Keck et al., 2002), the nucleus accumbens (Keck et al., 2002; Zangen & Hyodo, 2002) and dorsal striatum (Keck et al., 2002). It should be noted, however, that there are many methodological issues making interpretations from animal rTMS research difficult, such as the size of the head in relation to the coil size.

A few years later rTMS induced changes in dopamine were investigated for the first time in human subjects. Strafella et al. (2001) found an increased dopamine release after HF-rTMS over the left DLPFC in the ipsilateral nucleus accumbens of healthy subjects by use of a PET imaging (Strafella et al., 2001). The observation that increased dopamine levels were only found in the ipsilateral striatal area (site of stimulation) was particularly interesting, because it suggests that the increased release was exerted through cortico-striatal projections from the targeted DLPFC (Strafella et al., 2001). Taking this one step further, Pogarell and colleagues also found an increased striatal dopamine release in a small group of depressive patients after HF-rTMS over the left DLPFC by using SPECT (Pogarell et al., 2007; Pogarell et al., 2006). In these two studies, no correlation between the binding factors reflecting dopamine release and clinical outcome could be demonstrated. This needs to be investigated further in larger controlled studies (Pogarell et al., 2006).

In the study performed by Keck and colleagues (Keck et al., 2002), an rTMS-induced effect on dopamine was found by using intracerebral microdialysis, but no effects on norepinephrine and serotonin were found. This finding suggests that rTMS mainly targets the dopamine system. Nevertheless, there are some indications that rTMS might modulate serotonergic neurotransmission. For instance, Juckel et al. (Juckel, Mendlin & Jacobs, 1999) showed that electrical stimulation of the prefrontal cortex of the rat resulted in an increased serotonin level in the amygdala and hippocampus; a similar pattern of release may occur after stimulation by rTMS. In addition, studies on serotonergic receptors and binding sites (which indirectly provide a measure of availability of certain neurotransmitters in the brain) after a single TMS session in a rat model showed an increase in serotonergic binding sites (Kole, Fuchs, Ziemann, Paulus & Ebert, 1999), and down-regulation of receptors in cortical as well as subcortical areas (Ben-Shachar, Gazawi, Riboyad-Levin & Klein, 1999; Gur, Lerer, Dremencov & Newman, 2000). With the exception of Keck et al. (2000) who found no effects on serotonin, no rTMS research has been conducted on the serotoninergic system in depression models, or in human depressed patients. This makes claims about TMS-induced

changes on serotonin release highly speculative. Similarly speculative are claims regarding the effects of rTMS on the third member of the monoaminergic group, noradrenalin (norepinephrine). Limited studies are available and the findings are heterogeneous. Keck et al. (2000) found no changes on noradrenalin. Conversely, study investigating changes in monoaminergic transporter mRNA after a 20-day rTMS course in a mouse found increased levels of noradrenalin transport mRNA were associated with increased binding and uptake of this neurotransmitter (Ikeda, Kurosawa, Uchikawa, Kitayama & Nukina, 2005).

Another possible mechanism through which rTMS exerts its antidepressant effect involves the modulation of GABA and glutamate, which, respectively, are the main inhibitory and excitatory neurotransmitters. Both neurotransmitters are known to be associated with the pathology of depression and change with clinical improvement in depression (Petty, Kramer, Gullion & Rush, 1992; Sanacora, Rothman, Mason & Krystal, 2003). So far, only a few studies have directly addressed rTMS-induced changes in GABAergic neurotransmission. In an animal model, GABAergic levels were increased in hippocampal regions and striatum, and reduced in hypothalamic regions after 15 days of LF-rTMS stimulation (Yue, Xiao-Lin & Tao, 2009). The same authors looked at glutamatergic changes and found similar results: an increase in glutamate in striatal and hippocampal regions, but a decrease in the hypothalamus (Yue et al., 2009). Additionally, in an in vivo study of depressed patients with a specific focus on the nucleus accumbens, changes in glutamate levels were observed after successful treatment of 10 HF-rTMS sessions (Luborzewski et al., 2007). Interestingly, the pre-treatment baseline level was related to treatment effects. Responders showed lower pre-treatment glutamate levels, and showed the highest increase in glutamate after successful treatment (see also later section on 'optimizing treatment'). This suggests that in at least some of the patients, a reduction of depressive symptoms may happen through a restoration of relative glutamate levels (Luborzewski et al., 2007).

Repetitive TMS is known to exert changes in excitability thresholds on a neuronal level. It is known that LF- rTMS in particular induces prolonged decreases in motor cortex excitability (Chen et al., 1997), while HF-rTMS induces an increase in motor cortex excitability (Pascual-Leone, Valls-Solé, Wassermann & Hallett, 1994). Cortical excitability is thought to be to be maintained by a balance of neurotransmitter levels of GABA and glutamate. It can be hypothesized that glutamate and GABA in this animal model is mediated by excitability levels. To the best of the author's knowledge, only Luborzewski's study (Luborzewski et al., 2007) investigated rTMS induced changes in levels of glutamate in depressed patients. More research on the release of GABA and glutamate by means of using in vivo techniques is needed to better specify the involvement of these neurotransmitters. In addition, future studies should specifically address the relationships between GABA/Glutamate, treatment and outcome.

Neurotrophins

Another candidate as a mechanism for the rTMS treatment effect in depression is the modulation and release of neurotrophins. BDNF is a neurotrophin which plays a role in survival of neuronal cells and in synaptic plasticity and connectivity (Bath & Lee, 2006). In patients with depression, abnormal expression of BDNF has been observed (Shimizu et al.,

2003) and, moreover, an up-regulation as a result of antidepressant medication (Angelucci, Brenè & Mathé, 2005; Shimizu et al., 2003) has been demonstrated. Since there is an extensive literature that indicates a relation between BDNF and depression (and related outcomes), BDNF became another likely candidate to investigate in relation to the antidepressant treatment response to rTMS.

BDNF serum and plasma levels have, in fact, been investigated in several rTMS studies (Angelucci et al., 2004; Yukimasa et al., 2006; Zanardini et al., 2006). In a preliminary study by Lang et al. (Lang, Bajbouj, Gallinat & Hellweg, 2006) no changes in BDNF serum level were observed after 10 sessions of HF-rTMS treatment. However, other studies on HF-rTMS-induced effects in treatment of depression yielded different findings (Yukimasa et al., 2006; Zanardini et al., 2006). In one study, BDNF serum levels were assessed before and after a series of 5 rTMS sessions and considered in relation to treatment outcome as rated by the HAM-D. Half of the participants (N=8) were treated with a LF-rTMS design, while the other half (N=8) were treated with a HF-rTMS design. Results showed that BDNF serum levels significantly increased over the treatment period. Interestingly, no changes between the HF and LF group were found, i.e. both showed equal increases in BDNF levels (Zanardini et al., 2006). In a study by Yukimasa et al. (2006) a similar relationship between treatment response and BDNF plasma levels was observed in a group of 26 patients who were treated with HF-rTMS. BDNF plasma levels increased at the end of the treatment period, but solely in patients who could be classified as responders (>50% decrease in depressive symptoms as measured on the HAM-D scale) or partial responders (>25% decrease in depressive symptoms). Together, these findings suggest that rTMS is indeed able to induce effects on BDNF levels. The finding that BDNF levels were changed only in the responder group suggests that the BDNF level is related to the clinical outcome, rather than simply a physiological effect. This is further supported by the finding that responses to HF and LF-rTMS appear to be similar.

Genetics

In the above-mentioned studies, several likely candidates associated with (and perhaps responsible for) an rTMS-induced antidepressant response were discussed. Another group of candidates includes genetic effects. As discussed in the 'neurotrophin' section, the modulation of the expression of brain-derived neurotrophic factors (BDNF) is a likely modulating factor through which treatment response is exerted. Hence, it is not surprising, that some of the genetic studies have focused on BDNF mRNA expression (Müller, Toschi, Kresse, Post & Keck, 2000). Müller and colleagues investigated BDNF mRNA expression in an animal model involving applying 55 HF-rTMS sessions over a period of 11 weeks. They found significant increases in BDNF mRNA expression in the hippocampus (CA3 region) and parietal and piriform cortices. In addition, in an animal model of vascular dementia, mRNA expression in the hippocampal CA1 area was investigated in two groups of rats; one group received LF-rTMS and the other group received HF-rTMS for a period of six weeks. Both groups showed an increase in mRNA protein expressions of BDNF (Wang et al., 2010). However, in yet another genetics study, no rTMS induced effects on BDNF mRNA expression could be demonstrated (Hausmann, Weis, Marksteiner, Hinterhuber & Humpel, 2000), possibly due to a relatively small number of sessions. Further limitations are that effects

were not shown in a specific animal model of depression in any of these three studies. Also, the number of studies in this area is limited. For a discussion on genetic polymorphisms and treatment outcome in human patients see the section 'Optimizing treatment'.

New Developments

As a new and dynamic field, rTMS is the topic of a considerable research and innovative developments are numerous. These developments are of a diverse nature, including technological progress in equipment and software, protocol innovations and optimizations, and advances in the understanding of long-term effects. Some examples are the investigation of applicability of theta burst stimulation (the delivery of bursts of 50 Hz pulses usually at a rate of 5 Hz) and new equipment such as the H-coil for deeper brain stimulation.

Progress in protocols

In addition to the 'traditional' LF and HF frequency studies, a newly developed theta-burst stimulation (TBS) protocol has been proposed; referred to as 'patterned TMS'. This has been put forward as a technique that could have important implications for the treatment of conditions such as epilepsy, depression and Parkinson's Disease (Paulus, 2005). TBS usually involves short bursts of 50 Hz rTMS applied at a rate of 5Hz (hence the name theta burst stimulation). In fact there are two frequencies within one train of stimuli; the inter burst frequency of 50 Hz (e.g. 3 pulses at a rate of 50 Hz) and the frequency of delivery of the number of bursts within one second which is at a rate of 5 per second (5 Hz). TBS can be applied as either a continuous (cTBS), or intermittent (iTBS) train (Huang, Edwards, Rounis, Bhatia & Rothwell, 2005). See Figure 4 for an illustration of both types of TBS protocols.

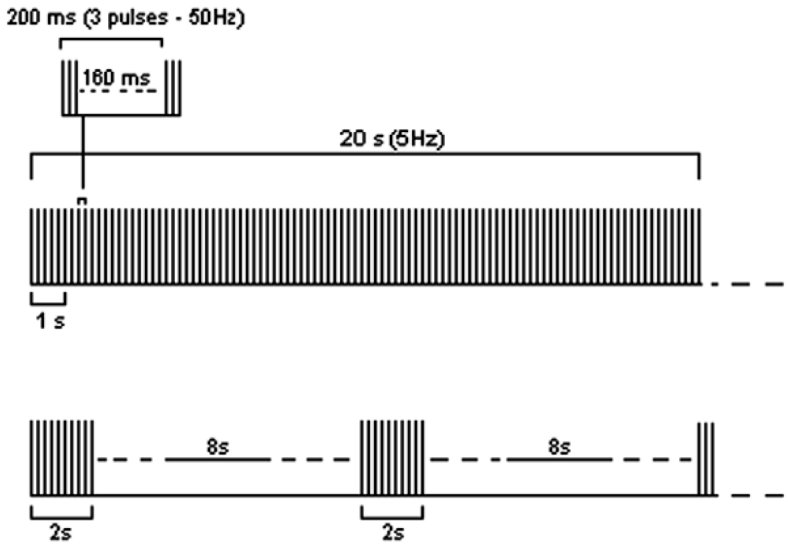


Figure 4: *examples of the two most common TBS protocols: continuous TBS (first trace) and intermittent TBS (second trace). Figure taken and adapted from Rossi et al. (2009).*

Until recently, this rapid delivery of pulses as happens in a TBS protocol was not possible due to technical limitation of older stimulators. TBS has therefore only been investigated since 2005 (Huang et al., 2005). In the years after its introduction, it has been shown that TBS induces changes in cortical excitability that may last longer than with traditional TMS protocols (Huang et al., 2009; Ishikawa et al., 2007). In regard to the observation of the more sustained effect, Chistyakov et al. (Chistyakov, Rubicsek, Kaplan, Zaaroor & Klein, 2010) suggested that TBS might be more effective than traditional HF and LF-rTMS in the treatment of depression. They assigned 33 patients to different types of TBS-TMS treatment protocols over either left or right DLPFC. Despite the relatively high response rate, these findings should be regarded as preliminary and non-specific since no changes between different types of protocols were observed. To the authors' knowledge, this is the only study that has investigated the antidepressant effect of TBS-TMS in the treatment of depression. However, since the TBS protocols are assumed to be more capable of inducing long-lasting effects, it is likely that their application in rTMS depression treatment will increase in coming years.

Technical progress

In response to limitations of currently used coils, a new type of coil 'the H-coil' (Brainsway) was developed. The coils that are in current use (figure of eight/circular coils) are thought to penetrate underlying brain tissue only to a depth of 1.5-2cm and are not capable of directly targeting deeper brain regions (Zangen, Roth, Voller & Hallett, 2005). H-coils, on the other hand, are capable of stimulating deeper brain regions (Zangen et al., 2005). To date, there are several reports in which it has been presented that brain stimulation by means of the H-coil is safe and that there is potential for use of the coil in clinical applications (Levkovitz et al., 2007; Zangen et al., 2005). The application of the H-coil in the treatment of depression is currently under investigation in a multi-site trial.

Optimizing treatment

A better understanding of the neurophysiological and clinical features of depressed patients who respond to rTMS, together with clarity on the neurobiological mechanisms of the induced effect of rTMS treatment in depression, will contribute to the development of more effective forms of rTMS. The field involved in identifying such features is referred to as personalized medicine: a research towards establishing patient's characteristics (clinical, physiological or parametric variables) related to (better) clinical outcome. Especially relevant to the rTMS area is the research on identifying objective markers of clinical response. Several studies have focused on addressing this question by investigating specific clinical features. Negative predictors for treatment outcome identified so far are age (Brakemeier, Luborzewski, Danker-Hopfe, Kathmann & Bajbouj, 2007; Fregni et al., 2006) and therapy resistance (Brakemeier et al., 2007; Brakemeier et al., 2008; Fregni et al., 2006). These results suggest that elderly patients and patients with a greater number of prior treatment failures are likely to benefit less from rTMS. However, this has not been confirmed by all studies in this area (Fitzgerald et al., 2006). In contrast, shorter duration of the depressive episode and high level of sleep disturbance are predictive of better treatment outcome (Brakemeier et al., 2007).

A different group of potential predictors can be obtained from the neurophysiological data. One study indicated that some patients with depression responded better to LF-rTMS, while others improved only after treatment with HF-rTMS (Kimbrell et al., 1999). These two patient groups differed on pre-treatment baseline regional cerebral blood flow. Patients with a relatively low level of rCBF generally responded better to HF-rTMS (20Hz), whereas patients displaying relatively high baseline rCBF levels showed a better response to LF-rTMS (Kimbrell et al., 1999). Baecken et al. (2009) showed that higher bilateral baseline metabolic activity in the DLPFC and anterior cingulate cortex correlated with better treatment outcome. In addition, Speer et al., (2009) correlated treatment outcome after 2 weeks of LF or HF-rTMS with pre-treatment baseline perfusion measures. Baseline hypo-perfusion was associated with a more beneficial effect of HF-rTMS compared to LF-rTMS (Speer et al., 2009).

While EEG measures have been relatively well studied in the prediction of treatment response to antidepressant medication (Bruder et al., 2008; Cook et al., 1999; Spronk et al., 2011), their potential in predicting response to rTMS treatment is generally considered limited but promising. In the search for physiological markers for treatment response to rTMS, Price and colleagues (Price, Lee, Garvey & Gibson, 2008) investigated alpha EEG activity measures, i.e. individual alpha power and frequency, and asymmetry index in 39 patients with treatment resistant depression. None of the measures were found to be a promising candidate for response prediction. Recently Daskalakis et al. (2008) were the first to report the potential predictive value of an EEG biomarker initially developed for prediction of treatment response to antidepressant medication. This biomarker (labeled antidepressant treatment response (ATR) index) is measured from frontal electrode positions and is based on the proportion of relative and absolute Theta power. In Daskalakis's study it was shown that subjects who could be classified as 'responders' after 6 weeks of treatment scored higher on this ATR index. As these early reports indicate, current knowledge of the utility of EEG in the prediction of antidepressant treatment outcome is limited. It has, however, been proposed as having great potential for predicting response to rTMS in the treatment of depression. For example, it has been suggested that rTMS can potentially interact with specific EEG frequency patterns (Funk & George, 2008). In accordance with this notion, Jin et al. (Jin, O'Halloran, Plon, Sandman & Potkin, 2006) compared different rTMS stimulation frequencies in the treatment of patients suffering from schizophrenia; two groups received treatment with conventional frequencies, but one group was treated with a stimulation frequency identical to their individualized frontal alpha peak. The group who received the individualized frequency showed a higher reduction in negative symptoms in comparison to the patients who were treated with standard stimulation frequencies. In a report by Arns et al. (2010) a similar approach was taken in the treatment of depression. However, in this study subjects were treated with a stimulation frequency of one Hz above their individualized alpha peak frequency. The results demonstrated this type of individualized stimulation frequency was not beneficial. In contrast, this study suggested that there could be differential effects of different TMS stimulation frequencies; more specifically, 9 Hz yielded different effects compared to 10 Hz TMS. Furthermore, the study by Arns et al. (2010) demonstrated a clear relation of an individual alpha peak frequency to clinical outcome, where a low alpha peak frequency (7-8 Hz) was associated with lower clinical efficacy. This was also shown in a study by Conca and colleagues (2000) who found

that non-responders to rTMS had a slower alpha peak frequency. Clearly, more studies are needed to further explore this.

In addition to demographical and physiological markers, genetic markers may have potential in the prediction of treatment outcome. Several genetic polymorphisms have been investigated in relation to antidepressant treatment outcome in medication studies, for example, BDNF, COMT and serotonin-related candidate genes (Benedetti et al., 2009; Peters et al., 2009; Zou et al., 2010). However, genetics as potential biomarkers for susceptibility to antidepressant medications is still a relatively novel concept, and only a limited amount of research has been conducted. This holds also for the investigation of genetic predictors of rTMS treatment outcome. As discussed previously in this chapter, several studies show treatment-induced changes on BDNF. To date, in respect to the rTMS treatment of depression several genetic polymorphisms have been proposed to be related to treatment outcome. Among them are the genetic polymorphisms associated with BDNF expression, the BDNF Val66Met (Bocchio-Chiavetto et al., 2008; Cheeran et al., 2008) and candidate genes related to expression of serotonin (Bocchio-Chiavetto et al., 2008; Zanardi et al., 2007) (for a discussion of BDNF and serotonin release, see the earlier section of this chapter 'mechanisms').

Bocchio-Chiabetto and colleagues (2008) demonstrated in their study that carriers of the LL variant of the 5-HTTLPR gene showed significantly greater decreases in depressive symptoms following rTMS (as reflected by % decrease on the HAM-D), in comparison to carriers of the S allele. The serotonin-related polymorphisms SERTPR and 5-HT(1A) have also been investigated in relation to depression treatment outcome (Zanardi et al., 2007). Results indicated that polymorphisms related to both genes were to some extent related to treatment outcome, but carriers of the 5HT(1A) C/C gene specifically received more benefit from active rTMS than sham rTMS. This was in contrast to polymorphisms carriers of the SERTPR gene, who showed response to treatment outcome regardless of the treatment condition (active or sham).

In addition to their finding on the relation of the 5-HTTLPR with treatment outcome, Bocchio-Chiabetto and colleagues (2008) demonstrated in the same study that BDNF Val/Val homozygotes were better responders than carriers of the Met allele (carriers of MET/MET or MET/VAL). These outcomes can be linked to the study results of Cheeran et al. (2008), who compared differences in excitability measures between Val/Val carriers and carriers of the Met allele. Subjects were investigated using two TBS protocols; a cTBS protocol which is thought to suppress excitability and an iTBS protocol which is known to generally cause an increase in excitability. Change in amplitude measures of the Motor Evoked Potential was taken as an outcome measure reflecting excitability. The results showed that Met allele carriers had less (or no) rTMS induced changes in excitability; in both TBS protocols no changes in excitability in either direction were evident. Highly speculatively, it can be argued that these results potentially indicate that this same group of Met carriers are less receptive to rTMS induced clinical improvement. However, it must be emphasized that iTBS and cTBS TMS protocols are very different from traditional HF and LF rTMS depression protocols.

In summary, although rTMS is a relative newcomer among the treatment options for depression, the investigation of 'individual characteristics' related to treatment response appears to be progressing rather rapidly. Developments to date seem to mainly focus on

fMRI and PET imaging studies and to a lesser extent on genetic polymorphism and EEG parameters. Possibly this is due to the observed direct and indirect interactions with underlying brain regions, and the fact that PET and fMRI imaging are especially effective for highlighting induced changes in regional blood flow and metabolism. The utility of genetic polymorphism in relation to predicting treatment response, in particular the BDNF gene, has potential. TMS devices now allow for a fairly extended choice in treatment parameters (e.g. stimulation intensity, location, frequency etc.). The application of physiological predictors may better guide the parameters to be selected in the future. Evidence for considerable clinical efficacy is required if rTMS is to become accepted as a regular treatment option for depression.

Acknowledgements

The authors would like to thank Michiel Kleinnijenhuis for reading the manuscript and providing valuable comments.

Chapter 9

Potential differential effects of 9 Hz rTMS and 10Hz rTMS in the treatment of depression.

Arns, M., Spronk, D., & Fitzgerald, P. B. (2010). Potential differential effects of 9 Hz rTMS and 10 Hz rTMS in the treatment of depression. *Brain Stimulation*, (3), 124-126.

The majority of high-frequency rTMS studies in depressed patients employ 10 Hz stimulation over the left dorsolateral prefrontal cortex (DLPFC). However, several placebo-controlled trials have used different stimulation frequencies such as 5, 10, 15, 17, 20 and 25 Hz (Schutter, 2009b) and all found antidepressant effects. The choice of high-stimulation frequencies to date, has remained fairly random and have rarely been based on individual physiological characteristics of a patient. To the author's knowledge, only 2 studies, neither in depressed patients, have employed an EEG based approach to establish the rTMS frequency which was linked to the individual patients' alpha peak frequency (iAPF). Klimesch et al. (2003) and Jin et al. (2006) both demonstrated that subjects with personalized individual alpha peak frequency (iAPF) determined rTMS had greater effects (better improvement at a mental rotation task (Klimesch et al., 2003) and a higher improvement in negative symptoms in a group of patients with schizophrenia (Jin et al., 2006)) in comparison with two groups that received treatment with 3Hz and 20 Hz stimulation frequencies. Both these studies demonstrated frequency specific effects titrated to the individual subject.

These two papers and the availability of full quantitative EEG (QEEG) data led us to investigate the relationship between the iAPF and the decrease in depressive symptoms in a group of depressed patients who were treated with a 10 Hz rTMS stimulation protocol (110% MT; ITI= 30s., 30 trains; Train length 5 s., Based on 5 cm. rule, for more details also see (Spronk et al., 2008)) treated in an open-label manner. The iAPF was quantified from location F3 during Eyes Closed EEG. Figure 1 shows the percentage decrease on the BDI against the frontal iAPF of the patients who received treatment with the standard stimulation frequency of 10 Hz (black). The black bars, representing treatment responses of 24 patients treated with 10 Hz rTMS, show a relation between iAPF where a lower APF was related to a smaller decrease in depressive symptoms. The most striking finding was that patients with an iAPF of 9 Hz (1 Hz below the stimulation frequency of 10 Hz) seemed to benefit most from the treatment. Based on these initial findings and the study by Klimesch (Klimesch et al., 2003), we adjusted our protocol to stimulate all clients at an individualized stimulation frequency of iAPF + 1 Hz (see Figure 1, grey bars). We kept all other stimulation parameters identical such as total number of stimuli, inter stimulus interval, percentage motor threshold etc.

Based on the fact that previous high-frequency studies have shown beneficial treatment effects for various stimulation frequencies (e.g. 5, 10, 15, 17, 20 and 25 Hz, (Schutter, 2009b)), there was no reason to assume that treatment frequencies other than 10 Hz would result in non-beneficial treatment effects. In contrast; by means of individualizing the stimulation frequency based to one's iAPF, larger and faster beneficial treatment effects were expected.

An interim analysis of the first 18 subjects treated with this iAPF + 1 Hz stimulation protocol, however, did not support our hypothesis. Overall, treatment efficacy for the group that was treated with the individualized stimulation frequency was generally lower as compared to the group who was treated with standard 10 Hz rTMS. This was mainly the result from the clients with an iAPF of 8 Hz (who were stimulated with 9 Hz). An independent sample t-test showed that within the group of patients with an iAPF 8 Hz, the patients who were treated with an individualized stimulation frequency of 9 Hz, showed a trend towards worse treatment effects as compared to the group who received the standard protocol with a

stimulation frequency of 10 Hz (p = 0.078). It has to be noted that this effect is not corrected for multiple tests it hence indicates only a small trend. Differences in treatment effect for patients who fell in the groups with other iAPF were not significant. For the 2 sub-groups with an iAPF of 8 Hz there were no differences between the average age (43 vs. 44. Yrs; p=0,75), BDI at intake (27 vs. 34; p=0.19) and percentage of females (50% vs. 43%). In the iAPF rTMS group there seemed to be more unmedicated subjects (3/7) as compared to the 10Hz rTMS group (1/8), however when comparing the difference in BDI scores between unmedicated vs. medicated patients the difference was respectively 5% vs. 11% making it unlikely that medication status could explain this finding. Previous medication failures were not available.

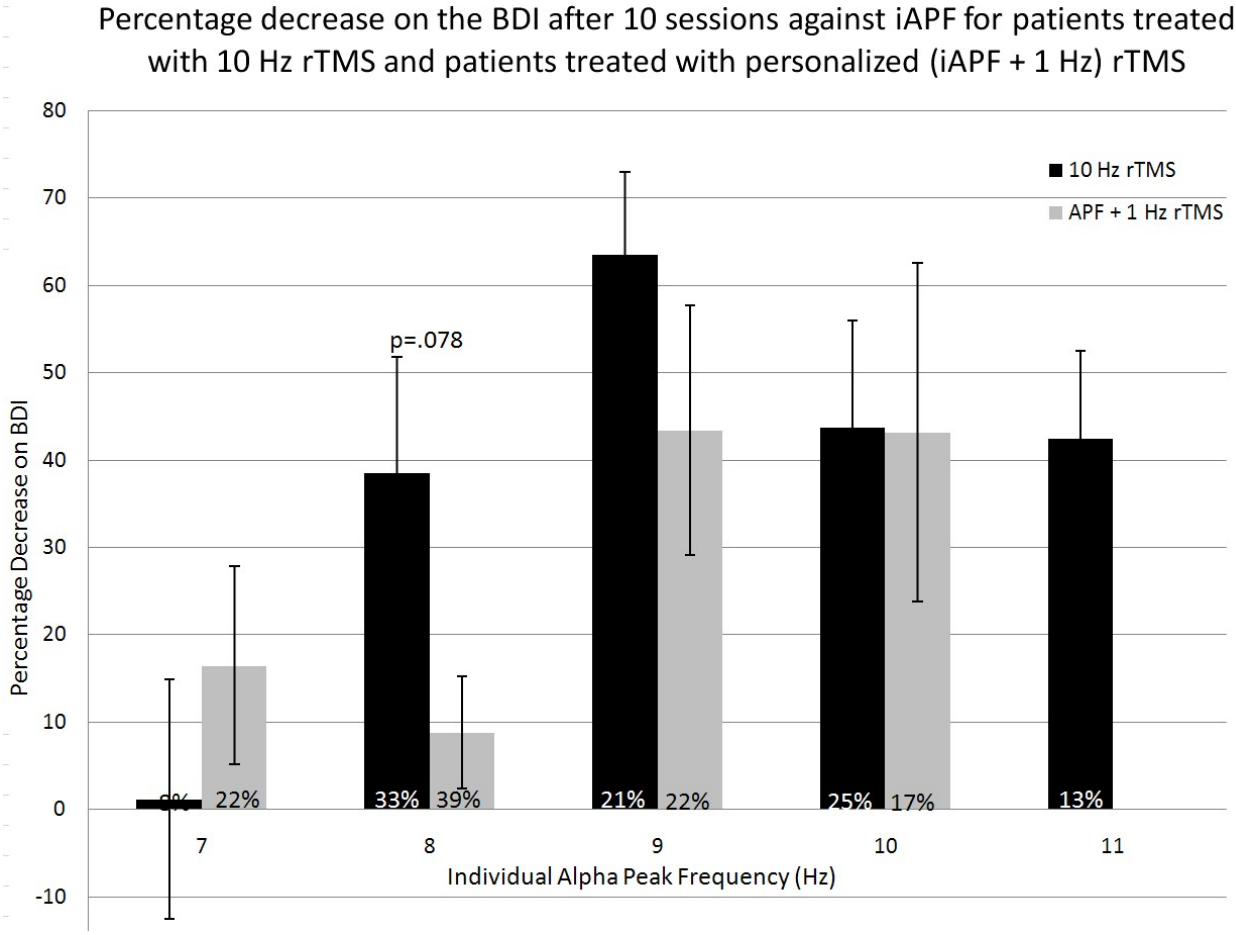


Figure 1: *This figure shows the percentage decrease on the BDI after 10 sessions rTMS plotted against the frontal iAPF of clients. Error bars indicate standard error of the mean. The Black group was the original group where all subjects were stimulated with 10 Hz and the Grey group was treated with iAPF + 1 Hz rTMS. Note the near significant lower response for only the group with an iAPF of 8 Hz (rTMS frequency of 9 Hz).The percentages at the bottom indicate the percentage of clients with that specific iAPF in that group. The '10 Hz rTMS' group consists of 24 subjects and the 'APF + 1 Hz rTMS' group consists of 18 subjects.*

These results suggest that there are possibly differential effects of different rTMS stimulation frequencies, which in turn might be dependent on individual characteristics such as the iAPF. Furthermore, our results do not support the proposition that iAPF + 1 Hz stimulation in depression improves clinical efficacy as measured by the decrease in BDI score after 10 sessions. Note that for all these patients rTMS was combined with psychotherapy which was exactly the same for both groups. It is unlikely that the psychotherapy should cause such differential effects within the short treatment period.

Few other studies using rTMS stimulation frequencies which are not harmonics of 10 Hz have been performed. For instance Bretlau et al. (2008) used 8 Hz (90%MT) and found a large effect size of 0.70, whereas Miniussi et al. (2005) used 1 Hz and 17 Hz stimulation of the Left DLPFC and found very modest effects. Interestingly, 17 Hz is almost a harmonic of 9 Hz, potentially connecting their findings to ours.

Finally, it can be concluded that, regardless of the chosen stimulation frequencies, the iAPF to some degree does predict treatment outcome to rTMS treatment in depression. In general a lower iAPF of 7-8 Hz was associated with a lower efficacy; this was true for both stimulation approaches. Conca et al. (2000) also found that non-responders to rTMS showed a lower iAPF (8.0 Hz) as compared to responders (9.5 Hz).

Further controlled studies are needed to elucidate the differential effects of different stimulation frequencies and investigate the potential relation to EEG parameters such as iAPF in order to further improve the clinical efficacy of rTMS.

Chapter 10

Neurophysiological predictors of non-response to rTMS in depression

Arns, M., Drinkenburg, W.H.I.M., Fitzgerald, P.B. & Kenemans, J.L. (In Revision) Neurophysiological predictors of non-response to rTMS in depression. *Brain Stimulation*.

Abstract

Background: The application of rTMS in depression has been very well investigated over the last few years. However, little is known about predictors of non-response associated with rTMS treatment.

Objective: This study examined neurophysiological parameters (EEG and ERP) in 90 depressed patients treated with rTMS and psychotherapy and sought to identify predictors of non-response.

Methods: This study is a multi-site open-label study assessing pre-treatment EEG and ERP measures associated with non-response to rTMS treatment.

Results: Non-responders were characterized by 1) Increased frontocentral theta EEG power, 2) a slower anterior individual alpha peak frequency, 3) a larger P300 amplitude, and 4) decreased pre-frontal delta and beta cordance. A discriminant analysis yielded a significant model, and subsequent ROC curve demonstrated an area under the curve of 0.814.

Conclusions: Several EEG variables demonstrated clear differences between R and NR such as the anterior iAPF, fronto-central Theta, P300 amplitude and pre-frontal cordance in the Delta and Beta band (representative of increased relative pre-frontal perfusion). Combining these biomarkers in a discriminant analysis resulted in a reliable identification of non-responders with low false positive rates. Future studies should prospectively replicate these findings and also further investigate appropriate treatments for the sub-groups of non-responders identified in this study, given that most of these biomarkers have also been found in antidepressant medication studies.

Introduction

The application of repetitive transcranial magnetic stimulation (rTMS) treatment in depression (MDD) has been investigated intensively over the last 15 years. Several meta-analyses have demonstrated that compared to placebo, the effects of high frequency (fast) rTMS (HF rTMS) applied to the left dorsolateral prefrontal cortex (DLPFC) and low frequency (slow) rTMS (LF rTMS) over the right DLPFC both have antidepressant effects (Schutter, 2009; Schutter, 2010). These and other results are suggesting that HF and LF rTMS in MDD yield similar clinical effects (Fitzgerald et al., 2003; Fitzgerald, Hoy, Daskalakis, & Kulkarni, 2009; Fitzgerald et al., 2010; Schutter, 2010). In depression, abnormal expression of BDNF has been observed (Shimizu et al., 2003) and is considered one of the most robust measures related to antidepressant response, which also led to the 'neurotrophin hypothesis of depression' (Duman & Monteggia, 2006). Both HF and LF rTMS have been shown to upregulate BDNF (Yukimasa et al., 2006; Zanardini et al., 2006), which is also found after antidepressant medication in MDD (Angelucci, Brenè, & Mathé, 2005; Shimizu et al., 2003). Furthermore, studies have found that responders to HF rTMS (Baeken et al., 2009; Langguth et al., 2007; Li et al., 2010; Teneback et al., 1999) and LF rTMS (Kito, Fujita, & Koga, 2008) are both characterized by increased metabolic activity in frontal regions and the anterior cingulate (Pizzagalli, 2011).

With the establishment of the efficacy of rTMS, there has been increased interest in finding potential predictors of clinical response. The value of clinical factors in predicting treatment outcome in MDD is very limited (Bagby, Ryder, & Cristi, 2002; Simon & Perlis, 2010) and a shift towards biomarkers is noticeable. In the light of this 'personalized medicine' approach to depression, recently both genetic and neuroimaging biomarkers have been explored and both are showing promising results in aiding treatment prediction using pre-treatment measures (Spronk, Arns, Barnett, Cooper, & Gordon, 2011; Williams et al., 2011).

Many studies have employed neurophysiological techniques such as electroencephalography (EEG), event-related potentials (ERP) and other neuroimaging techniques to investigate biomarkers for treatment response. Baseline neurophysiological and neuroimaging biomarkers for poor treatment outcome which have been replicated are 1) Increased delta and theta EEG power at baseline (Iosifescu et al., 2009; Knott, Mahoney, Kennedy, & Evans, 2000; Knott, Telner, Lapierre, Browne, & Horn, 1996); 2) A slow individual alpha peak frequency (iAPF: Arns, Spronk, & Fitzgerald, 2010; Conca et al., 2000; Ulrich, Renfordt, Zeller, & Frick, 1984); 3) a reduced P300 amplitude (Ancy, Gangadhar, & Janakiramaiah, 1996; Bruder et al., 2001; Bruder et al., 1995) and a prolonged P300 latency (Kalayam & Alexopoulos, 1999; Vandoolaeghe, van Hunsel, Nuyten, & Maes, 1998) and 4) decreased metabolic activity in frontal regions (Baeken et al., 2009; Kito et al., 2008; Langguth et al., 2007; Li et al., 2010; Teneback et al., 1999). In addition, some groups have focused on treatment emergent biomarkers, that is, changes in activity in the early stages of treatment on measures such as EEG Cordance (Cook, Hunter, Abrams, Siegman, & Leuchter, 2009) which was shown to have potential in the prediction of treatment outcome to antidepressants. However, in these approaches patients need to be on medication for at least 7 days in order to obtain these treatment emergent biomarkers.

The primary aim of the current study was to explore potential neurophysiological predictors of non-response to rTMS treatment. We hypothesized that non-responders to rTMS would demonstrate increased theta EEG power, lower iAPF, lower P300 amplitudes and slower P300 latencies prior to treatment. Furthermore, since EEG Cordance has also been found to better reflect cortical perfusion as compared to absolute or relative EEG power (Leuchter, Uijtdehaage, Cook, O'Hara, & Mandelkern, 1999) we hypothesized that non-responders to rTMS would demonstrate lower pre-frontal cordance, reflective of lower pre-frontal perfusion. In this study we only focused on biomarkers obtained at baseline and their relation to treatment outcome rather than treatment emergent biomarkers.

Methods

Design

This study was a multi-site open-label study. All files from patients enrolled in two clinics (Brainclinics Treatment and Psychologenpraktijk Timmers) between May 2007 and November 2009 were screened. Only data from patients with 1) a primary diagnosis of depression or Dysthymic disorder according to the MINI (MINI Plus Dutch version 5.0.0) and 2) a Becks Depression Inventory (BDI) score of 14 or higher who were treated with left DLPFC HF rTMS (10 Hz) or right DLPFC LF rTMS (1 Hz) were included for this study. Exclusion criteria were: previously treated with ECT, epilepsy, wearing a cardiac pacemaker, metal parts in the head and pregnancy. All patients signed an informed consent form before treatment was initiated.

Participants

The intake procedure consisted of a structured clinical interview (MINI), clinical questionnaires (BDI, DASS (Depression, Anxiety and Stress scale: (Henry & Crawford, 2005)), 5 factor personality test NEO-FFI) and a neurophysiological assessment to record QEEG and ERP's. Patients were screened for major depression or dysthymic disorder by a clinical psychologist using a structured interview (MINI, sections Depressive episode, Dysthymia, Suicide, Manic episode, Alcohol Dependence & Abuse and Mixed Anxiety/Depressive disorder).

All participants were asked to refrain from caffeine or nicotine intake for at least 2 hours prior to testing and all patients signed an informed consent form before treatment was initiated.

Pre-treatment QEEG and ERP's

EEG and ERP recordings were performed using a standardized methodology, details of this procedure have been provided in chapter 1, 2 and have been published elsewhere (Arns, Gunkelman, Breteler, & Spronk, 2008; Spronk, Arns, Bootsma, van Ruth, & Fitzgerald, 2008; Williams et al., 2005) and details of reliability, validity and across site-consistency of this EEG and ERP procedure have been published here (Clark et al., 2006; Paul et al., 2007; Williams et al., 2005). Patients' individual EEGs were screened for the presence of focal beta spindles at F3 (beta spindles exceeding 20 µV peak-to-peak amplitude (Niedermeyer & Da Silva,

2004)) or the presence of paroxysmal EEG activity, and this latter served as exclusion criterion for rTMS treatment.

rTMS Treatment

All patients were treated with left DLPFC HF rTMS (10 Hz) unless they demonstrated focal left frontal beta spindles in which case they were treated with right DLPFC LF TMS (1 Hz).

rTMS sessions were administered using a Magstim Rapid^2 (Magstim Company, Spring Gardens, UK) stimulator with a figure-of-8 coil (70 mm diameter). Patients received magnetic stimulation at 1) HF rTMS: 10 Hz over the left dorsolateral prefrontal cortex 5 cm anterior to the motor cortex area of the musculus abductor pollicis brevis at 110% of the motor threshold (30 trains, 5 s. duration ITI: 30 s: 1500 pulses per session) or 2) LF rTMS: 1 Hz over the right dorsolateral prefrontal cortex 5 cm anterior to the motor cortex area of the musculus abductor pollicis brevis at 110% of the motor threshold (120 trains, 10 second duration ITI 1 s: 1200 pulses per session). For some patients treated with LF rTMS, priming of 6 Hz was used before the 1 Hz rTMS (also see: Fitzgerald et al., 2008) consisting of 6 Hz stimulation at 90% MT (20 trains, 5 s. ITI 25 s.). In patients older than 55 yrs. of age the stimulation intensity was increased by 10% (in order to compensate for potential frontal atrophy, which seldom occurs before the age of 55 (Mizumasa et al., 2004)). Furthermore, rTMS treatment was complemented by psychotherapy by a skilled psychologist for all patients. BDI and DASS scores were assessed during intake, outtake and after every fifth session, to track progress of treatment. For non-responders and drop-outs, the last BDI was used as outtake (last observation carried forward). The total number of sessions were determined by the therapeutic response of the patient and this was on average 20.7 sessions.

Analysis

Individual Alpha peak frequency and Theta power.

For determination of the iAPF a method was used based on Doppelmayr and coworkers (Doppelmayr, Klimesch, Pachinger, & Ripper, 1998) and Lansbergen and coworkers (Lansbergen, Arns, van Dongen-Boomsma, Spronk, & Buitelaar, 2011) and in summary consisted of: EOG correction (Gratton, Coles, & Donchin, 1983), a linked ears montage (for F3, Fz, F4, Cz, P3, Pz, P4, O1, Oz and O2), filtering (1-40 Hz), automatic artifact removal (threshold of 150 µV), segmentation in 8 s. segments, and an FFT power spectrum calculation. This pipeline was applied to both eyes open (EO) and eyes closed (EC) conditions.

The power spectrum from EO was subtracted from the FFT from EC and within the range of 7-13 Hz the maximum alpha suppression was detrmined across P3, Pz, P4, O1, Oz and O2. The site where the maximum alpha suppression occurred was chosen as the site where the iAPF was scored by establishing the exact frequency at which the alpha suppression was maximal (posterior iAPF). The iAPF at frontal sites (F3, Fz and F4) was scored by determining

the maximum alpha suppression across these 3 sites and scoring the average peak frequency where the highest alpha suppression took place between 6 and 13 Hz (anterior iAPF).

Furthermore, for the Eyes Closed data an FFT with a Hamming window was conducted to extract power in the Theta band (4-7 Hz), which was then log transformed.

EEG Cordance

EEG Cordance is an EEG measure which integrates absolute and relative EEG power and has been demonstrated to better reflect cortical perfusion as compared to absolute or relative power (Leuchter et al., 1999). For Cordance analysis eyes closed EEG data were filtered with a high-pass of 0.5 Hz and a low-pass of 40 Hz, resampled to 256 samples per second and segmented in 2 second segments. Data were manually de-artifacted and the first 30 artifact free data segments were used to calculate Cordance using the BVA history template obtained from Leuchter et al. in Brain Vision Analyser 2.0. EEG Cordance for delta (0.5-4.0 Hz), theta (4.0-8.0 Hz), alpha (8.0-12.0) and beta (12.0-20.0 Hz) were averaged for left frontal (F3, FC3 and F7), right frontal (F4, FC4 and F8) and pre-frontal (Fp1, Fp2 and Fz) sites as a measure of cortical perfusion.

P300

Conventional ERP averages were calculated at Pz and Fz. The peaks (amplitude and latency) of the P300 for the target waveforms of the ERP component were identified (relative to a pre-stimulus baseline average of -300 to 0 ms).

Clinical outcome

The primary outcome measure is the response to treatment defined as reaching remission (BDI$\leq$12) or response (a more than 50% decrease in BDI) after treatment in agreement with the cut-offs as suggested by Riedel et al. (2010). Using this definition, patients were labeled as either a responder (R) or a non-responder (NR) to treatment. Furthermore, the effect size (ES: Hedges' D) was calculated (MetaWin 2.1) in order to compare these results to existing meta-analysis. In order to investigate possible differential treatment effects between HF and LF rTMS one-way ANOVA's were used to test for differences in age, education, number of sessions, BDI at intake, outtake and percentage improvement on BDI, as well as Chi-Square tests for differences in gender and percentage responders.

Response prediction

Differences between R and NR were analyzed using 1-way ANOVA's for 1) clinical baseline variables (Age, education, gender, BDI intake, suicide risk (MINI), DASS Depression, Anxiety, Stress and Personality factors: NEO-FFI, neuroticism, extraversion, openness, agreeableness, conscientiousness); and 2) neurophysiological variables (anterior and posterior iAPF, P300 amplitude and latency at Pz and Fz and left, right and pre-frontal cordance). For EEG theta

power a repeated measures ANOVA was used with factor electrode site (26 channels) and between subject factor responder status (R or NR).

Additionally, correlations were performed between the obtained predictors demonstrating a significant difference for R and NR and 1) clinical measures such as percentage improvement on the BDI, BDI at intake and outtake to investigate if the obtained markers are directly or indirectly related to treatment outcome and 2) among the obtained predictors of treatment outcome in order to investigate how independent the predictors are. Using the significant biomarkers a discriminant analysis as performed and a Receiver Operator Characteristic (ROC) curve was plotted to investigate how well these measures could be used to predict treatment outcome. An ROC curve is a graph displaying the true positive rate vs. the false positive rate for responder status.

Results

A total of 90 patients were enrolled meeting a primary diagnosis of MDD (N=86) or Dysthymia (N=4) (average age: 42.9 yrs., range 19-69 yrs.; 49 females and 41 males).

Clinical outcome

There were no differences in any of the clinical outcome measures and demographics between the HF and LF TMS groups. From the 70 responders, 58 (83%) achieved remission and the remainder demonstrated a more than 50% improvement on the BDI.

Table 1 summarizes the treatment effects of LF rTMS and HF rTMS. The response rate was on average 77.8% and patients on average had 20.66 sessions. The within subject Hedges' D effect size was 1.73 which can be considered a large ES.

Table 1: *The clinical response to HF and LF rTMS and the effects for the total group.*

Clinical Response	**LF rTMS**	**HF rTMS**	**P-Value**	**Total group**
Responders	78.8%	77.2%	0.997	77.8%
Number of sessions	19.3	21.4	0.168	20.66
BDI Intake	31.0 (SD 9.98)	29.9 (SD 9.03)	0.608	30.3 (SD 9.35)
BDI Outtake	12.6 (SD 11.73)	12.1 (SD 11.17)	0.847	12.3 (SD 11.31)
Percentage decrease BDI	60.8%	59.8%	0.889	60.2%
Hedges' d Intake-Outtake	ES =1.67	ES=1.74		ES=1.73

Response prediction

Given there were no baseline differences and differences in clinical response between LF and HF rTMS, both populations were grouped together in order to further investigate predictors of non-response to treatment.

There were no significant differences between R and NR for any of the baseline clinical measures (Age, education, gender, BDI intake, DASS Depression, Anxiety, Stress, Personality factors (NEO-FFI, neuroticism, extraversion, openness, agreeableness, conscientiousness) and suicide risk (MINI)).

Figure 1 shows the EEG power spectrum for eyes closed at frontal and parietal locations.

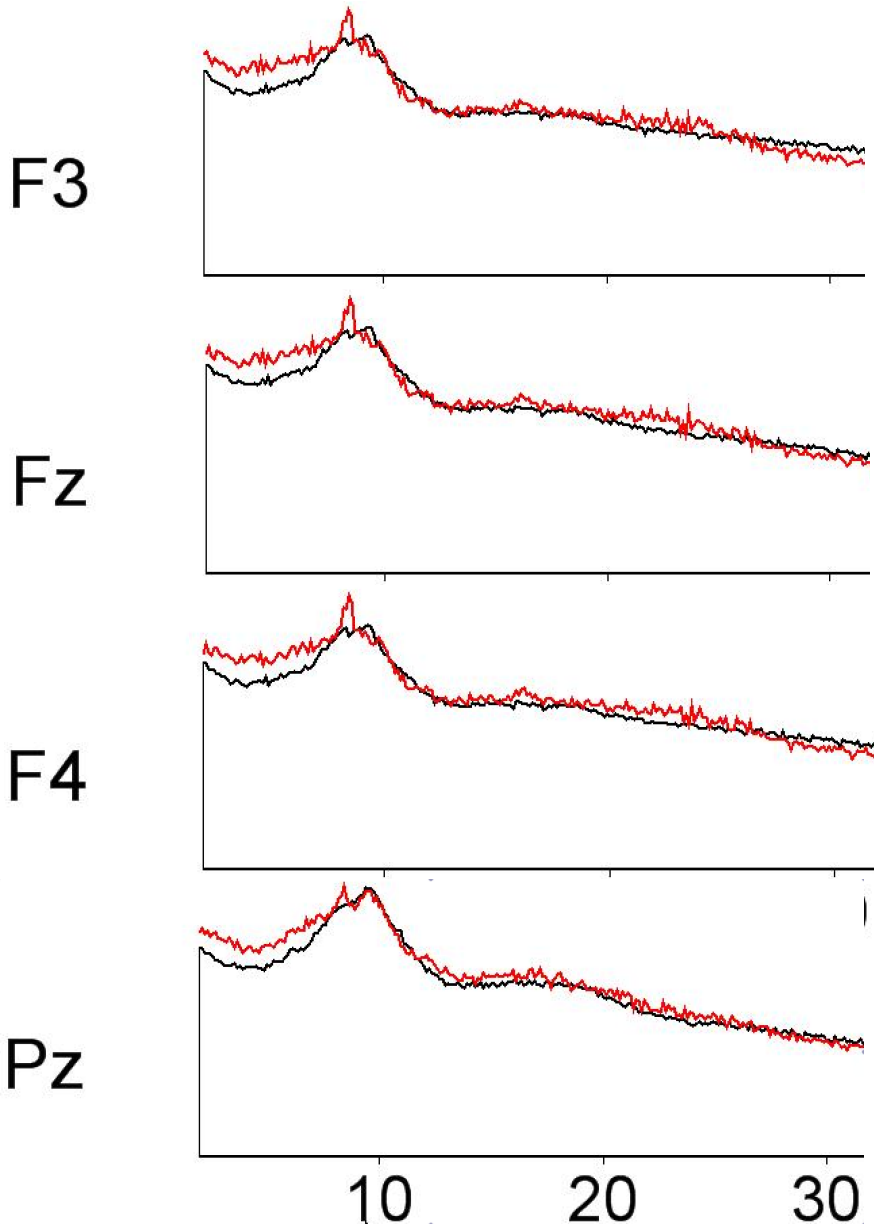


Figure 1: *The EEG power spectrum (FFT in Hz) for the Eyes Closed condition at F3, Fz, F4 and Pz for responders (black) and non-responders (red). Note the increased theta and the slower iAPF for non-responders, most prominent at frontal sites.*

EEG Theta power

For Theta EEG power, there was a significant effect for site (p=.000; F=61.000; DF=25, 61), responder status (p=.008; F=7.427; DF=1) and a significant site X responder status interaction (p=.046; F=1.711; DF=25, 61) reflecting that the R-NR difference was not equal across all sites. Hence 1-way ANOVA's were carried out. Only findings with p<.01 were considered significant thereby adjusting for multiple comparisons. There was a significantly greater Theta in NR with p<.01 for the following sites: F7 (p=.008), F3 (p=.009), F4 (.004), F8 (p=.002), FC3 (p=.006), FCz (p=.009), FC4 (p=.003), T3 (p=.008), Cz (p=.005), C4 (p=.003), T4 (p=.009), CP4 (p=.008) see figure 2.

Baseline Theta at these sites also significantly correlated with percentage improvement on the BDI and BDI at outtake for all these sites except T4, with the strongest correlation for F7 and percentage improvement on BDI (p=.005; r=-.296; DF=90) and for F8 and BDI at outtake (p=.004; r=.301; DF=90). High theta was thus associated with a weaker decline in BDI score and, consistently, a higher BDI score at outtake.

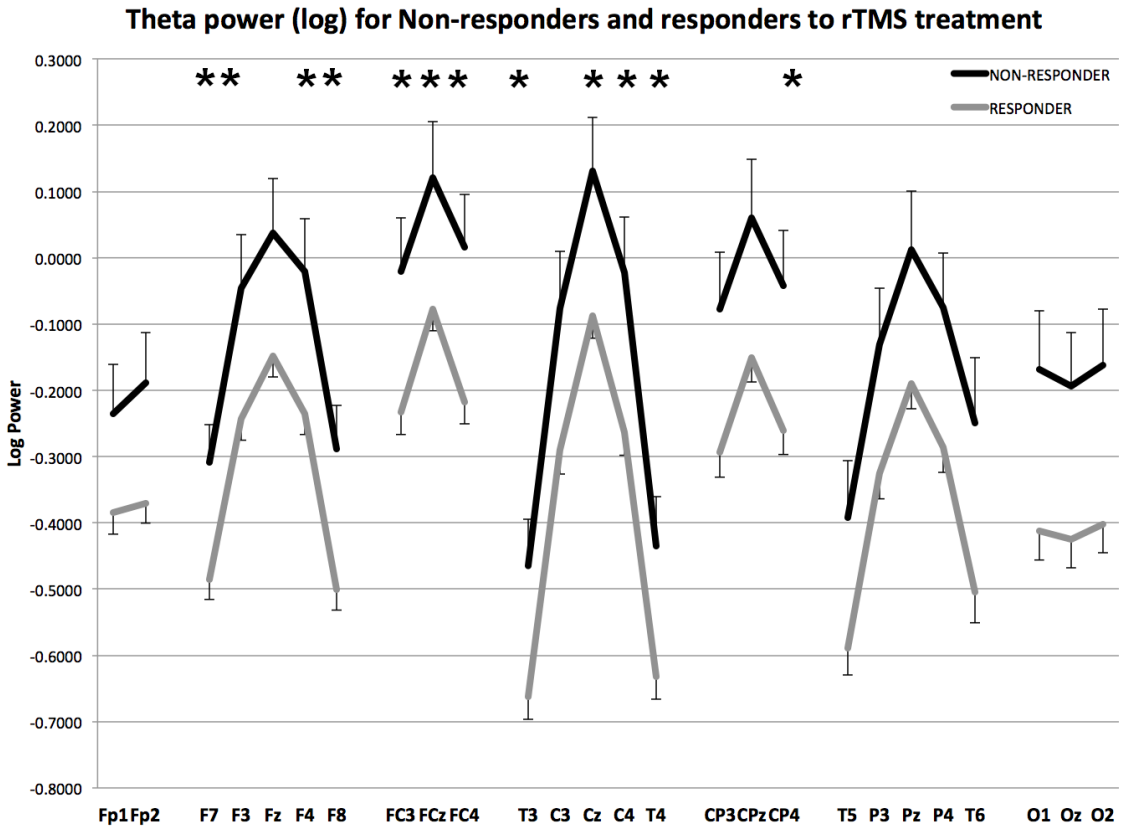


Figure 2: *Differences in Theta power during eyes closed between responders (black) and non-responders (red) to rTMS at baseline (* indicate significant differences at p<.01, error bars are SEM).*

Individual alpha peak frequency (iAPF)

There was no difference between R and NR in posterior iAPF (p=.258; F=1.295; DF=1, 85) but there was a significant difference in anterior iAPF where the NR had an average anterior iAPF of 8.30 Hz (SD=1.20) and R had an average anterior iAPF of 9.16 Hz (SD=1.14) (p=.005; F=8.303, DF=1, 84).

Baseline anterior iAPF also demonstrated a significant correlation with the percentage decrease on the BDI (p=.002; r=.326, DF=86) and BDI at outtake (p=.003; r= -.312, DF=86) but not with BDI at intake (p=.973; r= -.004; DF=86).

Cordance

R had a greater degree of pre-frontal Delta Cordance (p=.027; F=5.032; DF=1, 86) and pre-frontal Beta cordance (p=.039; F=4.395; DF=1,86) than NR but no difference for right and left frontal cordance nor for alpha or theta cordance (visualized in figure 3). Pre-frontal beta cordance also correlated significantly with percentage improvement on the BDI (p=.044; r=.215; DF=88) but prefrontal Delta cordance did not (p=.093; r=.180; DF=88).

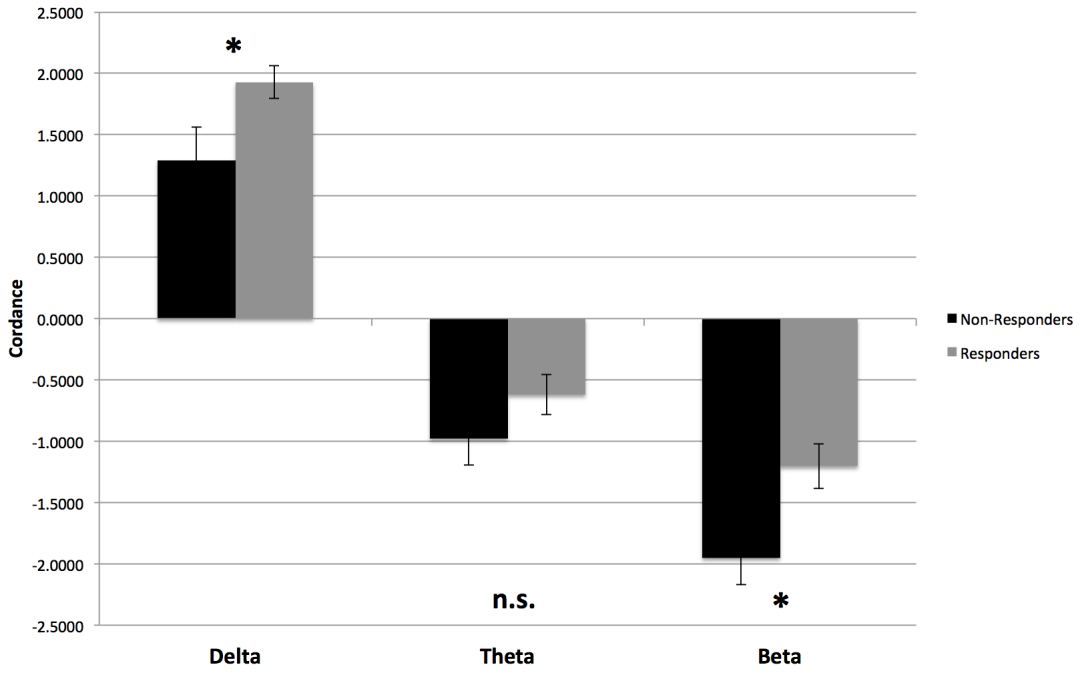


Figure 3: *The increased Delta and Beta cordance for R at prefrontal regions, suggesting more 'concordant' Delta and Beta activity representative of increased relative pre-frontal perfusion for R.*

P300

There was no difference between responders and non responders with respect to P300 latency at Fz (p=.862; F=.031; DF=1, 82), Pz (p=.867; F=.028; DF=1, 84) and P300 amplitude frontal (p=.487; F=.488; DF=1, 82) but there was a marginally significant difference for P300 amplitude at Pz (p=.054; F=3.831; DF=1, 84) where responders exhibited a lower P300 amplitude at Pz (11.2 µV; SD=5.72) as compared to non-responders (14.6 µV, SD=8.68), visualized in figure 4. There were no correlations between P300 amplitude and improvement on the BDI, nor with the BDI at intake or outtake.

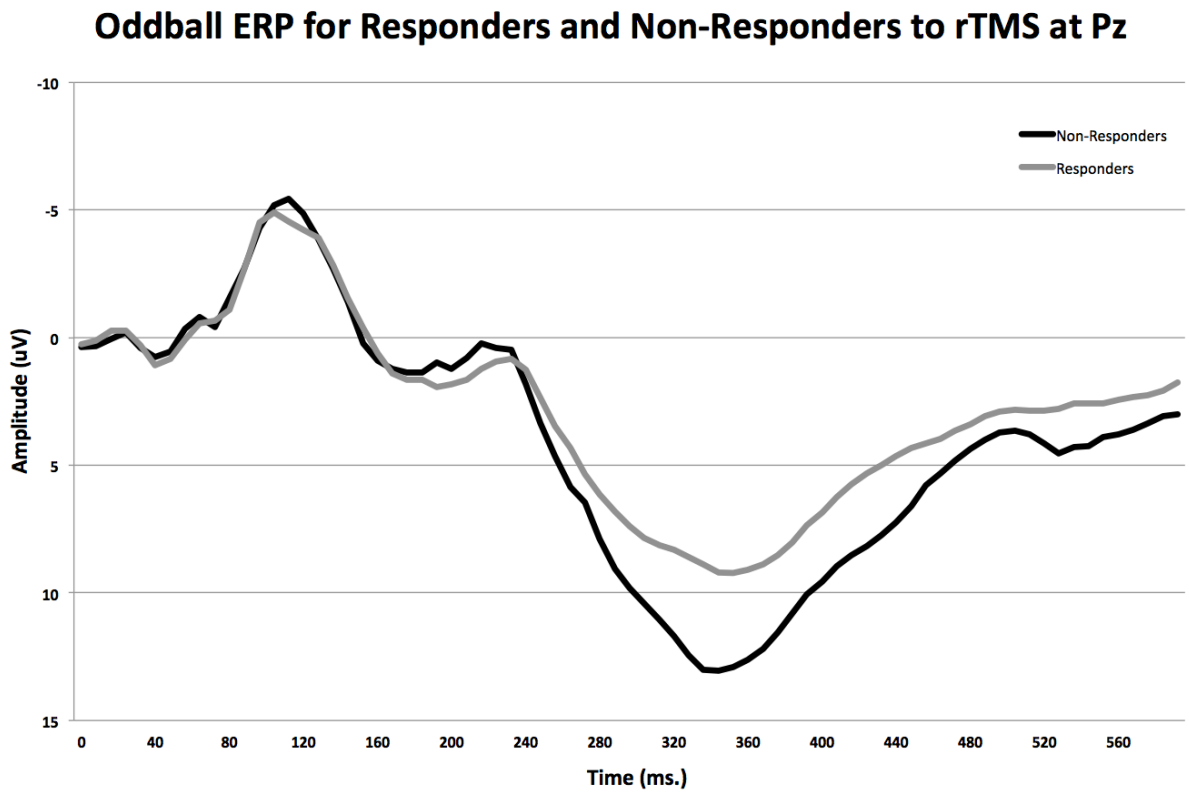


***Figure 4**: The oddball ERP grand average waveforms for Non-Responders (black) and Responders (grey) to rTMS treatment at Pz. Note the larger P300 amplitude for non-responders.*

Correlations between markers for treatment response

In order to assess if the obtained predictors were independent or might be a reflection of a shared underlying functional network, correlations were explored between P300 amplitude at Pz, anterior iAPF, Pre-frontal Delta and Beta cordance and Theta at F7 and F8.

P300 amplitude: There were no correlations between P300 amplitude and iAPF, pre-frontal cordance measures and Theta at F7 and F8.

Anterior iAPF: There were no correlations between anterior iAPF and P300 amplitude, pre-frontal cordance, but there was a negative correlation with Theta at F7 (p<.000; r=-.426; DF=86) and F8 (p<.000; r=-.499; DF=86).

For pre-frontal Delta and Beta cordance, there were no significant correlations with other variables.

These data suggest that the pre-frontal cordance and P300 amplitude are relatively independent measures, whereas Theta power at F7 and F8 and iAPF are highly correlated.

Discriminant analysis

A discriminant analysis was performed using the following measures: P300 amplitude at Pz, prefrontal Delta and Beta cordance and anterior iAPF. The grouping variable was responder status. The model resulted in a significant Wilks' Lambda (p=.001; Wilks' Lambda =.781; Chi-square=19.050; DF=4). The area under the ROC curve was 0.814. As can bee seen in the ROC curve in figure 6 (showing the specificity and sensitivity for non-responders), when accepting a 10% false positive rate, 53% of the non-responders could be identified and when accepting a 5% false positive rate, 41% of the non-responders could be identified using the 4 biomarkers at baseline.

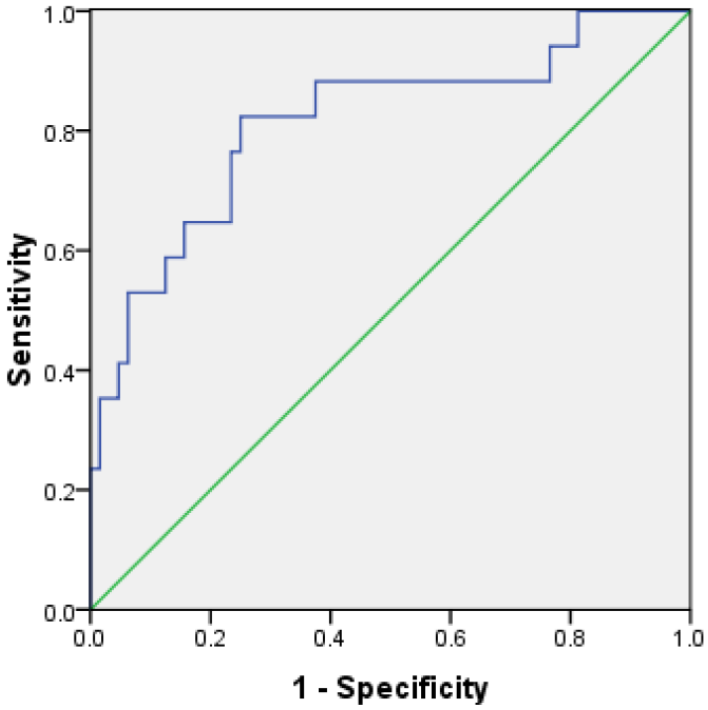


Figure 5: *Receiver Operating Characteristic curve of the obtained discriminant function predicting non-response to rTMS combining the following biomarkers: P300 amplitude, Pre-frontal Delta and beta cordance and anterior iAPF. ROC are is 0.814*

Medication status

From all patients, 32.2% (N=29) were unmedicated at the beginning of treatment. Twenty-one patients were medicated with a first-line antidepressant such as an SSRI or SNRI and the remaining 40 patients took combined medication. There were no differences between the medicated and unmedicated patients for clinical outcome measures such as BDI at intake, outtake, improvement on BDI, number of sessions, responder status and also not for the

significant predictors of treatment outcome described above (all p>.1) demonstrating that medication status did not confound the results in this study.

Discussion

The primary aim of this study was to investigate predictors of non-response to rTMS treatment. Clinical measures at baseline such as anxiety, depression, stress, suicide risk, medication status etc. were not found to be related to treatment outcome. EEG and ERP measures did demonstrate clear differences between responders (R) and non-responders (NR).

The increased theta for NR is in line with previous studies demonstrating non-response to antidepressant medication to be associated with increased theta (Iosifescu et al., 2009; Knott et al., 2000; Knott et al., 1996). As can be seen in figure 2 the increased theta is most specifically increased in right and left fronto-central locations and not limited to frontal midline sites. Frontal midline theta has been localized to the medial prefrontal cortex and anterior cingulate (Asada, Fukuda, Tsunoda, Yamaguchi, & Tonoike, 1999; Ishii et al., 1999) and a recent meta-analysis has demonstrated that theta in the rostral anterior cingulate is associated with improved response to antidepressant treatment (Pizzagalli, 2011). Hence, our findings point rather to a generalized increased theta in non-responders as opposed to frontal midline theta originating from the anterior cingulate. The studies from Knott et al. (Knott et al., 2000; Knott et al., 1996) as well as Iosifescu et al. (2009) also reported a generalized increase in theta in NR. These results might hence be interpreted as a sub-group characterized by a decreased EEG vigilance regulation (Arns, Gunkelman, Olbrich, Sander & Hegerl, 2010; Hegerl, Himmerich, Engmann, & Hensch, 2010) characterized by frontal theta, whereas typically in depression higher EEG vigilance regulation – expressed as hyperstable or rigid parietal alpha or A1 stages - is reported (Hegerl, Wilk, Olbrich, Schoenknecht, & Sander, 2011; Ulrich & Fürstenberg, 1999). Given that patients with a decreased EEG vigilance regulation respond better to stimulant medication (Manic Depression: Bschor, Müller-Oerlinghausen, & Ulrich, 2001; Hegerl et al., 2010; Schoenknecht, Olbrich, Sander, Spindler, & Hegerl, 2010; ADHD: Arns et al., 2008; Sander, Arns, Olbrich, & Hegerl, 2010) it is tempting to speculate if this subgroup of non-responders might respond better to stimulant medication. Suffin and Emory (1995), did report that this sub-group of depressed patients does respond to stimulant medication, recently replicated by (Debattista et al., 2010). However further research is required to investigate this speculation.

The finding of a slower (anterior) iAPF in NR is in line with previous work on rTMS (Arns et al., 2010; Conca et al., 2000) and medication (Ulrich et al., 1984). A slow iAPF has also been shown to be a predictor for non-response to stimulant medication in ADHD (Arns et al., 2008) and to antipsychotics (Itil, Marasa, Saletu, Davis, & Mucciardi, 1975). Hence this sub-group of non-responders might represent a non-specific sub-group of patients who fail to respond to treatment. In a previous study we have investigated if personalizing the rTMS frequency based on the anterior iAPF would improve clinical efficacy, which was not found to be the case (Arns et al., 2010), whereas this was found to result in more specific clinical effects in rTMS treatment for schizophrenia (Jin et al., 2006). Future research should investigate further to which treatment this sub-group could be most responsive.

The slow anterior iAPF and frontal theta demonstrated a high correlation. This is in line with several earlier studies demonstrating a slow iAPF can confound theta EEG power constrained to a fixed frequency band (Doppelmayr et al., 1998; Lansbergen et al., 2011). In this study the main aim was to replicate earlier findings hence a fixed theta-frequency band was chosen, and as can be seen in figure 1, NR exhibited both a slowed iAPF and increased theta. Future studies should hence more clearly dissociate these 2 measures, maybe by using personalized frequency bandwidths similar to those used by Doppelmayr and coworkers (Doppelmayr et al., 1998).

Decreased pre-frontal cordance in the delta and beta band was found for NR - indicative of a less 'concordant' EEG state possibly reflective of lower relative perfusion in the underlying cortex (Leuchter et al., 1999). This finding of decreased concordance over prefrontal areas for NR is in line with previous studies (HF rTMS: Baeken et al., 2009; Langguth et al., 2007; Li et al., 2010; Teneback et al., 1999; LF rTMS: Kito et al., 2008) and hence lower concordance of frontal areas can be considered a predictor for non-response.

Finally, NR exhibited a higher P300 amplitude at Pz as compared to NR, contrary to previous studies (Medication: Bruder et al., 2001; Bruder et al., 1995; ECT: Ancy et al., 1996). Bruder and coworkers (Bruder et al., 2002) found that patients with anxiety demonstrated larger P300 amplitudes whereas patients with a depression and no comorbid anxiety demonstrated a reduced P300 amplitude as compared to healthy controls. Hence, it might be speculated that the NR with a larger P300 amplitude represent a sub-group with more comorbid anxiety. However, post-hoc analysis did not demonstrate a correlation between anxiety and P300 amplitude.

When the 4 biomarkers (anterior iAPF, P300 amplitude at Pz, pre-frontal delta and beta cordance) were combined in a discriminant analysis they yielded a moderate predictive power to identify non-responders using these baseline measures, as can be judged from the ROC curve in figure 6. When a false positive rate of 10% is acceptable (i.e. from the patients classified as a non-responder, 10% would have been a responder), 53% of the non-responders could have been selected a-priori, resulting in a higher efficacy by excluding these non-responders a-priori. In comparison, Leuchter et al. (2009) using the ATR (an EEG based 'treatment-emergent biomarker') obtained an ROC of 0.77 and Cook et al. (2009) using theta cordance obtained an ROC area of 0.76. Compared to these ROC areas, the obtained area of 0.814 can be considered high, especially taking into account that this study only investigated measures assessed at baseline instead of a treatment-emergent biomarker such as cordance or ATR. Therefore, these results show promise for future applications of neurophysiological biomarkers to be applied in practice and select the appropriate patients for rTMS treatment. However, these results first need to be replicated prospectively in an independent sample before use is warranted in practice.

Clinical effects

In this study we found that HF and LF rTMS combined with psychotherapy resulted in an overall response rate of 77.8%. If only remission is considered, the response rate in this study was 64%. In comparison to previous rTMS studies these efficacy rates tend to be rather high, however these results reflect the efficacy of combined rTMS with

psychotherapy. Keller et al. (2000) demonstrated in a large study that psychotherapy combined with medication also resulted in a large response rate of 73% whereas either treatment as a mono-therapy had a response rate of 48%. Furthermore, most previous rTMS studies consisted of samples with high rates of treatment resistance, which is known to result in lower response rates (Brakemeier, Luborzewski, Danker-Hopfe, Kathmann, & Bajbouj, 2007; Fregni et al., 2006; George et al., 2010). In this study we did not systematically track treatment resistance but 32.2% of patients were not on medication when the treatment was initiated and 23.3% of patients (21 out of 61 medicated patients) were medicated with a 'first-choice' type of antidepressant medication such as an SSRI or SNRI, suggesting the majority of patients (55.5%) had a low 'treatment resistance'. Therefore, these results tend to be in line with results from combined psychotherapy and antidepressant medication and further demonstrate the feasibility of combining psychotherapy and rTMS treatment in clinical practice.

Limitations

This study did not employ a double blind placebo controlled design, hence it cannot be ruled out that the results are partly explained by placebo effects. Furthermore, in this study we combined psychotherapy with rTMS making it difficult to disentangle whether the obtained predictors reflect generic predictors for non-response, or a predictor for non-response to either rTMS or psychotherapy. In any case non-responders did not respond to treatment, hence did not respond to rTMS nor psychotherapy nor to the placebo aspect. Hence, the combination of measures maybe useful as generic predictors of non-response in clinical practice. Since these same predictors have also been found in medication studies further supports this notion.

The open-label nature of this study is another weakness combined with the fact that most patients were medicated. Prospective replication of these results is required.

Conclusion

Several EEG variables demonstrated clear differences between R and NR such as the anterior iAPF, fronto-central Theta, P300 amplitude and pre-frontal cordance in the Delta and Beta band (representative of increased relative pre-frontal perfusion). Combining these biomarkers in a discriminant analysis resulted in a reliable identification of non-responders with low false positive rates.

More studies are required to replicate these findings and also focus on explaining these predictors for non-response (since these have also been found to be related to non-response after antidepressant medication) and investigate to what treatments these sub-groups might respond. These results also demonstrate the feasibility of combining rTMS treatment with psychotherapy, and suggest this may result in improved efficacy of the combined treatment as reflected in a large effect size.

Acknowledgement

We want to acknowledge the support of Andrew Leuchter, Ian Cook and Suhail Naimat in providing us with the required cordance history template and support for analyzing and interpreting the EEG Cordance data. Furthermore, we wish to acknowledge Michelle Wang and Brainnet for providing the analyzed ERP data, Harm Jan Wieringa from Medcat in facilitating the use of Brain Vision Analyzer, Aukje Bootsma, Anne Schreiber, Hanneke Friessen, Niels Veth and Desiree Spronk for their help and support in the treatment and data collection of the reported data. Finally we would like to thank our colleagues at Psychologenpraktijk Timmers for sharing the rTMS treatment data, especially Dagmar Timmers. PBF is supported by a NHMRC Practitioner Fellowship.

Financial disclosures

In the last 2 years PBF has received equipment for research from MagVenture A/S and Brainsway Ltd. MA is author on a patent application on neuromodulation and EEG/ERP. The other authors have no conflict of interest.

Summary and conclusions

Summary

The primary aim of this thesis was to investigate what the value of neurophysiological techniques such as EEG and ERPs is in predicting treatment outcome in ADHD and depression. This thesis presented promising findings for these techniques and the application of these techniques to personalize treatments in ADHD and depression, thus improving treatment efficacy. This treatment modalities investigated in this thesis were stimulant medication, antidepressants, neurofeedback in ADHD and rTMS for depression. The results suggest there are several predictors predicting someone will not respond to treatment, so called predictors for non-response. Some of these appear to be generic predictors for non-response within a disorder such as antidepressant treatments (for both antidepressants and rTMS in Depression). On the other hand an endophenotype was found which predicts non-response to most current treatments in both ADHD and depression.

The main findings related to predicting non-response are summarized below.

Impaired vigilance regulation

Impaired vigilance regulation was found to be a core feature in ADHD, explaining the symptoms of ADHD and also explaining why psychostimulants provide clinical benefit in ADHD based on the EEG vigilance model, by its vigilance stabilizing properties. In this case this concerns a predictor for improved treatment outcome.

In a sub-group of non-responders to various antidepressant treatments (antidepressants and rTMS), suggestions for this same impaired vigilance regulation (excess theta) were obtained (Chapter 10; Prichep et al., 1993; Suffin & Emory 1995; Debattista et al., 2010). Several studies have demonstrated that this subgroup of patients (with excess theta) respond well to stimulant medication which is usually prescribed in ADHD (Depression: Suffin & Emory 1995; Debattista 2010; Manic Depression: Bschor et al. 2001; Schoenknecht 2010).

In this thesis it is speculated that the core-pathophysiology of this specific sub-type lies in sleep problems such as sleep onset insomnia and delayed circadian phase, resulting in impaired vigilance regulation during daytime. Psychostimulants have been found to be effective for this EEG subtype in both ADHD and depression, however these exert their effects by increasing daytime vigilance and result in ‘symptom suppression’, but not affecting the core pathophysiology, namely the sleep problems and circadian phase. Therefore, future studies should investigate further if treatments hypothesized to directly improve sleep onset insomnia and circadian phase indeed improved ADHD and depressive symptoms as was demonstrated for melatonin in ADHD (Hoebert, van der Heijden, van Geijlswijk, & Smits, 2009) or SMR neurofeedback in sleep (Cortoos et al., 2010; Hoedlmoser et al., 2008; Sterman et al., 1970). Such treatments should also specifically aim to find interventions resulting in sustained effect.

Individual alpha peak frequency (iAPF)

An often-overlooked feature of the EEG, namely the presence of a slow iAPF was found to be a solid predictor of non-response to various treatments such as psychostimulants in ADHD (chapter 2), rTMS in depression (chapter 9 and 10 and Conca et al., 2000) as well as

antidepressants (Ulrich et al., 1984). A slow iAPF is clearly associated with reduced cerebral blood flow, and procedures such as carotid endartectomy (Uclés, Almarcegui, Lorente, Romero, & Marco, 1997; Vriens, Wieneke, Van Huffelen, Visser, & Eikelboom, 2000) and hyperbaric oxygen therapy (Murata, Suzuki, Hasegawa, Nohara, & Kurachi, 2005) have been shown to result in a faster iAPF and both procedures increase the availability of oxygen and/or cerebral bloodflow. Given the high heritability of the iAPF (van Beijsterveldt & van Baal, 2002), the stability of this measure over time (Kondacs & Szabó, 1999), its clear relation to cerebral blood flow and its substantial prevalence in ADHD and depression this measure can be considered an endophenotype associated with non-response for conventional treatments in ADHD and depression. Future research should investigate further to what treatments patients with this endophenotype do respond and further studies should confirm that this endophenotype is specific enough to reliably select patients who will not respond to treatment before they initiate treatment. Possibly, this endophenotype can stimulate new research into biomarker-based treatment.

Discussion

Recently the landscape in psychiatry is undergoing a dramatic change. Some recent large-scale studies investigating the effects of conventional treatments for ADHD and depression in practice have demonstrated on the group-level limited efficacy of antidepressant medication and cognitive behavioral therapy in depression (STAR*D: Rush et al., 2006), an overestimation of the effects of cognitive-behavioural therapy for depression as a result of publication bias (Cuijpers, Smit, Bohlmeijer, Hollon, & Andersson, 2010) and limited long-term effects of stimulant medication, multicomponent behavior therapy and multimodal treatment in ADHD (NIMH-MTA trial: Molina et al., 2009). Furthermore, several large pharmaceutical companies have announced to *'…pull the plug on drug discovery in some areas of neuroscience….'* (Miller, 2010) including GlaxoSmithKline (GSK) and AstraZeneca. This can be considered a worrying development, since there is still much to improve in treatments for depression and ADHD. Therefore, a move beyond data regarding the average effectiveness of treatment, to identify the best treatment for any individual (Simon & Perlis, 2010) or personalized medicine is crucial. In personalized medicine it is the goal to prescribe the right treatment, for the right person at the right time as opposed to the current 'trial-and-error' approach, by using biomarkers of endophenotypes.

In addition to this develoment we also witness a shift from a 'systemic treatment approach' (i.e. systemically applying medication to the whole body) to a more 'focal treatment approach' also subsumed under the term 'Neuromodulation'. In this development there are currently many new treatments developed and applied such as deep-brain stimulation in depression (Hamani et al., 2011); Parkinson: (Zahodne et al., 2009), intracranial stimulation of primary and secondary auditory cortex in tinnitus (De Ridder et al., 2006); rTMS in depression (Schutter 2010; Schutter 2009a), fMRI neurofeedback in pain (deCharms et al., 2005), neurofeedback in ADHD (Arns, de Ridder, Strehl, Breteler & Coenen, 2009), Vagus Nerve Stimulation (VNS) in depression (Daban, Martinez-Aran, Cruz & Vieta, 2008) etc. Figure 1 shows an overview of different milestones achieved for several non-pharmacological neuromodulation techniques such as approval of techniques by the EU or FDA and introductions of new techniques (From: Moreines, McClintock & Holtzheimer, 2011). This figure further illustrates the increase in milestones for neuromodulation techniques across the last 10-15 years.

Along with the development of these new techniques it is interesting to note that the application of some of these neuromodulation approaches do not solely rely on a DSM-IV diagnosis, but lean more towards identifying dysfunctional brain networks and application of treatment to specifically modulate those networks. For example, deep brain stimulation studies specifically aim to modulate the subcallosal cingulate gyrus (Hamani et al., 2011), fMRI neurofeedback patients learn to specifically regulate activity in the rostral anterior cingulate (deCharms et al., 2005) and for neurofeedback treatment in ADHD, the protocol can be personalized to specific deviating EEG patterns (also see chapter 6).

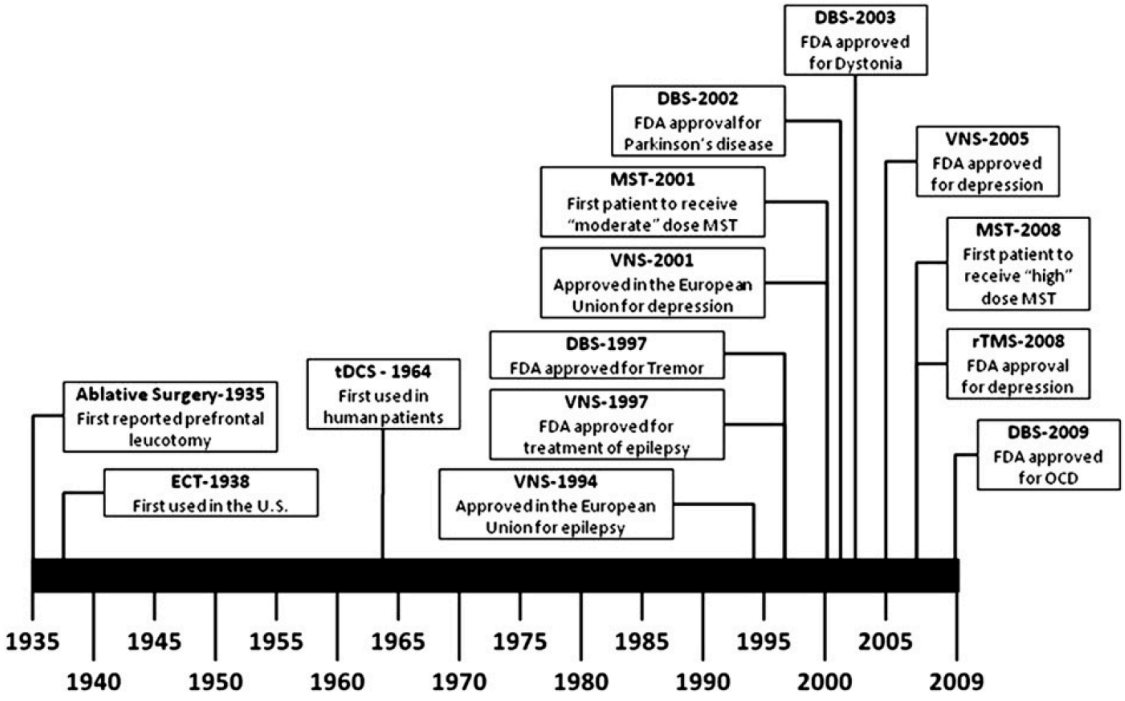


Figure 1: A historical overview of milestones related to several neuromodulation techniques. Note the increase in milestones over the last 10-15 years. From: Moreines, McClintock & Holtzheimer (2011).

As pointed out in the introduction of this thesis and above, a focus on biomarkers and endophenotypes which can predict treatment outcome will become crucial to improving treatments for ADHD and depression. The development of personalized medicine is hence a very important development in psychiatry. The main aim of this thesis has been to investigate if there are reliable predictors for response and non-response to various treatments in ADHD and depression, with a focus on predictors for non-response. In the following the main findings from the studies presented in this thesis are presented and the implications of these findings for the future of personalized medicine are discussed.

ADHD

Based on the previous chapters several sub-groups of ADHD have emerged with relevance to treatment response. Below these sub-groups will be described in more detail and a more theoretical background on the etiology of these sub-groups and recommendations for future research and implications for treatment is provided.

Impaired vigilance regulation

The main finding from the ADHD studies is that a specific sub-group of ADHD patients was found who can be characterized by a lower vigilance and more unstable vigilance regulation who are responsive to stimulant medication. This is consistent with a review on sleep

problems in ADHD where the most consistent finding across studies was that of daytime excessive sleepiness (Cohen-Zion & Ancoli-Israel, 2004). In chapter 2 it was reported that ADHD children characterized by frontal alpha and frontal theta – reflective of lower vigilance stages - were the best responders to stimulant medication. Furthermore, in chapter 3 further indications were found that ADHD patients were characterized by a lower vigilance as well as a more unstable vigilance regulation. There also was a tendency for the ADHD patients with the lowest EEG vigilance to perform worst on a CPT test, reflective of inattention and impulsivity, and these patients tended to respond better to medication as well. These findings are in line with the EEG Vigilance model originally developed by Bente (Bente, 1964) and recently further developed by Hegerl (Hegerl et al., 2010), and are hypothesized to explain the ADHD symptoms and subtypes. As can be seen in figure 2 below, a trait-like unstable vigilance regulation explains the cognitive deficits characteristic for ADHD and ADD such as impaired sustained attention. Furthermore, the vigilance autostabilization behavior explains the hyperactivity aspect of ADHD as an attempt to upregulate vigilance.

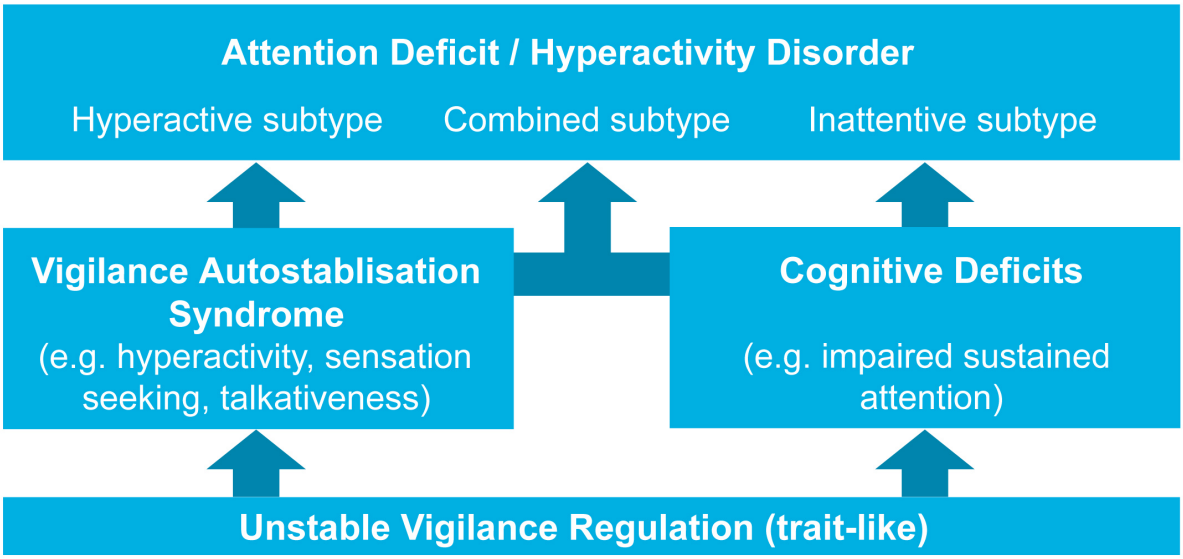


Figure 2: *This figure provides an overview of the relation between an unstable vigilance regulation and the behavioral symptoms of ADHD (adapted from Hegerl et al. 2009).*

The EEG vigilance model is more focused on examining the temporal dynamics of the EEG rather than focusing on the EEG activity averaged across time. The different vigilance stages are reflective of the same underlying process (vigilance) and hence changes in alpha or theta power alone are of little value in establishing a relationship with behavior. The EEG Vigilance model explains the relationship between EEG phenomena and behavior by means of vigilance regulation. The interesting aspect of this model is that this relationship between behavior and EEG is not a linear relationship, explaining why in chapter 4 no consistent relationship between EEG power measures and neuropsychological performance was found. The following example illustrates this further.

After a tiring day the EEG vigilance regulation of a healthy person will become unstable and demonstrate more of the lower vigilance stages. This has a very well known EEG signature often referred to as 'fatigue' or 'drowsiness' expressed as alpha anteriorisation (Broughton & Hasan, 1995; Connemann et al., 2005; De Gennaro et al., 2001; De Gennaro et al., 2004; De Gennaro et al., 2005; Pivik & Harman, 1995) and increased frontal slow waves (Strijkstra et al., 2003; Tanaka et al., 1996; Tanaka et al., 1997), in the EEG vigilance model referred to as stage A2-A3 and B2-B3 respectively. In young children we all know the example of the hyperactive, 'high-spirited' behavior in over-tired children, as a clear example of vigilance autostabilization behavior (i.e. keeping himself awake). A healthy adult displaying this type of EEG – assuming he is at home and it is almost bedtime – will subjectively feel sleepy and decide to go to bed (i.e. the adult will decide to 'withdraw' from the environment and seek an environment with low external stimulation and increase the chance to fall asleep).

However, when this same healthy adult is driving a car and exhibits the same reduced EEG Vigilance and is drowsy, he will turn up the volume of the music… open the window… turn-down the air-conditioning… close the window… and so on. Hence the healthy adult will exhibit autostabilization behavior in order to keep himself awake. Furthermore, when the car in front of him will unexpectedly brake, he will be more likely to respond slowly (impaired sustained attention) and the likelihood of a car accident increases due to this reduced vigilance or fatigue (Miller, 1995).

This example nicely illustrates that the same EEG state – depending on the environment – can result in completely different behavior (sleep vs. 'hyperactive' behavior), thereby explaining why the relationship between EEG and behavior is not a linear relationship, but rather a 'binary relationship'. Furthermore, as pointed out above, changes in alpha or theta averaged across time provide little information, since both are reflective of the same process, namely vigilance. Therefore, for future studies investigating the relationship between resting EEG and cognition it is recommended to rather employ an overall EEG vigilance metric rather then investigating the averaged spectral content 'in isolation' and also investigate this during a task. For example in a future study it is planned to investigate the EEG Vigilance stages in patients with ADHD during a CPT task and investigate if lower vigilance stages preceding a target requiring a response, result more often in an omission to respond, reflective of inattention (false negative errors). Previous studies have investigated the relationship between alpha and theta and cognitive processes and have reported that *during* a task increased alpha is related to memory load (Jensen & Mazaheri, 2010; Jensen et al., 2002) and increased theta is related to short-term memory (Klimesch, 1996; Osipova et al., 2006). These studies hence reflect *task-induced synchronization* in the theta and alpha band to be associated with improved mnemonic function. However, studies investigating pre-stimulus EEG power have demonstrated that increased pre-stimulus alpha is associated with a decrease in visual discrimination ability (van Dijk, Schoffelen, Oostenveld, & Jensen, 2008), with false alarms in a Go-NoGo task (Mazaheri, Nieuwenhuis, van Dijk, & Jensen, 2009) and attentional lapses (O'Connell et al., 2009). This latter study found that alpha started to increase already up to 20 s. before a missed target (O'Connell et al., 2009). Furthermore, Romani et al (1988) specifically investigated if vigilance, classified using the EEG, was related to subsequent ERP amplitudes and latencies and found that lower pre-stimulus vigilance levels (increased theta and delta) were associated with subsequent slower N100 latencies. They also found indications that subjects with a more unstable vigilance

(greater fluctuations) were characterized by slower N100 latencies but also reduced N100 amplitudes with 'less vigilant' prestimulus stages (Romani, Callieco, & Cosi, 1988). These results suggest that EEG vigilance stages could indeed explain attentional lapses (contrary to the interpretation by Van Dijk et al. (2008)). However, all these studies were conducted in healthy volunteers and all investigated average EEG power in a specific frequency band, whereas as pointed out above one should rather investigate the EEG vigilance level where anterior alpha and theta reflect a continuum of decreasing stages of EEG vigilance.

Sleep problems as the core pathophysiology of the vigilance sub-group in ADHD

The reduced EEG Vigilance described in the example above can be observed when driving a car very late at night while being fatigued, but can also be caused by sleep deprivation or impairments in vigilance regulation and maintenance. As explained in Hegerl et al., (2010): '*…sleep deficits or other factors inducing an unstable vigilance trigger an autoregulatory behavioral syndrome with hyperactivity, sensation seeking and distractibility. This behavioral syndrome has the function to stabilize vigilance by creating a highly stimulating environment. In vulnerable individuals, the autoregulatory mechanism overrides the physiological tendency to seek sleep, aggravates the sleep deficits, worsens the vigilance instability and thereby starts a vicious circle…*'.

ADHD has been associated with sleepiness, shortened sleep latency (Golan et al., 2004), primary sleep disorders, sleep related movement disorders and parasomnias (Chervin et al., 2002; Konofal, Lecendreux & Cortese, 2010; Walters, Silvestri, Zucconi, Chandrashekariah & Konofal, 2008) and ADHD-like behavior can be induced in children by sleep restriction (Fallone et al., 2001; Golan et al., 2004) and improved by reducing sleep deficits (Dahl et al., 1991). Recently, Van Veen (Van Veen et al., 2010) reported in a sample of adult ADHD patients that 78% had sleep-onset insomnia, confirmed by actigraphy and associated with a delayed nighttime melatonin onset. A similar rate of 73% sleep onset insomnia has been reported in children with ADHD (Van der Heijden, Smits, Van Someren & Gunning, 2005). These data suggest that at least a subgroup of patients with ADHD is characterized by a delayed endogenous circadian phase associated with delayed sleep onset (Van Veen et al., 2010). Several studies have investigated the effects of melatonin as an aid to shift this circadian phase and most have reported clear improvements in sleep onset insomnia (Hoebert, van der Heijden, van Geijlswijk & Smits, 2009; Van der Heijden, Smits, Van Someren, Ridderinkhof & Gunning, 2007), however after 4 weeks treatment no improvements of ADHD symptoms and cognition were reported (Van der Heijden et al., 2007), whereas after long-term treatment improvements of behavior and mood were reported only for those children who were still using melatonin and discontinuation usually resulting in a relapse into sleep onset insomnia (Hoebert et al., 2009). This suggests that in this sub-group, normalizing sleep onset insomnia can be achieved by improving circadian regulation by for example melatonin, albeit with a delayed-onset of effect on ADHD symptoms. The effects of stimulant medication on sleep parameters demonstrates a discrepancy between objective and subjective findings, except for prolonged sleep latency and prolonged onset to first REM cycle (Cohen-Zion & Ancoli-Israel, 2004; Corkum, Tannock, & Moldofsky, 1998) at least demonstrating that stimulant medication does not improve

sleep in ADHD. Therefore, the efficacy of stimulant medication has to be sought into the vigilance stabilizing properties during the day.

In chapter 5 and chapter 6 it was shown that neurofeedback treatment in ADHD has been well investigated and this treatment is showing promising results in the treatment of ADHD. The exact working mechanism of this treatment is not well understood, but is thought to be related to the patients' ability to operantly condition brain oscillating activity (Sherlin et al., 2011). The most often reported protocols used in ADHD are Theta/Beta neurofeedback and SMR neurofeedback and as was reported in chapter 5, no differential effects of these protocols could be found based on studies providing one of these protocols for a whole group of patients. However, chapter 6 provided some preliminary evidence that selecting either of these protocols based on the pre-treatment EEG could improve treatment outcomes, most specifically for the domain of inattention.

Several studies have demonstrated that SMR neurofeedback results in increased sleep spindle density during sleep (Hoedlmoser et al., 2008; Sterman et al., 1970) and improves sleep (Cortoos et al., 2010; Hoedlmoser et al., 2008). This suggests that this type of neurofeedback specifically targets the sleep problems, which in turn results in vigilance stabilization (i.e. restore the 'trait like unstable vigilance regulation', also see figure 2). In this view then, sleep problems are considered to be the core pathophysiology in ADHD. In turn vigilance stabilization results in improvements of inattention and hyperactivity/impulsivity in ADHD. Interestingly in chapter 6, it was found that a sub-group who was treated with SMR neurofeedback demonstrated clear neurophysiological changes (increased N200 and P300 amplitude) in oddball ERP and EEG along with clear clinical improvements on core ADHD symptoms. These could be specific effects of this protocol on brain function and subjective reports, although this is still uncertain given the lack of control group. In this regard it is also interesting to note that all patients improved significantly on sleep problems assessed using the Pittsburgh Sleep Quality Inventory (PSQI; unpublished observation), further supporting this notion.

The theta/beta neurofeedback protocol aims at reducing fronto-central theta and increasing beta. In terms of the vigilance model it could be hypothesized that this treatment teaches patients to stabilize their vigilance by decreasing the occurrence of lower vigilance stages, characterized by theta (vigilance stage B2-3) and demonstrating more occurrences of desynchronized beta EEG. More research is required to further substantiate this and investigate the exact working mechanism of theta/beta neurofeedback.

Summarizing, there appears to be a subgroup of ADHD patients in whom there is an impaired vigilance regulation, most likely associated with sleep problems such as sleep onset insomnia. Based on chapter 1, if we consider the frontal slow (B2-3), frontal alpha (A3) and low voltage EEG (B1) as states of lower EEG vigilance, this prevalence is estimated to be 55%. Based on the studies discussed above on sleep onset insomnia this prevalence is estimated at 75% (Van der Heijden et al., 2007; Van Veen et al., 2010). This sleep onset insomnia has been related to a delayed circadian rhythm (Van Veen et al., 2010), and hence normalizing this circadian regulation is hypothesized to improve vigilance regulation and thereby improve ADHD symptoms. These patients respond well to stimulant medication, due to its vigilance stabilizing properties. However, in this view the effects of stimulant medication have to be seen as a symptom suppression not affecting the core pathophysiology of ADHD,

but only increasing daytime vigilance. The effects of melatonin – if timed in the appropriate circadian phase - seem to more directly affect the core pathophysiology via its normalizing effect on sleep, albeit with a delayed effect on clinical ADHD symptoms. In line with this delayed onset of effect of melatonin on ADHD symptoms, an interesting hypothesis deserving further study is that maybe neurofeedback can require many fewer sessions, and should be stopped when sleep is normalized. The effects of melatonin however, disappear when it is discontinued. Hence future studies should investigate further how this ADHD sub-group can be identified more reliably by EEG, polysomnography or maybe by sleep parameters such as the 'dim light melatonin onset' or DLMO measure reported in several studies (Hoebert et al., 2009; Van der Heijden et al., 2007; Van Veen et al., 2010). Furthermore, future studies should investigate how these sleep problems could be treated more effectively with *sustained* effects by for example bright light, sleep hygiene or SMR neurofeedback.

The 'slow individual alpha peak frequency' sub-group.

The most consistent finding which emerged throughout all studies reported in this thesis is the utility of the slow individual alpha peak frequency (iAPF) sub-group for both ADHD and depression. As pointed out in chapter 1, this measure has often been reported in the older EEG literature and has largely been ignored by many researchers employing QEEG techniques, most likely due to the difficulty of reliably calculating this in an automated fashion. It was found that ADHD patients with a slow iAPF – in contrast to patients with frontal theta - do not respond well to stimulant medication, whereas at baseline they present among the worst performers on a CPT test (inattention and impulsivity errors), illustrating the importance of dissociating these 2 subgroups.

In Figure 3 (from chapter 1 and 3), this is illustrated in more detail. This figure shows the spectral content of ADHD children (red) and data from a control group (black) for both frontal (Fz) and parietal (Pz) locations. The dotted lines reflect the groups with a 'normal EEG' and the solid lines show the spectral power of the sub-groups with a 'Frontal Slow' (top) or 'Slowed Alpha peak frequency' (bottom). As can be seen the spectral content for the Frontal Slow group is increased in the theta frequency range mainly at Fz, as would be expected. However, the ADHD group with the Slowed iAPF at Pz showed an average APF of 7.5 Hz. In the frontal locations this also shows up as an 'increased theta EEG power' whereas this obviously is due to the excessive slowing of the iAPF and should be considered slow alpha, not theta.

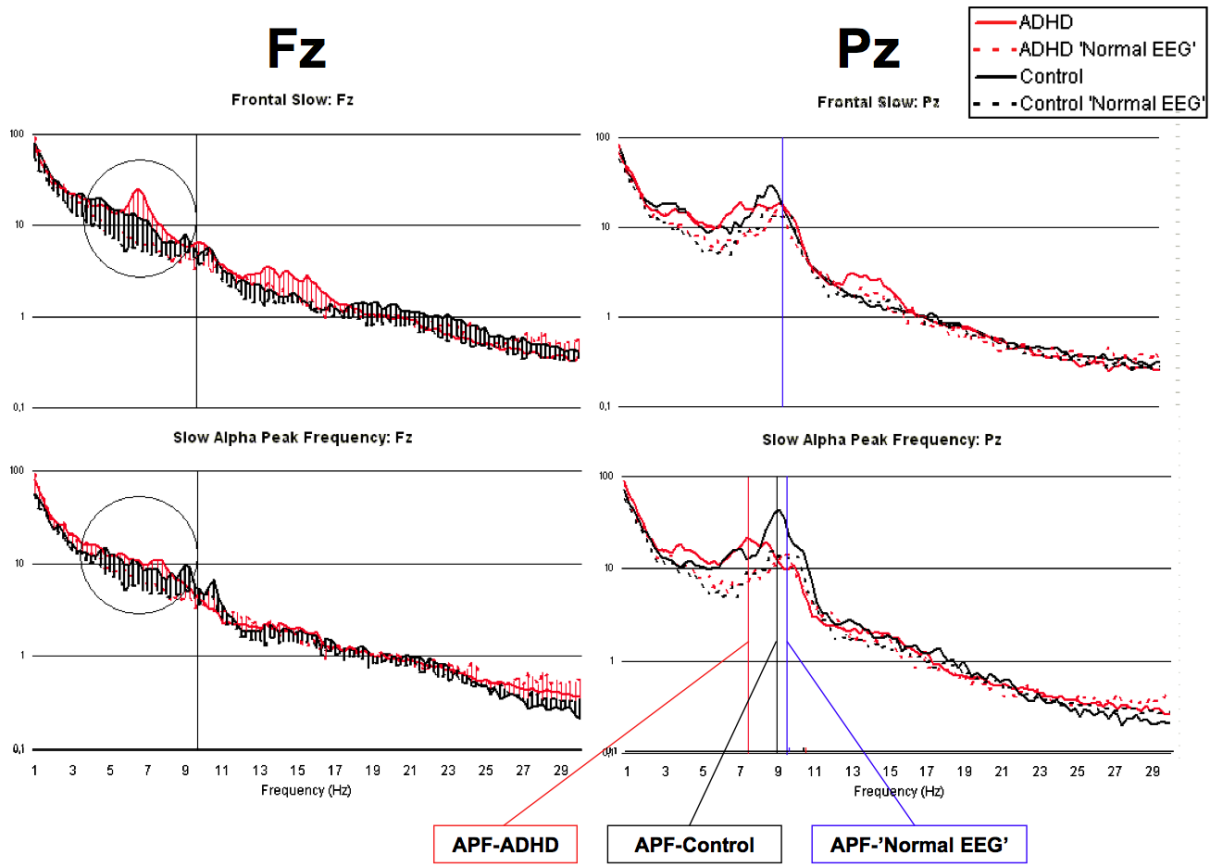


Figure 3: *This figure clearly demonstrates that the sub-group with a slowed alpha peak frequency (bottom), present parietally, also exhibit elevated 'theta EEG Power' at frontal sites. However, this is not true 'frontal slow', but simply the effect of the slowed alpha peak frequency. This demonstrates that a raised theta/beta ratio at least also includes the slow APF sub-group, which neurophysiologically is a different group, as demonstrated with respect to treatment outcome to stimulant medication. For more details on this figure also see chapter 1.*

In chapter 4, it was further demonstrated using a quantitative approach that the often reported increased theta/beta ratio in ADHD actually combines both the frontal slow group (interpreted as the 'impaired vigilance regulation subgroup' see above) as well as the slow iAPF subgroup. Therefore, although the theta/beta ratio and the 'excess theta' can discriminate a group of children with a DSM-IV diagnosis of ADHD very well from healthy controls (Boutros et al., 2005; Monastra et al., 1999; Snyder & Hall, 2006), this measure is probably not a specific measure since it incorporates different subtypes of ADHD. From a personalized medicine perspective this is not optimal, since these sub-types respond differentially to medication and are hypothesized to have a different underlying pathophysiology.

This also helps explain the contradictory findings between Chabot et al. (1999; 2001) who found that their excess theta group (described as *'generalized excess of theta absolute and relative power, decreased alpha mean frequency, and frontal theta hypercoherence')* exhibited a lower response to stimulant medication, suggesting they included patients with a low iAPF, versus Clarke et al. (Clarke, Barry, McCarthy & Selikowitz, 2002; Clarke, Barry, McCarthy, Selikowitz & Brown, 2002) and Suffin and Emory (1995) who found that

responders to stimulant medication demonstrated increased theta and increased theta/beta ratios.

In chapter 6 it was found that there was no relation between a slow iAPF and the outcome to neurofeedback in ADHD in inattention and impulsivity/hyperactivity. In this sample the prevalence of a slow iAPF might have been too low (iAPF < 8 Hz: N=1 for parietoccipital iAPF and N=6 for frontal iAPF from total N=19) to find a clear relationship between a slow iAPF and treatment outcome on ADHD rating scales. Therefore the conclusion that neurofeedback can be considered an effective treatment for those patients with a slow iAPF who do not respond to stimulant medication is unjustified at this moment. More research with larger samples are required to further investigate that.

Further implications for treatment related to this sub-type will be discussed in the next section on depression, since this sub-type appears as a non-specific predictor for non-response to treatments across disorders.

Excess beta sub-group

There is also clear evidence that in addition to the above discussed 2 sub-groups, a third sub-group exists that is characterized by excess beta or beta spindles, and makes up 13-20% of the ADHD population (Chabot & Serfontein, 1996; Clarke et al., 1998; Clarke et al., 2001b) and which was also observed in chapter 2 and chapter 6. Several studies demonstrated that these patients do respond to stimulant medication (Chabot et al., 1999; Clarke et al., 2003b; Hermens et al., 2005). Relatively little is known about this excess beta group and about beta spindles. The latter are generally observed as a medication effect due to benzodiazepines (Blume, 2006) or barbiturates (Schwartz, Feldstein, Fink, Shapiro & Itil, 1971). Furthermore, Clarke et al. (2001c) reported this ADHD sub-group was more prone to moody behavior and temper tantrums and Barry et al. (2009) reported that the ERP's of this sub-group differed substantially from ADHD children without excess beta, suggesting a different dysfunctional network explaining their complaints. Interestingly the ERP's of the excess beta sub-group appear more normal than those of the ADHD sub-group without excess beta.

Originally Gibbs and Gibbs (1950) distinguished two types of predominantly fast EEG, a moderate increased beta, which they termed 'F1' and a marked increased beta, which they termed 'F2'. Records of the F1 type were initially considered as 'abnormal' until the 1940's, whereas since that time Gibbs and Gibbs only considered the F2 type as 'abnormal'. However, currently electroencephalographers have shown a more lenient philosophy towards fast tracings (From: Niedermeyer & Da Silva (2004) page 161). At this moment the only abnormal EEG pattern in the beta range is the 'paroxysmal fast activity' or 'beta band seizure pattern', which most often occurs during non-REM sleep, but also during waking (Stern & Engel, 2004). This pattern is quite rare (4 in 3000) and most often seen in Lennox-Gastaut syndrome (Halasz, Janszky, Barcs & Szcs, 2004). Vogel (1970) also described an EEG pattern of 'occipital slow beta waves' or also termed 'quick alpha variants 16-19/sec' which responds in the same way as alpha to eyes opening and also has a similar topographic distribution. This pattern was only found in 0.6% of a large population of healthy air-force applicants, given it's very low prevalence and occipital dominance, this subtype is unlikely the explanation of the 'excess beta' or 'beta spindling' sub-type observed in ADHD.

Therefore, the ADHD sub-group with excess beta or beta spindling (assuming the paroxysmal fast activity has been excluded) can neurologically be considered a 'normal variant'. However, neurophysiologically this can be considered a separate sub-group of ADHD, which does respond to stimulant medication (Chabot et al., 1999; Clarke et al., 2003b; Hermens et al., 2005). More research is required to investigate the exact underlying neurophysiology of this sub-type and if other treatments could more specifically target this excess beta or beta spindling.

Depression

After the EEG phenotype model was applied in ADHD (chapter 2) this same method was also applied in depression. The results are summarized in supplement 1 of chapter 7. The results demonstrated a larger heterogeneity in EEG phenotypes in depression and hence the sample for whom pre- and post-treatment data were available was too small to reliably investigate the value of the EEG Phenotype model to predict treatment outcome in depression. It was observed that even with larger samples of patients (N> 200) treated with rTMS the EEG Phenotype model did not provide clear predictive patterns (unpublished observation), therefore in the depression studies presented in chapter 7 and chapter 10 a more 'integrative approach' using combinations of measures which yielded better results was used. In the following the most consistent findings for depression, also in relation to the literature, are highlighted.

Excess theta or decreased theta?

The increased theta in non-responders to rTMS in chapter 10 is in line with previous studies demonstrating non-responders to antidepressant medication to exhibit increased theta (Iosifescu et al., 2009; Knott et al., 2000; Knott et al., 1996). As can be seen in figure 2 of chapter 10 (page 181), theta is most specifically increased in fronto-central locations and not specifically at frontal midline sites, whereas in chapter 7 it was found that increased theta at Fz was associated with improved treatment outcome to antidepressant medication. Frontal midline theta has been localized to the medial prefrontal cortex and anterior cingulate (Asada et al., 1999; Ishii et al., 1999) and a recent meta-analysis has demonstrated that theta in the rostral anterior cingulate cortex is associated with improved response to antidepressant treatment (Pizzagalli, 2011). Hence, the findings from chapter 10 point rather to a generalized increased theta in non-responders as opposed to frontal midline theta originating from the anterior cingulate in line with Knott et al. (2000; 1996) and Iosifescu et al. (2009).

Figure 4 is from a study by Hegerl et al. (2011) and demonstrates EEG Vigilance regulation in patients with depression (N=30) compared to matched controls (N=30). As can be seen from this figure there is a clear difference in EEG vigilance regulation for depressed patients as compared to matched controls. In line with the theory, depressed patients exhibit a hyperstable vigilance regulation expressed by increased A1 stages (parietal alpha) and decreased B2/3 and C stages (frontal theta) which is consistent with a study by Ulrich and Fürstenberg (1999) and other studies demonstrating increased parietal alpha in depression (Itil, 1983; Pollock & Schneider, 1990). Furthermore, the EEG Phenotype results presented in

supplement 1 of chapter 7 demonstrates a tendecy that the frontal alpha EEG Phenotype was less prevalent in depression suggestive of less A3 vigilance stages – and hence higher vigilance. Vogel (1970) described a 'Monotonous High Alpha Waves' pattern, with a simple autosomal dominance of inheritance. The description of this EEG pattern found by Vogel ('Kontinuität') is very similar to the 'hyperrigid' or 'hyperstable' EEG vigilance found by Hegerl et al. (2011) and hence suggests this indeed reflects a 'trait' like EEG vigilance regulation.

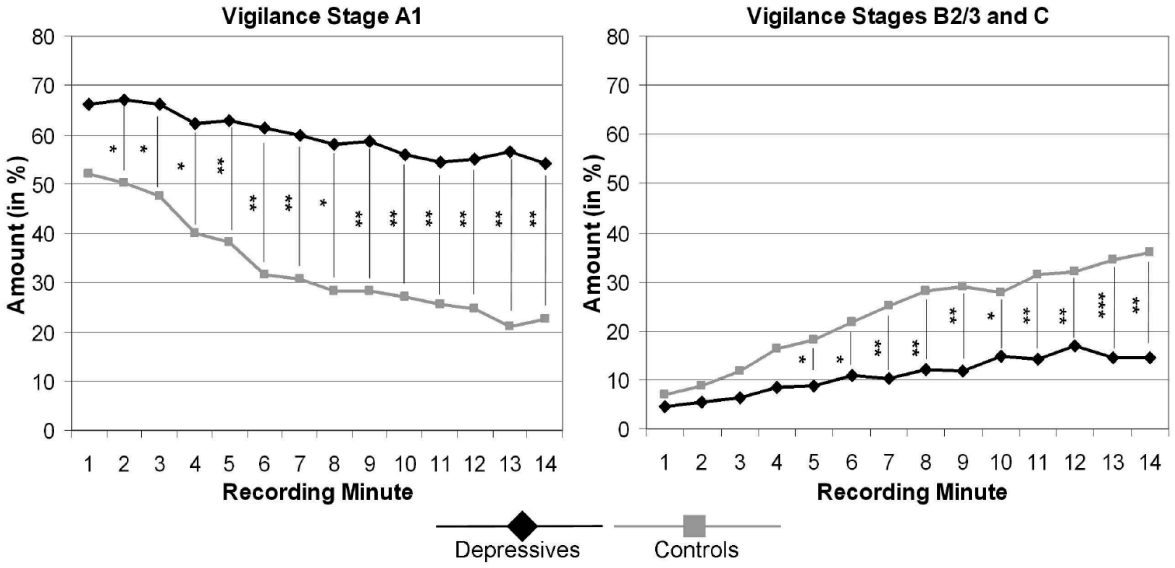


Figure 4: EEG Vigilance regulation over the time course of 15 minutes in depressed patients and healthy controls. Depressed patients demonstrate a hyperstable vigilance regulation, expressed by more A1 stages (parietal alpha) and fewer B2/3 and C stages (frontal theta). From: Hegerl et al. (2011).

Furthermore, increased pre-treatment alpha has been associated with improved treatment outcome to antidepressant medication (Bruder et al., 2001; Ulrich et al., 1984) and most antidepressants also result in a decrease of alpha activity (see Itil (1983) for an overview). Therefore, the sub-group of non-responders from chapter 10 characterized by frontal theta might hence be interpreted as a sub-group characterized by a *decreased* EEG vigilance regulation (Arns et al., 2010a; Hegerl et al., 2010), as opposed to the typically reported *increased or* hyperstable vigilance regulation ('hyperstable' parietal alpha) as pointed out above. Given that patients with a decreased EEG vigilance regulation respond better to stimulant medication (Manic Depression: Bschor et al., 2001; Hegerl et al., 2010; Schoenknecht et al., 2010; ADHD: Arns et al., 2008; Sander et al., 2010) it is tempting to speculate if this subgroup of non-responders might respond better to stimulant medication, or other vigilance stabilizing treatments. Stimulant medication has been applied successfully in a sub-group of depression with excess theta by Suffin and Emory (1995) which was replicated in a prospective randomized controlled trial (Debattista et al., 2010). Furthermore, a recent Cochrane review also found that psychostimulants have clinical effects in depression on mood and fatigue, altough there were very few controlled studies which could be included limiting the extent to which this finding genealizes (Candy, Jones, Williams, Tookman, & King, 2008). Therefore, along the same lines as discussed above in relation to sleep problems as the core pathophysiology of ADHD, future research should focus on investigating EEG vigilance regulation and the existence of sleep problems in this

sub-group of non-responders in order to develop an appropriate treatment for these patients. Figure 4 also clearly demonstrates that for depression eyes closed EEG recordings of up to 15 minutes are required to reliably demonstrate differences in EEG vigilance regulation, which is the main reason why this was not tested in our data, which have been limited to 2 minutes eyes closed.

Summarizing, responders to antidepressant treatments such as antidepressants and rTMS are generally characterized by increased parieto-occipital alpha (or a 'hyperstable' vigilance regulation) and increased theta in the rostral anterior cingulate (Pizzagalli, 2011) reflected as frontal-midline theta (Chapter 7; Asada et al., 1999; Ishii et al., 1999). A sub-group of non-responders to antidepressant treatments are characterized by generalized increased frontal theta reflective of decreased EEG vigilance regulation. It is hypothesized that this latter group might be better responders to vigilance stabilizing treatments such as psychostimulants or sleep onset normalizing treatments such as melatonin. In this regard it is interesting to note that recently a new antidepressant has entered the market with affinity to the melatonine MT1/MT2 receptor named Agomelatine (Demyttenaera, In Press). A final sub-group of non-responders to (antidepressant) treatments are characterized by a slowed alpha peak frequency, which will be discussed in more detail below.

The 'slow individual alpha peak frequency' sub-group: continued…

As pointed out in the section on ADHD, ADHD patients with a slow iAPF were found to be non-responders to stimulant medication. Furthermore, in chapter 6, it was demonstrated that there was a clear relationship between the iAPF at baseline and subsequent improvement in comorbid depressive symptoms as a result of neurofeedback. Chapter 9 and 10 provided further evidence that this measure is a clear predictor for non-response to rTMS treatment in depression, whereas other studies have also found that a slow iAPF is related to unfavorable treatment outcome to rTMS (Conca et al., 2000), antidepressant medication (Ulrich et al., 1984) and antipsychotic medication (Itil et al., 1975). This suggests that a slow iAPF might be considered a non-specific predictor for non-response to treatments across disorders. This sub-group comprises a substantial proportion of patients (28% in ADHD (chapter 2), 17% in depression (chapter 10)) and hence the question arises: *'to what treatment might these patients respond?'*.

Neurophysiology of the iAPF

Much research has been conducted on the relationship between iAPF and cognition, for an extensive review see Klimesch (1999). Most of these studies have been performed in healthy subjects and these mainly provide information about the neuropsychological significance of this measure in 'normal' brain function such as its relation to memory. In this section we are specifically interested in methods that influence the iAPF in order to evaluate what specific methods might be worthwhile exploring as a treatment for the above described sub-group of patients with a slow iAPF. Hence, here a focus is laid on studies that have demonstrated to increase or decrease the iAPF, to elucidate possible treatments for this sub-group.

The iAPF is highly stable across time within subjects (Kondacs & Szabó, 1999) and is considered a highly heritable trait, with between 71-83% of the variance explained by heritability (Posthuma et al., 2001; Beijsterveld & van Baal, 2002), hence the iAPF can be considered a true endophenotype in line with the definition by Gotessman and Gould (2003) as explained in the introduction. Alpha activity has been shown to be generated in thalamocortical feedback loops of excitatory and inhibitory nerve cells (Lopes da Silva, 1991; Steriade et al., 1990). The thalamo-cortical basis of alpha suggests that the iAPF might be reflective of the cortex polling information from the thalamus, and the cortex relaying back information to the thalamus. A higher iAPF may therefore reflect faster information processing, in line with the many studies suggesting a high iAPF is associated with improved cognitive performance such as working memory (Clark et al., 2004), semantic memory (Klimesch, 1996) and with faster reaction times in complex tasks (Jin et al., 2006). Conversely, the most typical neurological syndrome exhibiting a slow iAPF is Alzheimer's disease (AD), whereby the degree of slowing is also associated with the severity of AD (Rodriguez, Copello, Vitali, Perego & Nobili, 1999) and AD is also characterized by impaired semantic memory and working memory.

In pain research it has been found that in healthy patients noxious stimuli will acutely result in an increased iAPF (Nir, Sinai, Raz, Sprecher & Yarnitsky, 2010), possibly reflective of a 'fight-flight' response. Furthermore, in this study there also was a significant correlation between baseline iAPF and the subjective pain rating to the same noxious stimulus, where patients with a higher iAPF rated the same pain stimulus as more painful (Nir et al., 2010). In contrast, in chronic pain patients a slow iAPF has been reported (Boord et al., 2008; Sarnthein, Stern, Aufenberg, Rousson & Jeanmonod, 2006), however when such patients are treated with central lateral thalectomy (which resulted in 95% pain relief at 12 months) the iAPF normalized again to normal levels (Sarnthein et al., 2006). These studies suggest that even though the iAPF is a stable heritable and reproducible trait (Kondacs & Szabó, 1999; Posthuma et al., 2001), the iAPF is responsive when 'threat' is perceived such as pain stimuli. It can be speculated that this 'threat' related increase in iAPF serves the function of increased alertness in order to respond faster in threat situations. However, when a threat becomes chronic in nature a slower iAPF is observed as in the above pain studies, which has also been demonstrated in burnout syndrome (van Luijtelaar, Verbraak, van den Bunt, Keijsers & Arns, 2010), maybe serving a 'gating function' to reduce the amount of information projected to the cortex in order to better cope with the pain or with the information processing demands in burnout syndrome. Interestingly, when the pain is resolved a complete normalization of the iAPF occurs (Sarnthein et al., 2006).

Medication and the iAPF

Ulrich et al. (1984) reported that non-responders to antidepressant medication were characterized by a posterior slower iAPF (8 Hz vs. 9.5 Hz) at baseline, and furthermore that responders to medication exhibited an increase in iAPF, also see figure 5, suggesting that antidepressants do increase the iAPF but only in patients with a 'normal' iAPF to start with.

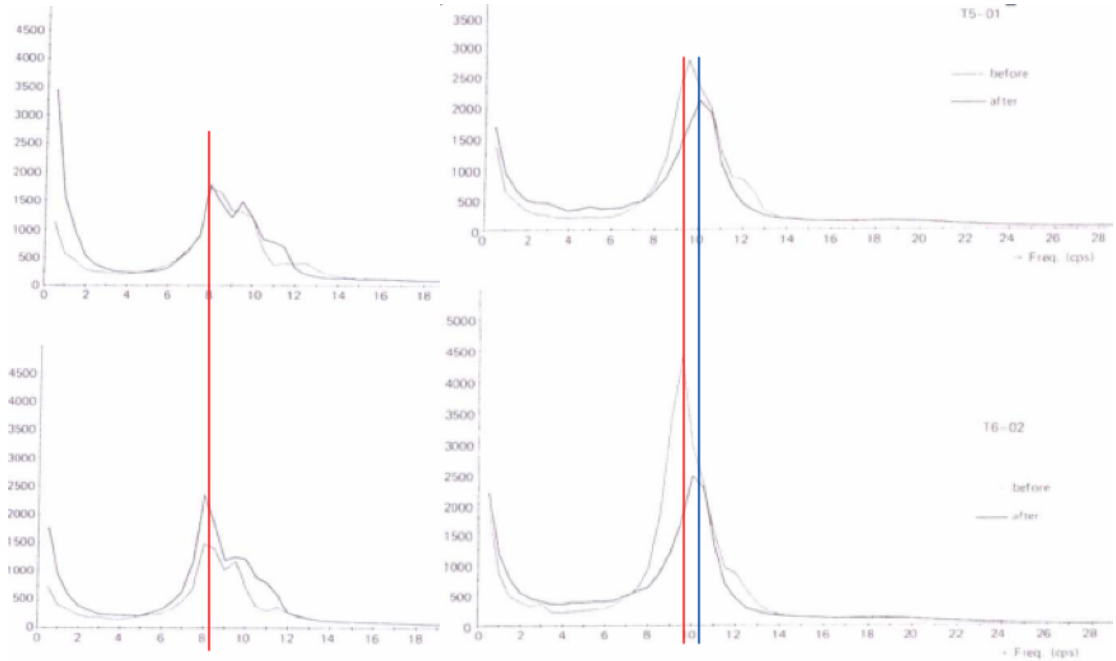


Figure 5: The power spectral plots of non-responders (left) and responders (right) to antidepressant medication at posterior sites. Note the decreased alpha power and lower iAPF (8 Hz) in non-responders. The red line indicates the iAPF pre-treatment and the blue line the iAPF post-treatment. Only responders to medication exhibited an increase in iAPF of approx. 0.5 Hz. Figure from (Ulrich et al., 1984).

Furthermore, nicotine has been shown to acutely result in an increased iAPF (Foulds et al., 1994; Knott, 1988; Lindgren, Molander, Verbaan, Lunell & Rosén, 1999) and so does acute piracetam (Saletu, Grünberger, Linzmayer & Stöhr, 1984).

Neuromodulation and the iAPF

Modulation of the iAPF by neurofeedback was first shown by Kamiya (Kamiya, 1968) and subsequent studies in healthy volunteers have clearly demonstrated that people are able to uptrain their upper alpha, suggestive of increasing the iAPF, with subsequent behavioral improvements in a mental rotation task (Hanslmayr, Sauseng, Doppelmayr, Schabus & Klimesch, 2005; Zoefel, Huster & Herrmann, 2010). However, all these studies have been performed in healthy volunteers with generally 'normal' iAPF's so it is unclear if this technique could be helpful for patients with a slow iAPF. Also in chapter 6 it was not possible to draw any definitive conclusions about the possible role of neurofeedback for this sub-group on ADHD complaints, and future studies are required to investigate this.

Only one study employing 10 Hz rTMS over the left frontal cortex has reported an acute increase of iAPF, which lasted for 2 minutes (Okamura, Jing & Takigawa, 2001). However, our results from chapter 9 and 10 have demonstrated that non-responders to rTMS were characterized by a slow iAPF, suggesting regular rTMS is unlikely to be a likely candidate for this sub-group. One study demonstrated in schizophrenia that rTMS at the iAPF

demonstrated better effects on negative symptoms than LF or HF rTMS (Jin et al., 2006), however we were unable to replicate this in depression in chapter 9.

Cerebral blood flow (CBF)

In 1934 Hans Berger (1934) already described a slowing of the EEG as a result of reduced oxygen (from: Kraaier, Van Huffelen & Wieneke, 1988). Since that time a decrease in iAPF is considered the most sensitive measure to demonstrate the effects of low oxygen supply to the brain such as in cerebral ischemia (Kraaier et al., 1988; Van der Worp, Kraaier, Wieneke & Van Huffelen, 1991) and carotid artery occlusion (Mosmans, Jonkman & Veering, 1983). In patients with minor cerebral ischemia with visually assessed normal EEGs, slowing of the iAPF is found on the affected side (Van der Worp et al., 1991). Carotid Endarterectomy is a procedure used to prevent stroke by correcting stenosis in the carotid artery and hence enhancing the blood supply to the brain. This procedure has been shown to improve cerebral circulation, and subsequently resulted in an increased iAPF after treatment (Uclés, Almarcegui, Lorente, Romero & Marco, 1997; Vriens, Wieneke, Van Huffelen, Visser & Eikelboom, 2000), specifically in those patients with an iAPF below 9 Hz (Vriens et al., 2000). Another study also demonstrated clear increases of more than 1 Hz in the iAPF in patients with carbon monoxide poisoning after hyperbaric oxygen treatment (Murata, Suzuki, Hasegawa, Nohara & Kurachi, 2005).

Recently, a direct relationship between regional CBF and iAPF has been established, where increased iAPF was associated with increased rCBF, most specifically in the bilateral inferior frontal gyrus (BA 45) and right insular cortex (BA 13) (Jann, Koenig, Dierks, Boesch & Federspiel, 2010). These structures are suggested to play a role in the modulation of attention and preparedness for external input or arousal, relevant for task execution (Jann et al., 2010). These results further demonstrate a direct relationship between iAPF and cerebral perfusion on one hand and their relationship to the modulation of attention and arousal on the other hand, which are also impaired in both ADHD and depression.

In this light it is also interesting to note that midazolam (a benzodiazepine) has been shown to decrease cerebral blood flow (CBF) by 30% whereas a benzodiazepine antagonist reversed this effect but had no effects on CBF when administered alone (Forster, Juge, Louis & Nahory, 1987). Furthermore, in another study, hyperbaric oxygen (which increases oxygen availability in the brain) and flumazenil (a benzodiazepine antagonist) both counteracted the EEG activation induced by midazolam (Russell, Vance & Graybeal, 1995). Given that benzodiazepines have been shown to decrease the iAPF (specifically Carbamazepine, and oxcarbazepine: Clemens et al., 2006), these studies suggest interplay between the GABA-ergic system and cerebral blood-flow.

Development of new treatments for this sub-group?

Summarizing, the sub-group with a slow iAPF in our studies and in other studies (Conca et al., 2000; Itil et al., 1975; Ulrich et al., 1984) have been found to be non-responders to various treatments. After reviewing the literature on the iAPF above, it is concluded that a slow iAPF is clearly associated with reduced cerebral blood flow and it is proposed that this

measure is an endophenotype reflective of treatment resistance. Several medications have demonstrated small increases in iAPF such as nicotine and piracetam, however more studies are required to investigate if these medication effects are specific and substantial enough effects on the iAPF.

Future studies should further investigate in this sub-group of patients if any organic explanations for this sub-type exist such as cerebral ischemia, stenosis and oxygen deficiencies during birth. If such organic explanations are confirmed such causes should be investigated further and if possible treated directly to investigate if that results in a normalization of the iAPF and also resolves the depressive or ADHD complaints presented with. If such factors are ruled out, speculatively, the most likely candidate for achieving treatment response in this-subgroup is by methods which increase the cerebral blood flow, given the improvements in iAPF as demonstrated with carotid endarterectomy (Uclés et al., 1997; Vriens et al., 2000) or hyperbaric oxygen therapy (Murata et al., 2005).

Other potential techniques which should deserve further study in this regard are:

1) Near-infrared spectroscopy (NIRS) biofeedback. This technique measures blood oxygenation and deoxygenation in the underlying cortex (Plichta et al., 2006) and real-time applications of this technique for brain-computer interfaces have already been developed (Kanoh, Murayama, Miyamoto, Yoshinobu & Kawashima, 2009). Currently a first study employing this technique in children with ADHD is underway in Tübingen (Strehl, personal communication).
2) Transcranial Doppler Sonography Biofeedback: This technique measures the blood flow velocity in the basal cerebral arteries and can feed these back in real time. The feasibility of this approach was demonstrated in a recent study (Duschek, Schuepbach, Doll, Werner & Reyes Del Paso, 2010).
3) Hyperbaric Oxygen therapy: This technique consists of exposing people to higher oxygen concentrations in an atmospheric pressure chamber in order to improve the oxygen availability in the body and is proposed to decrease inflammatory responses (Granpeesheh et al., 2010). This technique is an evidence based treatment for decompression sickness, under investigation for wound healing and often applied in the treatment of autism (Granpeesheh et al., 2010). However, whereas an initial study found beneficial effects of this treatment for autism (Rossignol et al., 2009), several recent controlled studies were unable to find an effect (Granpeesheh et al., 2010; Jepson et al., 2010). Rather then investigating this treatment in a DSM-IV based group of patients, future studies should investigate this treatment specifically in the slow iAPF sub-group to investigate if this treatment might provide benefit.

The question arises whether for these patients it is sufficient to ‘normalize’ their iAPF for their depressive and ADHD symptoms to improve, or whether the normalization of the iAPF will make them more susceptible to regular treatments, which should also be further investigated.

Final remarks

In line with the recent developments outlined in the beginning of this chapter, this chapter has summarized several clear biomarkers of non-response to treatments in ADHD and Depression. The iAPF has been found to be a solid marker for non-response to various treatments such as stimulant medication, antidepressant medication and rTMS. Given the iAPF is the most reproducible and heritable aspect of the EEG (Posthuma et al., 2001; van Beijsterveldt et al., 2002; Smit et al., 2005), has been associated with the COMT gene (Bodenmann et al., 2009) and is clearly associated with cerebral blood flow, it is proposed here that this measure is an endophenotype related to treatment resistance in depression. Future studies should incorporate this endophenotype to further investigate new treatments for this substantial sub-group of patients.

Finally, it can be concluded that especially in the field of electroencephalography, it is important to be aware of the long and rich history of research rather than only focusing on recent research, since the example of the iAPF clearly demonstrates that with the introduction of new techniques such as QEEG, old well established facts might be overlooked and result in blind-spots such as illustrated with the example of the excess 'theta' in ADHD research actually combining a slow iAPF *and* real theta and the robust status of the iAPF as an endophenotype for non-response.

References

Adrian, E. D., & Matthews, B. H. C. (1934). The berger rhythm: Potential changes from the occipital lobes in man. *Brain*, *57*(4), 355.

Allen, J. J., Coan, J. A., & Nazarian, M. (2004). Issues and assumptions on the road from raw signals to metrics of frontal EEG asymmetry in emotion. *Biological Psychology*, *67*(1-2), 183-218.

Allen, J. J., Harmon-Jones, E., & Cavender, J. H. (2001). Manipulation of frontal EEG asymmetry through biofeedback alters self-reported emotional responses and facial EMG. *Psychophysiology*, *38*(4), 685-93.

Ancy, J., Gangadhar, B. N., & Janakiramaiah, N. (1996). "Normal' P300 amplitude predicts rapid response to ECT in melancholia. *Journal of Affective Disorders*, *41*(3), 211-5.

Angelucci, F., Brenè, S., & Mathé, A. A. (2005). BDNF in schizophrenia, depression and corresponding animal models. *Molecular Psychiatry*, *10*(4), 345-52.

Angelucci, F., Oliviero, A., Pilato, F., Saturno, E., Dileone, M., Versace, V., et al. (2004). Transcranial magnetic stimulation and BDNF plasma levels in amyotrophic lateral sclerosis. *Neuroreport*, *15*(4), 717-20.

Anokhin, A., Steinlein, O., Fischer, C., Mao, Y., Vogt, P., Schalt, E., & Vogel, F. (1992). A genetic study of the human low-voltage electroencephalogram. *Hum Genet*, *90*(1-2), 99-112.

Anokhin, A. P., Heath, A. C., & Myers, E. (2006). Genetic and environmental influences on frontal EEG asymmetry: A twin study. *Biological Psychology*, *71*(3), 289-95. doi:10.1016/j.biopsycho.2005.06.004

Aoyama, Y., Hanaoka, N., Kameyama, M., Suda, M., Sato, T., Song, M., et al. (2009). Stimulus intensity dependence of cerebral blood volume changes in left frontal lobe by low-frequency rTMS to right frontal lobe: A near-infrared spectroscopy study. *Neuroscience Research*, *63*(1), 47-51.

Arias, B., Serretti, A., Lorenzi, C., Gastó, C., Catalán, R., & Fañanás, L. (2006). Analysis of COMT gene (val 158 met polymorphism) in the clinical response to ssris in depressive patients of european origin. *Journal of Affective Disorders*, *90*(2-3), 251-6.

Arnold, L. E., Lofthouse, N., Hersch, S., Pan, X., Hurt, E., Bates, B., et al. (In press). *Neurofeedback for Attention-Deficit/Hyperactivity Disorder: Double-Blind Sham-Controlled Randomized Pilot Feasibility Trial*

*A*rns, M. (2008). Personalized medicine: Nieuwe ontwikkelingen in de diagnostiek en behandeling van ADHD en depressie. *De Psycholoog*, (September).

Arns, M. (2010). Historical archives: The beginning. *Journal of Neurotherapy*, *14*(4), 291-292.

Arns, M., de Ridder, S., Strehl, U., Breteler, M., & Coenen, A. (2009). Efficacy of neurofeedback treatment in ADHD: The effects on inattention, impulsivity and hyperactivity: A meta-analysis. *Clinical EEG and Neuroscience*, *40*(3), 180-9.

Arns, M., Gunkelman, J., Breteler, M., & Spronk, D. (2008). EEG phenotypes predict treatment outcome to stimulants in children with ADHD. *Journal of Integrative Neuroscience*, *7*(3), 421-38.

Arns, M., Gunkelman, J., Olbrich, S., Sander, C., & Hegerl, U. (2010a). EEG vigilance and phenotypes in neuropsychiatry: Implications for intervention. In R. Coben & J. Evans (Eds.), *Neuromodulation and neurofeedback: Techniques and applications* (R. Coben & J. Evans, Eds.). Elsevier.

Arns, M., Spronk, D., & Fitzgerald, P. B. (2010). Potential differential effects of 9 Hz rTMS and 10 Hz rTMS in the treatment of depression. *Brain Stimulation*, (3), 124-126.

Asada, H., Fukuda, Y., Tsunoda, S., Yamaguchi, M., & Tonoike, M. (1999). Frontal midline theta rhythms reflect alternative activation of prefrontal cortex and anterior cingulate cortex in humans. *Neuroscience Letters*, *274*(1), 29-32.

Avery, D. H., Holtzheimer, P. E., Fawaz, W., Russo, J., Neumaier, J., Dunner, D. L., et al. (2006). A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. *Biological Psychiatry*, *59*(2), 187-94.

Baddeley, A., Emslie, H., & Nimmo-Smith, I. (1993). The spot-the-word test: A robust estimate of verbal intelligence based on lexical decision. *The British Journal of Clinical Psychology / the British Psychological Society*, *32 (Pt 1)*, 55-65.

Baehr, E., Rosenfeld, J. P., & Baehr, R. (1997). The clinical use of an alpha asymmetry protocol in the neurofeedback treatment of depression: Two case studies. *Journal of Neurotherapy*, *2*(3), 10-23.

Baehr, E., Rosenfeld, J. P., & Baehr, R. (2001). Clinical use of an alpha asymmetry neurofeedback protocol in the treatment of mood disorders: Follow-Up study one to five years post therapy. *Journal of Neurotherapy*, *4*(4), 11-18.

Baehr, E., Rosenfeld, J. P., Baehr, R., & Earnest, C. (1998). Comparison of two EEG asymmetry indices in depressed patients vs. Normal controls. *International Journal of Psychophysiology, 31*(1), 89-92.

Baeken, C., De Raedt, R., Van Hove, C., Clerinx, P., De Mey, J., & Bossuyt, A. (2009). Hf-Rtms treatment in medication-resistant melancholic depression: Results from 18FDG-PET brain imaging. *CNS Spectrums*, *14*(8), 439-48.

Baeyens, D., Roeyers, H., & Walle, J. V. (2006). Subtypes of attention-deficit/hyperactivity disorder (ADHD): Distinct or related disorders across measurement levels? *Child Psychiatry and Human Development*, *36*(4), 403-417.

Bagby, R. M., Ryder, A. G., & Cristi, C. (2002). Psychosocial and clinical predictors of response to pharmacotherapy for depression. *Journal of Psychiatry & Neuroscience : JPN*, *27*(4), 250-7.

Bakhshayesh, A. R. (2007). *Die wirksamkeit von neurofeedback im vergleich zum emg-biofeedback bei der behandlung von adhs-kindern, PhD Thesis.*

*B*arbini, B., Bertelli, S., Colombo, C., & Smeraldi, E. (1996). Sleep loss, a possible factor in augmenting manic episode. *Psychiatry Research*, *65*(2), 121-5.

Bares, M., Brunovsky, M., Kopecek, M., Novak, T., Stopkova, P., Kozeny, J., et al. (2008). Early reduction in prefrontal theta QEEG cordance value predicts response to venlafaxine treatment in patients with resistant depressive disorder. *European Psychiatry, 23*(5), 350-5.

Bares, M., Brunovsky, M., Kopecek, M., Stopkova, P., Novak, T., Kozeny, J., et al. (2007). Changes in QEEG prefrontal cordance as a predictor of response to antidepressants in patients with treatment resistant depressive disorder: A pilot study. *Journal of Psychiatric Research*, *41*(3-4), 319-25.

Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). Non-Invasive magnetic stimulation of human motor cortex. *Lancet*, *1*(8437), 1106-7.

Barry, R. J., Clarke, A. R., & Johnstone, S. J. (2003). A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. *Clinical Neurophysiology*, *114*(2), 171-183.

Barry, R. J., Clarke, A. R., Johnstone, S. J., & Brown, C. R. (2009). EEG differences in children between eyes-closed and eyes-open resting conditions. *Clinical Neurophysiology*, *120*(10), 1806-11.

Barry, R. J., Clarke, A. R., Johnstone, S. J., Magee, C. A., & Rushby, J. A. (2007). EEG differences between eyes-closed and eyes-open resting conditions. *Clinical Neurophysiology*, *118*(12), 2765-73.

Barry, R. J., Clarke, A. R., McCarthy, R., Selikowitz, M., & Brown, C. R. (2009). Event-Related potentials in children with attention-deficit/hyperactivity disorder and excess beta activity in the EEG. *Acta Neuropsychologica*, *7*(4), 249.

Barry, R. J., Johnstone, S. J., & Clarke, A. R. (2003). A review of electrophysiology in attention-deficit/hyperactivity disorder: II. Event-Related potentials. *Clinical Neurophysiology*, *114*(2), 184-198.

Bath, K. G. & Lee, F. S. (2006). Variant BDNF (val66met) impact on brain structure and function. *Cognitive, Affective & Behavioral Neuroscience*, *6*(1), 79-85.

Baune, B. T., Hohoff, C., Berger, K., Neumann, A., Mortensen, S., Roehrs, T., et al. (2008). Association of the COMT val158met variant with antidepressant treatment response in major depression. *Neuropsychopharmacology, 33*(4), 924-32.

Baxter, L. R., Schwartz, J. M., Phelps, M. E., Mazziotta, J. C., Guze, B. H., Selin, C. E., et al. (1989). Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Archives of General Psychiatry*, *46*(3), 243-50.

Beckmann, H. & Heinemann, H. (1976). [Proceedings: D-Amphetamine in manic syndrome (author's transl)]. *Arzneimittelforschung*, *26*(6), 1185-6.

Bench, C. J., Frackowiak, R. S., & Dolan, R. J. (1995). Changes in regional cerebral blood flow on recovery from depression. *Psychological Medicine*, *25*(2), 247-61.

Benedetti, F., Colombo, C., Pirovano, A., Marino, E., & Smeraldi, E. (2009). The catechol-o-methyltransferase val(108/158)met polymorphism affects antidepressant response to paroxetine in a naturalistic setting. *Psychopharmacology*, *203*(1), 155-60.

Ben-Shachar, D., Belmaker, R. H., Grisaru, N., & Klein, E. (1997). Transcranial magnetic stimulation induces alterations in brain monoamines. *Journal of Neural Transmission, 104*(2-3), 191-7.

Ben-Shachar, D., Gazawi, H., Riboyad-Levin, J., & Klein, E. (1999). Chronic repetitive transcranial magnetic stimulation alters beta-adrenergic and 5-HT2 receptor characteristics in rat brain. *Brain Research*, *816*(1), 78-83.

Bente, D. (1964). *Die insuffizienz des vigilitatstonus.* Thesis, Habilitationsschrift, Erlangen 1964.

Berger, H. (1929). Uber das elektrenkephalogramm des menschen. *Archiv Für Psychiatrie Und Nervenkrankheiten*, *87*, 527-570.

Bickford, R. G., Guidi, M., Fortesque, P., & Swenson, M. (1987). Magnetic stimulation of human peripheral nerve and brain: Response enhancement by combined magnetoelectrical technique. *Neurosurgery*, *20*(1), 110-6.

Bierut, L. J., Saccone, N. L., Rice, J. P., Goate, A., Foroud, T., Edenberg, H., et al. (2002). Defining alcohol-related phenotypes in humans. The collaborative study on the genetics of alcoholism. *Alcohol Res Health*, *26*(3), 208-13.

Biver, F., Goldman, S., Delvenne, V., Luxen, A., De Maertelaer, V., Hubain, P., et al. (1994). Frontal and parietal metabolic disturbances in unipolar depression. *Biological Psychiatry*, *36*(6), 381-8.

Blackwood, D. H., Whalley, L. J., Christie, J. E., Blackburn, I. M., St Clair, D. M., & McInnes, A. (1987). Changes in auditory P3 event-related potential in schizophrenia and depression. *The British Journal of Psychiatry, 150*, 154-60.

Blazer, D. G., Kessler, R. C., McGonagle, K. A., & Swartz, M. S. (1994). The prevalence and distribution of major depression in a national community sample: The national comorbidity survey. *The American Journal of Psychiatry*, *151*(7), 979-86.

Blume, W. T. (2006). Drug effects on EEG. *Journal of Clinical Neurophysiology*, *23*(4), 306.

Bocchio-Chiavetto, L., Miniussi, C., Zanardini, R., Gazzoli, A., Bignotti, S., Specchia, C., et al. (2008). 5-HTTLPR and BDNF val66met polymorphisms and response to rTMS treatment in drug resistant depression. *Neuroscience Letters*, *437*(2), 130-4.

Bodenmann, S., Rusterholz, T., Dürr, R., Stoll, C., Bachmann, V., Geissler, E., et al. (2009). The functional val158met polymorphism of COMT predicts interindividual differences in brain alpha oscillations in young men. *The Journal of Neuroscience, 29*(35), 10855-62.

Bogner, H. R., Bruce, M. L., Reynolds, C. F., Mulsant, B. H., Cary, M. S., Morales, K., et al. (2007). The effects of memory, attention, and executive dysfunction on outcomes of depression in a primary care intervention trial: The PROSPECT study. *International Journal of Geriatric Psychiatry*, *22*(9), 922-9.

Boord, P., Siddall, P. J., Tran, Y., Herbert, D., Middleton, J., & Craig, A. (2008). Electroencephalographic slowing and reduced reactivity in neuropathic pain following spinal cord injury. *Spinal Cord : The Official Journal of the International Medical Society of Paraplegia*, *46*(2), 118-23.

Boutros, N., Fraenkel, L., & Feingold, A. (2005). A four-step approach for developing diagnostic tests in psychiatry: EEG in ADHD as a test case. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *17*(4), 455-64.

Brakemeier, E. L., Luborzewski, A., Danker-Hopfe, H., Kathmann, N., & Bajbouj, M. (2007). Positive predictors for antidepressive response to prefrontal repetitive transcranial magnetic stimulation (rTMS). *Journal of Psychiatric Research*, *41*(5), 395-403.

Brakemeier, E. L., Wilbertz, G., Rodax, S., Danker-Hopfe, H., Zinka, B., Zwanzger, P., et al. (2008). Patterns of response to repetitive transcranial magnetic stimulation (rTMS) in major depression: Replication study in drug-free patients. *Journal of Affective Disorders*, *108*(1-2), 59-70.

Bresnahan, S. M. & Barry, R. J. (2002). Specificity of quantitative EEG analysis in adults with attention deficit hyperactivity disorder. *Psychiatry Research*, *112*(2), 133-44.

Bresnahan, S. M., Anderson, J. W., & Barry, R. J. (1999). Age-Related changes in quantitative EEG in attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *46*(12), 1690-7.

Bretlau, L. G., Lunde, M., Lindberg, L., Undén, M., Dissing, S., & Bech, P. (2008). Repetitive transcranial magnetic stimulation (rTMS) in combination with escitalopram in patients with

treatment-resistant major depression: A double-blind, randomised, sham-controlled trial. *Pharmacopsychiatry*, *41*(2), 41-7.

Broughton, R. & Hasan, J. (1995). Quantitative topographic electroencephalographic mapping during drowsiness and sleep onset. *Journal of Clinical Neurophysiology, 12*(4), 372-86.

Brown, W. A. & Mueller, B. (1979). Alleviation of manic symptoms with catecholamine agonists. *The American Journal of Psychiatry*, *136*(2), 230-1.

Bruder, G., Tenke, C., Jayser, J., Leite, P., McGrath, P., & Quitkin, F. (2001). Pretreatment differences in erps between SSRI antidepressant responders and non-responders. In *41Stannual meeting of the society for psychophysiological research (SPR), montreal, canada, october.*

*B*ruder, G. E., Kayser, J., Tenke, C. E., Leite, P., Schneier, F. R., Stewart, J. W., et al. (2002). Cognitive erps in depressive and anxiety disorders during tonal and phonetic oddball tasks. *Clinical EEG (Electroencephalography)*, *33*(3), 119-24.

Bruder, G. E., Sedoruk, J. P., Stewart, J. W., McGrath, P. J., Quitkin, F. M., & Tenke, C. E. (2008). Electroencephalographic alpha measures predict therapeutic response to a selective serotonin reuptake inhibitor antidepressant: Pre- and post-treatment findings. *Biological Psychiatry*, *63*(12), 1171-7.

Bruder, G. E., Stewart, J. W., Tenke, C. E., McGrath, P. J., Leite, P., Bhattacharya, N., et al. (2001). Electroencephalographic and perceptual asymmetry differences between responders and nonresponders to an SSRI antidepressant. *Biological Psychiatry*, *49*(5), 416-25.

Bruder, G. E., Tenke, C. E., Stewart, J. W., Towey, J. P., Leite, P., Voglmaier, M., et al. (1995). Brain event-related potentials to complex tones in depressed patients: Relations to perceptual asymmetry and clinical features. *Psychophysiology*, *32*(4), 373-81.

Brumaghim, J. T. & Klorman, R. (1998). Methylphenidate's effects on paired-associate learning and event-related potentials of young adults. *Psychophysiology*, *35*, 73-85.

Bschor, T., Müller-Oerlinghausen, B., & Ulrich, G. (2001). Decreased level of EEG-vigilance in acute mania as a possible predictor for a rapid effect of methylphenidate: A case study. *Clinical EEG (Electroencephalography)*, *32*(1), 36-9.

Bukstein, O. (2008). Substance use disorders in adolescents with attention-deficit/ hyperactivity disorder. *Adolesc Med State Art Rev*, *19*(2), 242-253, viii.

Callaway, E., Halliday, R., & Naylor, H. (1983). Hyperactive children's event-related potentials fail to support underarousal and maturational-lag theories. *Archives of General Psychiatry*, *40*(11), 1243-8.

Candy, M., Jones, L., Williams, R., Tookman, A., & King, M. (2008). Psychostimulants for depression. *Cochrane Database of Systematic Reviews (Online)*, (2), CD006722. doi:10.1002/14651858.CD006722.pub2

Capute, A. J., Niedermeyer, E. F. L., & Richardson, F. (1968). The electroencephalogram in children with minimal cerebral dysfunction. *Pediatrics*, *41*(6), 1104.

Cardoso, E. F., Fregni, F., Martins Maia, F., Boggio, P. S., Luis Myczkowski, M., Coracini, K., et al. (2008). Rtms treatment for depression in parkinson's disease increases BOLD responses in the left prefrontal cortex. *The International Journal of Neuropsychopharmacology, 11*(2), 173-83.

Cash, S. S., Halgren, E., Dehghani, N., Rossetti, A. O., Thesen, T., Wang, C., et al. (2009). The human k-complex represents an isolated cortical down-state. *Science, 324*(5930), 1084-7.

Castellanos, F. X. & Tannock, R. (2002). Neuroscience of attention-deficit/hyperactivity disorder: The search for endophenotypes. *Nature Reviews. Neuroscience*, *3*(8), 617-28.

Catafau, A. M., Perez, V., Gironell, A., Martin, J. C., Kulisevsky, J., Estorch, M., et al. (2001). SPECT mapping of cerebral activity changes induced by repetitive transcranial magnetic stimulation in depressed patients. A pilot study. *Psychiatry Research*, *106*(3), 151-60.

Chabot, R. J. & Serfontein, G. (1996). Quantitative electroencephalographic profiles of children with attention deficit disorder. *Biological Psychiatry*, *40*(10), 951-63.

Chabot, R. J., di Michele, F., Prichep, L., & John, E. R. (2001). The clinical role of computerized EEG in the evaluation and treatment of learning and attention disorders in children and adolescents. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *13*(2), 171-86.

Chabot, R. J., Merkin, H., Wood, L. M., Davenport, T. L., & Serfontein, G. (1996). Sensitivity and specificity of QEEG in children with attention deficit or specific developmental learning disorders. *Clinical EEG (Electroencephalography)*, *27*(1), 26-34.

Chabot, R. J., Orgill, A. A., Crawford, G., Harris, M. J., & Serfontein, G. (1999). Behavioral and electrophysiologic predictors of treatment response to stimulants in children with attention disorders. *Journal of Child Neurology*, *14*(6), 343.

Chase, M. H. & Harper, R. M. (1971). Somatomotor and visceromotor correlates of operantly conditioned 12-14 c/sec sensorimotor cortical activity. *Electroencephalography and Clinical Neurophysiology*, *31*(1), 85-92.

Cheeran, B., Talelli, P., Mori, F., Koch, G., Suppa, A., Edwards, M., et al. (2008). A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. *The Journal of Physiology*, *586*(Pt 23), 5717-25.

Chen, B., Dowlatshahi, D., MacQueen, G. M., Wang, J. F., & Young, L. T. (2001). Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. *Biological Psychiatry*, *50*(4), 260-265.

Chen, R., Gerloff, C., Classen, J., Wassermann, E. M., Hallett, M., & Cohen, L. G. (1997). Safety of different inter-train intervals for repetitive transcranial magnetic stimulation and recommendations for safe ranges of stimulation parameters. *Electroencephalography and Clinical Neurophysiology*, *105*(6), 415-21.

Chervin, R. D., Archbold, K. H., Dillon, J. E., Pituch, K. J., Panahi, P., Dahl, R. E., et al. (2002). Associations between symptoms of inattention, hyperactivity, restless legs, and periodic leg movements. *Sleep*, *25*(2), 213-8.

Chistyakov, A. V., Rubicsek, O., Kaplan, B., Zaaroor, M., & Klein, E. (2010). Safety, tolerability and preliminary evidence for antidepressant efficacy of theta-burst transcranial magnetic stimulation in patients with major depression. *The International Journal of Neuropsychopharmacology,* 1-7.

Choi, M. J., Kang, R. H., Lim, S. W., Oh, K. S., & Lee, M. S. (2006). Brain-Derived neurotrophic factor gene polymorphism (val66met) and citalopram response in major depressive disorder. *Brain Research*, *1118*(1), 176-82.

Choi, S. W., Chi, S. E., Chung, S. Y., Kim, J. W., Ahn, C. Y., & Kim, H. T. (2011). Is alpha wave neurofeedback effective with randomized clinical trials in depression? A pilot study. *Neuropsychobiology*, *63*(1), 43-51.

Clark, C. R., Paul, R. H., Williams, L. M., Arns, M., Fallahpour, K., Handmer, C., et al. (2006). Standardized assessment of cognitive functioning during development and aging using an automated touchscreen battery. *Archives of Clinical Neuropsychology, 21*(5), 449-67.

Clarke, A. R., Barry, R. J., Bond, D., McCarthy, R., & Selikowitz, M. (2002). Effects of stimulant medications on the EEG of children with attention-deficit/hyperactivity disorder. *Psychopharmacology*, *164*(3), 277-84.

Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (1998). EEG analysis in attention-deficit/hyperactivity disorder: A comparative study of two subtypes. *Psychiatry Research*, *81*(1), 19-29.

Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (2001a). Age and sex effects in the EEG: Differences in two subtypes of attention-deficit/hyperactivity disorder. *Clinical Neurophysiology*, *112*(5), 815-26.

Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (2001b). Eeg-Defined subtypes of children with attention-deficit/hyperactivity disorder. *Clinical Neurophysiology*, *112*(11), 2098-2105.

Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (2001c). Excess beta activity in children with attention-deficit/hyperactivity disorder: An atypical electrophysiological group. *Psychiatry Research*, *103*(2-3), 205-18.

Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (2002). EEG analysis of children with attention-deficit/hyperactivity disorder and comorbid reading disabilities. *Journal of Learning Disabilities*, *35*(3), 276.

Clarke, A. R., Barry, R. J., McCarthy, R., Selikowitz, M., & Brown, C. R. (2002). EEG evidence for a new conceptualisation of attention deficit hyperactivity disorder. *Clinical Neurophysiology*, *113*(7), 1036-44.

Clarke, A. R., Barry, R. J., McCarthy, R., Selikowitz, M., & Croft, R. J. (2002). EEG differences between good and poor responders to methylphenidate in boys with the inattentive type of attention-deficit/hyperactivity disorder. *Clinical Neurophysiology*, *113*(8), 1191-8.

Clarke, A. R., Barry, R. J., McCarthy, R., Selikowitz, M., Brown, C. R., & Croft, R. J. (2003a). Effects of stimulant medications on the EEG of children with attention-deficit/hyperactivity disorder predominantly inattentive type. *International Journal of Psychophysiology, 47*(2), 129-37.

Clarke, A. R., Barry, R. J., McCarthy, R., Selikowitz, M., Clarke, D. C., & Croft, R. J. (2003b). Effects of stimulant medications on children with attention-deficit/hyperactivity disorder and excessive beta activity in their EEG. *Clinical Neurophysiology*, *114*(9), 1729-37.

Clemens, B., Ménes, A., Piros, P., Bessenyei, M., Altmann, A., Jerney, J., et al. (2006). Quantitative EEG effects of carbamazepine, oxcarbazepine, valproate, lamotrigine, and possible clinical relevance of the findings. *Epilepsy Research*, *70*(2-3), 190-9.

Coben, R., Arns, M., & Kouijzer, E. J. (2010). Enduring effects of neurofeedback in children. In R. Coben & J. Evans (Eds.), *Neuromodulation and neurofeedback: Techniques and applications* (R. Coben & J. Evans, Eds.). Elsevier.

Cohen, J. (1992). A power primer. *Psychological Bulletin*, *112*(1), 155.

Cohn, R. & Nardini, J. E. (1958). The correlation of bilateral occipital slow activity in the human EEG with certain disorders of behavior. *The American Journal of Psychiatry*, *115*(1), 44-54.

Colon, E., Hommes, O. R., & de Weerd, J. P. (1981). Relation between EEG and disability scores in multiple sclerosis. *Clinical Neurology and Neurosurgery*, *83*(3), 163-8.

Conca, A., Swoboda, E., König, P., Koppi, S., Beraus, W., Künz, A., et al. (2000). Clinical impacts of single transcranial magnetic stimulation (stms) as an add-on therapy in severely depressed patients under SSRI treatment. *Human Psychopharmacology*, *15*(6), 429-438.

Connemann, B. J., Mann, K., Lange-Asschenfeldt, C., Ruchsow, M., Schreckenberger, M., Bartenstein, P., et al. (2005). Anterior limbic alpha-like activity: A low resolution electromagnetic tomography study with lorazepam challenge. *Clinical Neurophysiology*, *116*(4), 886-94.

Conners, C. K., Sitarenios, G., Parker, J. D., & Epstein, J. N. (1998). The revised conners' parent rating scale (CPRS-R): Factor structure, reliability, and criterion validity. *Journal of Abnormal Child Psychology*, *26*(4), 257-68.

Cook, I. A. & Leuchter, A. F. (2001). Prefrontal changes and treatment response prediction in depression. *Seminars in Clinical Neuropsychiatry*, *6*(2), 113-20.

Cook, I. A., Hunter, A. M., Abrams, M., Siegman, B., & Leuchter, A. F. (2009). Midline and right frontal brain function as a physiologic biomarker of remission in major depression. *Psychiatry Research: Neuroimaging.*

*C*ook, I. A., Leuchter, A. F., Morgan, M., Witte, E., Stubbeman, W. F., Abrams, M., et al. (2002). Early changes in prefrontal activity characterize clinical responders to antidepressants. *Neuropsychopharmacology, 27*(1), 120-31.

Cook, I. A., Leuchter, A. F., Morgan, M. L., Stubbeman, W., Siegman, B., & Abrams, M. (2005). Changes in prefrontal activity characterize clinical response in SSRI nonresponders: A pilot study. *Journal of Psychiatric Research*, *39*(5), 461-6.

Cook, I. A., Leuchter, A. F., Witte, E., Abrams, M., Uijtdehaage, S. H., Stubbeman, W., et al. (1999). Neurophysiologic predictors of treatment response to fluoxetine in major depression. *Psychiatry Research*, *85*(3), 263-73.

Coons, H. W., Peloquin, L. J., Klorman, R., Bauer, L. O., Ryan, R. M., Perlmutter, R. A., et al. (1981). Effect of methylphenidate on young adult's vigilance and event-related potentials. *Electroencephalography and Clinical Neurophysiology*, *51*, 373-387.

Cooper, N. J., Keage, H., Hermens, D., Williams, L. M., Debrota, D., Clark, C. R., et al. (2005). The dose-dependent effect of methylphenidate on performance, cognition and psychophysiology. *Journal of Integrative Neuroscience*, *4*(1), 123-44.

Corkum, P., Tannock, R., & Moldofsky, H. (1998). Sleep disturbances in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *37*(6), 637-646.

Cormier, E. (2008). Attention deficit/hyperactivity disorder: A review and update. *J Pediatr Nurs*, *23*(5), 345-357.

Cortoos, A., De Valck, E., Arns, M., Breteler, M. H., & Cluydts, R. (2010). An exploratory study on the effects of tele-neurofeedback and tele-biofeedback on objective and subjective sleep in patients with primary insomnia. *Applied Psychophysiology and Biofeedback*, *35*(2), 125-34.

Cryan, J. F. & O'Leary, O. F. (2010). Neuroscience. A glutamate pathway to faster-acting antidepressants? *Science, 329*(5994), 913-4.

Cuijpers, P., Smit, F., Bohlmeijer, E., Hollon, S. D., & Andersson, G. (2010). Efficacy of cognitive-behavioural therapy and other psychological treatments for adult depression: Meta-Analytic study of publication bias. *The British Journal of Psychiatry : The Journal of Mental Science*, *196*, 173-8.

Cummings, J. L. (1993). The neuroanatomy of depression. *The Journal of Clinical Psychiatry*, *54 Suppl*, 14-20.

Daban, C., Martinez-Aran, A., Cruz, N., & Vieta, E. (2008). Safety and efficacy of vagus nerve stimulation in treatment-resistant depression. A systematic review. *Journal of Affective Disorders*, *110*(1-2), 1-15.

Dahl, R. E., Pelham, W. E., & Wierson, M. (1991). The role of sleep disturbances in attention deficit disorder symptoms: A case study. *J Pediatr Psychol*, *16*(2), 229-39.

Danos, P., Kasper, S., Scholl, H. P., Kaiser, J., Ruhrmann, S., Höflich, G., et al. (1994). Clinical response to sleep deprivation and auditory-evoked potentials--preliminary results. *Pharmacopsychiatry*, *27*(2), 70-1.

Daskalakis, Z., Fitzgerald, P., Greenwald, S., & Devlin, P. (2008). EEG ATR measures clinical response to rTMS treatment in MDD. *Brain Stimulation*, *1*(3), 268-268.

Davids, E., Kis, B., Specka, M., & Gastpar, M. (2006). A pilot clinical trial of oxcarbazepine in adults with attention-deficit hyperactivity disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *30*(6), 1033-8.

Davidson, M. A. (2008). ADHD in adults: A review of the literature. *Journal of Attention Disorders*, *11*(6), 628-641.

Davidson, R. J. (1998). Anterior electrophysiological asymmetries, emotion, and depression: Conceptual and methodological conundrums. *Psychophysiology*, *35*(5), 607-14.

Daviss, W. B. (2008). A review of co-morbid depression in pediatric ADHD: Etiology, phenomenology, and treatment. *Journal of Child and Adolescent Psychopharmacology*, *18*(6), 565-571.

Debattista, C., Kinrys, G., Hoffman, D., Goldstein, C., Zajecka, J., Kocsis, J., et al. (2010). The use of referenced-EEG (rEEG) in assisting medication selection for the treatment of depression. *Journal of Psychiatric Research*, 45(1), 64-75.

Debener, S., Beauducel, A., Nessler, D., Brocke, B., Heilemann, H., & Kayser, J. (2000). Is resting anterior EEG alpha asymmetry a trait marker for depression? Findings for healthy adults and clinically depressed patients. *Neuropsychobiology*, *41*(1), 31-7.

DeBeus, R., Ball, J. D., DeBeus, M. E., & Harrington, R. (2004). Attention training with ADHD children: Preliminary findings in a double-blind placebo-controlled study. *Journal of Neurotherapy*, *8*, 145-148.

deCharms, R. C., Maeda, F., Glover, G. H., Ludlow, D., Pauly, J. M., Soneji, D., et al. (2005). Control over brain activation and pain learned by using real-time functional MRI. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(51), 18626-31.

DeFrance, J. F., Smith, S., Schweitzer, F. C., Ginsberg, L., & Sands, S. (1996). Topographical analyses of attention disorders of childhood. *The International Journal of Neuroscience*, *87*(1-2), 41-61.

Demyttenaere, K. (2011). Agomelatine: A narrative review. *European Neuropsychopharmacology:* doi:10.1016/j.euroneuro.2011.07.004.

d'Elia, G. & Perris, C. (1973). Cerebral functional dominance and depression. An analysis of EEG amplitude in depressed patients. *Acta Psychiatrica Scandinavica*, *49*(3), 191.

di Michele, F., Prichep, L., John, E. R., & Chabot, R. J. (2005). The neurophysiology of attention-deficit/hyperactivity disorder. *International Journal of Psychophysiology, 58*(1), 81-93.

Domschke, K., Lawford, B., Laje, G., Berger, K., Young, R., Morris, P., et al. (2009). Brain-Derived neurotrophic factor (BDNF) gene: No major impact on antidepressant treatment response. *The International Journal of Neuropsychopharmacology,* 1-9.

Doppelmayr, M., Klimesch, W., Pachinger, T., & Ripper, B. (1998). Individual differences in brain dynamics: Important implications for the calculation of event-related band power. *Biological Cybernetics*, *79*(1), 49-57.

Drechsler, R., Straub, M., Doehnert, M., Heinrich, H., Steinhausen, H. C., & Brandeis, D. (2007). Controlled evaluation of a neurofeedback training of slow cortical potentials in children with attention deficit/hyperactivity disorder (ADHD). *Behavioral and Brain Functions : BBF*, *3*(1), 35.

Drevets, W. C., Price, J. L., & Furey, M. L. (2008). Brain structural and functional abnormalities in mood disorders: Implications for neurocircuitry models of depression. *Brain Structure & Function*, *213*(1-2), 93-118.

DSM-IV (1994). DSM-IV: Diagnostic and statistical manual of mental disorders.

Ducci, F., Enoch, M. A., Yuan, Q., Shen, P. H., White, K. V., Hodgkinson, C., et al. (2009). HTR3B is associated with alcoholism with antisocial behavior and alpha EEG power--an intermediate phenotype for alcoholism and co-morbid behaviors. *Alcohol*, *43*(1), 73-84.

Duman, R. S. & Monteggia, L. M. (2006). A neurotrophic model for stress-related mood disorders. *Biological Psychiatry*, *59*(12), 1116-27.

Dunkin, J. J., Leuchter, A. F., Cook, I. A., Kasl-Godley, J. E., Abrams, M., & Rosenberg-Thompson, S. (2000). Executive dysfunction predicts nonresponse to fluoxetine in major depression. *Journal of Affective Disorders*, *60*(1), 13-23.

Durup, G. & Fessard, A. (1935). I. L'électrencéphalogramme de l'homme. Observations psycho-physiologiques relatives à l'action des stimuli visuels et auditifs. *L'année Psychologique*, *36*(1), 1-32.

Duschek, S., Schuepbach, D., Doll, A., Werner, N. S., & Reyes Del Paso, G. A. (2010). Self-Regulation of cerebral blood flow by means of transcranial doppler sonography biofeedback. *Annals of Behavioral Medicine : A Publication of the Society of Behavioral Medicine.*

*E*gner, T. & Sterman, M. B. (2006). Neurofeedback treatment of epilepsy: From basic rationale to practical application. *Expert Review of Neurotherapeutics*, *6*(2), 247-57.

Ehlers, C. L., Garcia-Andrade, C., Wall, T. L., Cloutier, D., & Phillips, E. (1999). Electroencephalographic responses to alcohol challenge in native american mission indians. *Biological Psychiatry*, *45*(6), 776-87.

Ehlers, C. L., Gizer, I. R., Phillips, E., & Wilhelmsen, K. C. (2010). EEG alpha phenotypes: Linkage analyses and relation to alcohol dependence in an american indian community study. *BMC Med Genet*, *11*, 43. doi:10.1186/1471-2350-11-43

Enoch, M. A., Schuckit, M. A., Johnson, B. A., & Goldman, D. (2003). Genetics of alcoholism using intermediate phenotypes. *Alcohol Clin Exp Res*, *27*(2), 169-76. doi:10.1097/01.ALC.0000052702.77807.8C

Enoch, M. A., Shen, P. H., Ducci, F., Yuan, Q., Liu, J., White, K. V., . . . Goldman, D. (2008). Common genetic origins for EEG, alcoholism and anxiety: The role of CRH-BP. *Plos One*, *3*(10), e3620. doi:10.1371/journal.pone.0003620

Enoch, M. A., White, K. V., Harris, C. R., Rohrbaugh, J. W., & Goldman, D. (2002). The relationship between two intermediate phenotypes for alcoholism: Low voltage alpha EEG and low P300 ERP amplitude. *J Stud Alcohol*, *63*(5), 509-17.

Eranti, S., Mogg, A., Pluck, G., Landau, S., Purvis, R., Brown, R. G., et al. (2007). A randomized, controlled trial with 6-month follow-up of repetitive transcranial magnetic stimulation and electroconvulsive therapy for severe depression. *The American Journal of Psychiatry*, *164*(1), 73-81.

Eysenck, H. J. (1990). Biological dimensions of personality. *Handbook of Personality: Theory and Research*, 244-276.

Fallone, G., Acebo, C., Arnedt, J. T., Seifer, R., & Carskadon, M. A. (2001). Effects of acute sleep restriction on behavior, sustained attention, and response inhibition in children. *Perceptual and Motor Skills*, *93*(1), 213-29.

Faraone, S. V. & Buitelaar, J. (2009). Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. *European Child & Adolescent Psychiatry*, *19*(4), 353-364.

Faraone, S. V., Biederman, J., & Mick, E. (2006). The age-dependent decline of attention deficit hyperactivity disorder: A meta-analysis of follow-up studies. *Psychological Medicine*, *36*(2), 159-65.

Faraone, S. V., Sergeant, J., Gillberg, C., & Biederman, J. (2003). The worldwide prevalence of ADHD: Is it an american condition? *World Psychiatry : Official Journal of the World Psychiatric Association (WPA)*, *2*(2), 104-13.

Fine, A. H., Goldman, L., & Sandford, J. (1994). Innovative techniques in the treatment of ADHD: An analysis of the impact of EEG biofeedback training and a cognitive computer generated training. *American Psychological Association, Los Angeles, CA.*

*F*ink, M. (2010). Remembering the lost neuroscience of pharmaco-eeg. *Acta Psychiatrica Scandinavica*, *121*(3), 161-173.

Fitzgerald, P. B. & Daskalakis, Z. J. (2008). A review of repetitive transcranial magnetic stimulation use in the treatment of schizophrenia. *Canadian Journal of Psychiatry. Revue Canadienne De Psychiatrie*, *53*(9), 567-76.

Fitzgerald, P. B., Benitez, J., de Castella, A., Daskalakis, Z. J., Brown, T. L., & Kulkarni, J. (2006). A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. *The American Journal of Psychiatry*, *163*(1), 88-94.

Fitzgerald, P. B., Brown, T. L., Marston, N. A. U., Daskalakis, Z. J., de Castella, A., & Kulkarni, J. (2003). Transcranial magnetic stimulation in the treatment of depression: A double-blind, placebo-controlled trial. *Archives of General Psychiatry*, *60*(10), 1002.

Fitzgerald, P. B., Hoy, K., Daskalakis, Z. J., & Kulkarni, J. (2009). A randomized trial of the anti-depressant effects of low- and high-frequency transcranial magnetic stimulation in treatment-resistant depression. *depression and Anxiety*, *26*(3), 229-34.

Fitzgerald, P. B., Hoy, K., Gunewardene, R., Slack, C., Ibrahim, S., Bailey, M., et al. (2010). A randomized trial of unilateral and bilateral prefrontal cortex transcranial magnetic stimulation in treatment-resistant major depression. *Psychological Medicine*, 1-10.

Fitzgerald, P. B., Hoy, K., McQueen, S., Herring, S., Segrave, R., Been, G., et al. (2008). Priming stimulation enhances the effectiveness of low-frequency right prefrontal cortex transcranial magnetic stimulation in major depression. *Journal of Clinical Psychopharmacology*, *28*(1), 52-8.

Fitzgerald, P. B., Huntsman, S., Gunewardene, R., Kulkarni, J., & Daskalakis, Z. J. (2006). A randomized trial of low-frequency right-prefrontal-cortex transcranial magnetic stimulation as augmentation in treatment-resistant major depression. *The International Journal of Neuropsychopharmacology, 9*(6), 655-66.

Fitzgerald, P. B., Oxley, T. J., Laird, A. R., Kulkarni, J., Egan, G. F., & Daskalakis, Z. J. (2006). An analysis of functional neuroimaging studies of dorsolateral prefrontal cortical activity in depression. *Psychiatry Research*, *148*(1), 33-45.

Fitzgerald, P. B., Sritharan, A., Daskalakis, Z. J., de Castella, A. R., Kulkarni, J., & Egan, G. (2007). A functional magnetic resonance imaging study of the effects of low frequency right prefrontal transcranial magnetic stimulation in depression. *Journal of Clinical Psychopharmacology*, *27*(5), 488-92.

Forster, A., Juge, O., Louis, M., & Nahory, A. (1987). Effects of a specific benzodiazepine antagonist (RO 15-1788) on cerebral blood flow. *Anesthesia and Analgesia*, *66*(4), 309-13.

Foulds, J., McSorley, K., Sneddon, J., Feyerabend, C., Jarvis, M. J., & Russell, M. A. (1994). Effect of subcutaneous nicotine injections of EEG alpha frequency in non-smokers: A placebo-controlled pilot study. *Psychopharmacology*, *115*(1-2), 163-6.

Fregni, F., Marcolin, M. A., Myczkowski, M., Amiaz, R., Hasey, G., Rumi, D. O., et al. (2006). Predictors of antidepressant response in clinical trials of transcranial magnetic stimulation. *The International Journal of Neuropsychopharmacology, 9*(6), 641-54.

Fuchs, T., Birbaumer, N., Lutzenberger, W., Gruzelier, J. H., & Kaiser, J. (2003). Neurofeedback treatment for attention-deficit/hyperactivity disorder in children: A comparison with methylphenidate. *Applied Psychophysiology and Biofeedback*, *28*(1), 1-12.

Funk, A. P. & George, M. S. (2008). Prefrontal EEG asymmetry as a potential biomarker of antidepressant treatment response with transcranial magnetic stimulation (TMS): A case series. *Clinical EEG and Neuroscience*, *39*(3), 125-30.

Gangadhar, B. N., Ancy, J., Janakiramaiah, N., & Umapathy, C. (1993). P300 amplitude in non-bipolar, melancholic depression. *Journal of Affective Disorders*, *28*(1), 57-60.

Gani, C., Birbaumer, N., & Strehl, U. (2008). Long term effects after feedback of slow cortical potentials and of theta-beta-amplitudes in children with attentiondeficit/hyperactivity disorder (ADHD). *Int J Bioelectromagn*, *10*(4), 209-232.

Garcia-Toro, M., Pascual-Leone, A., Romera, M., Gonzalez, A., Mico, J., Ibarra, O., et al. (2001). *British medical journal*. Journal of Neurology, Neurosurgery, and Psychiatry.

Gasser, T., Bächer, P., & Möcks, J. (1982). Transformations towards the normal distribution of broad band spectral parameters of the EEG. *Electroencephalography and Clinical Neurophysiology*, *53*(1), 119-24.

Gatt, J. M., Kuan, S. A., Dobson-Stone, C., Paul, R. H., Joffe, R. T., Kemp, A. H., et al. (2008). Association between BDNF val66met polymorphism and trait depression is mediated via resting EEG alpha band activity. *Biological Psychology*, *79*(2), 275-84.

De Gennaro, L. & Ferrara, M. (2003). Sleep spindles: An overview. *Sleep Medicine Reviews*, *7*(5), 423-40.

De Gennaro, L., Ferrara, M., Curcio, G., & Cristiani, R. (2001). Antero-Posterior EEG changes during the wakefulness-sleep transition. *Clinical Neurophysiology*, *112*(10), 1901-11.

De Gennaro, L., Vecchio, F., Ferrara, M., Curcio, G., Rossini, P. M., & Babiloni, C. (2004). Changes in fronto-posterior functional coupling at sleep onset in humans. *Journal of Sleep Research*, *13*(3), 209-17.

De Gennaro, L., Vecchio, F., Ferrara, M., Curcio, G., Rossini, P. M., & Babiloni, C. (2005). Antero-Posterior functional coupling at sleep onset: Changes as a function of increased sleep pressure. *Brain Research Bulletin*, *65*(2), 133-40.

George, M. S., Lisanby, S. H., Avery, D., McDonald, W. M., Durkalski, V., Pavlicova, M., et al. (2010). Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: A sham-controlled randomized trial. *Archives of General Psychiatry*, *67*(5), 507-16.

George, M. S., Wassermann, E. M., Kimbrell, T. A., Little, J. T., Williams, W. E., Danielson, A. L., et al. (1997). Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: A placebo-controlled crossover trial. *The American Journal of Psychiatry*, *154*(12), 1752-6.

George, M. S., Wassermann, E. M., Williams, W. A., Callahan, A., Ketter, T. A., Basser, P., et al. (1995). Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *Neuroreport*, *6*(14), 1853-6.

Gevensleben, H., Holl, B., Albrecht, B., Schlamp, D., Kratz, O., Studer, P., et al. (2010). Neurofeedback training in children with ADHD: 6-Month follow-up of a randomised controlled trial. *European Child & Adolescent Psychiatry*, *19*(9), 715-24.

Gevensleben, H., Holl, B., Albrecht, B., Vogel, C., Schlamp, D., Kratz, O., et al. (2009). Is neurofeedback an efficacious treatment for ADHD? A randomised controlled clinical trial. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *50*(7), 780-9.

Ghuman, J. K., Arnold, L. E., & Anthony, B. J. (2008). Psychopharmacological and other treatments in preschool children with attention-deficit/hyperactivity disorder: Current evidence and practice. *Journal of Child and Adolescent Psychopharmacology*, *18*(5), 413-47.

Gibbs, F. A., & Gibbs, E. L. (1950). Atlas of electroencephalography, vol 1. Cambridge, MA: Addison-Wesley.

Golan, N., Shahar, E., Ravid, S., & Pillar, G. (2004). Sleep disorders and daytime sleepiness in children with attention-deficit/hyperactive disorder. *Sleep*, *27*(2), 261-6.

Goodwin, J. E. (1947). The significance of alpha variants in the EEG, and their relationship to an epileptiform syndrome. *The American Journal of Psychiatry*, *104*(6), 369-79.

Gordon, E. (2003). Integrative neuroscience in psychiatry: The role of a standardized database. *Australasian Psychiatry*, *11*(2), 156-163.

Gordon, E., Cooper, N., Rennie, C., Hermens, D., & Williams, L. M. (2005). Integrative neuroscience: The role of a standardized database. *Clinical EEG and Neuroscience*, *36*(2), 64-75.

Gordon, E. (2007). Integrating genomics and neuromarkers for the era of brain-related personalized medicine. *personalized Medicine*, *4*(2), 201-215.

Gordon, E., Cooper, N., Rennie, C., Hermens, D., & Williams, L. M. (2005). Integrative neuroscience: The role of a standardized database. *Clinical EEG and Neuroscience*, *36*(2), 64-75.

Gordon, E., Liddell, B. J., Brown, K. J., Bryant, R., Clark, C. R., DAS, P., et al. (2007). Integrating objective gene-brain-behavior markers of psychiatric disorders. *Journal of Integrative Neuroscience*, *6*(1), 1-34.

Gorlyn, M., Keilp, J. G., Grunebaum, M. F., Taylor, B. P., Oquendo, M. A., Bruder, G. E., et al. (2008). Neuropsychological characteristics as predictors of SSRI treatment response in depressed subjects. *Journal of Neural Transmission, 115*(8), 1213-9.

Gottesman, I. I. & Gould, T. D. (2003). The endophenotype concept in psychiatry: Etymology and strategic intentions. *The American Journal of Psychiatry*, *160*(4), 636-45.

Gottesman, I. I. & Shields, J. (1967). A polygenic theory of schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, *58*(1), 199.

Gottesman, I. I. & Shields, J. (1972). Schizophrenia and genetics: A twin study vantage point.

Graham, M. A. & Dietlein, L. F. (1965). Technical details of data acquisition for normative EEG reference library. Analysis of central nervous system and cardiovascular data using computer methods. *NASA SP-72*, 433.

Granpeesheh, D., Tarbox, J., Dixon, D. R., Wilke, A. E., Allen, M. S., & Bradstreet, J. J. (2010). Randomized trial of hyperbaric oxygen therapy for children with autism. *Research in Autism Spectrum Disorders*, *4*(2), 268-275.

Gratton, G., Coles, M. G., & Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalography and Clinical Neurophysiology*, *55*(4), 468-84.

Greenhill, L. L., Halperin, J. M., & Abikoff, H. (1999). Stimulant medications. *Journal of the American Academy of Child & Adolescent Psychiatry*, *38*(5), 503-512.

Gross, M., Nakamura, L., Pascual-Leone, A., & Fregni, F. (2007). Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. The earlier rTMS studies. *Acta Psychiatrica Scandinavica*, *116*(3), 165-73.

Grunhaus, L., Schreiber, S., Dolberg, O. T., Polak, D., & Dannon, P. N. (2003). A randomized controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. *Biological Psychiatry*, *53*(4), 324-31.

Gur, E., Lerer, B., Dremencov, E., & Newman, M. E. (2000). Chronic repetitive transcranial magnetic stimulation induces subsensitivity of presynaptic serotonergic autoreceptor activity in rat brain. *Neuroreport*, *11*(13), 2925-9.

Hagemann, D. (2004). Individual differences in anterior EEG asymmetry: Methodological problems and solutions. *Biological Psychology*, *67*(1-2), 157-82.

Hagemann, D., Naumann, E., & Thayer, J. F. (2001). The quest for the EEG reference revisited: A glance from brain asymmetry research. *Psychophysiology*, *38*(5), 847-57.

Hagemann, D., Naumann, E., Becker, G., Maier, S., & Bartussek, D. (1998). Frontal brain asymmetry and affective style: A conceptual replication. *Psychophysiology*, *35*(4), 372-88.

Halasz, P., Janszky, J., Barcs, G., & Szcs, A. (2004). Generalised paroxysmal fast activity (GPFA) is not always a sign of malignant epileptic encephalopathy. *Seizure*, *13*(4), 270-276.

Hallett, M. (2007). Transcranial magnetic stimulation: A primer. *Neuron*, *55*(2), 187-99.

Hamani, C., Mayberg, H., Stone, S., Laxton, A., Haber, S., & Lozano, A. M. (2011). The subcallosal cingulate gyrus in the context of major depression. *Biological Psychiatry*, *69*(4), 301-8.

Hammond, D. C. (2008). Comprehensive neurofeedback bibliography: 2007 update. *Journal of Neurotherapy*, *11*(3), 45-60.

Hanaoka, N., Aoyama, Y., Kameyama, M., Fukuda, M., & Mikuni, M. (2007). Deactivation and activation of left frontal lobe during and after low-frequency repetitive transcranial magnetic stimulation over right prefrontal cortex: A near-infrared spectroscopy study. *Neuroscience Letters*, *414*(2), 99-104.

Hans Berger (H) (1934). Uber das elektrenkephalogramm des menschen: Neunte mitteilung. *Arch Fur Psychiatrie.*

*H*anslmayr, S., Sauseng, P., Doppelmayr, M., Schabus, M., & Klimesch, W. (2005). Increasing individual upper alpha power by neurofeedback improves cognitive performance in human subjects. *Applied Psychophysiology and Biofeedback*, *30*(1), 1-10.

Haug, K., Warnstedt, M., Alekov, A. K., Sander, T., Ramírez, A., Poser, B., et al. (2003). Mutations in CLCN2 encoding a voltage-gated chloride channel are associated with idiopathic generalized epilepsies. *Nature Genetics*, *33*(4), 527-32.

Hausmann, A., Weis, C., Marksteiner, J., Hinterhuber, H., & Humpel, C. (2000). Chronic repetitive transcranial magnetic stimulation enhances c-fos in the parietal cortex and hippocampus. *Brain Research. Molecular Brain Research*, *76*(2), 355-62.

Hayashi, K., Tsuda, N., Sawa, T., & Hagihira, S. (2007). Ketamine increases the frequency of electroencephalographic bicoherence peak on the alpha spindle area induced with propofol. *British Journal of Anaesthesia*, *99*(3), 389-95.

Hegerl, U., Bottlender, R., Gallinat, J., Kuss, H. J., Ackenheil, M., & Möller, H. J. (1998). The serotonin syndrome scale: First results on validity. *European Archives of Psychiatry and Clinical Neuroscience*, *248*(2), 96-103.

Hegerl, U., Himmerich, H., Engmann, B., & Hensch, T. (2010). Mania and attention-deficit/hyperactivity disorder: Common symptomatology, common pathophysiology and common treatment? *Current Opinion in Psychiatry*, *23*(1), 1-7.

Hegerl, U., Olbrich, S., Schönknecht, P., & Sander, C. (2008). [Manic behavior as an autoregulatory attempt to stabilize vigilance]. *Der Nervenarzt*, *79*(11), 1283-4, 1286-90.

Hegerl, U., Sander, C., Olbrich, S., & Schoenknecht, P. (2009). Are psychostimulants a treatment option in mania? *Pharmacopsychiatry*, *42*(5), 169-74.

Hegerl, U., Stein, M., Mulert, C., Mergl, R., Olbrich, S., Dichgans, E., et al. (2008). Eeg-Vigilance differences between patients with borderline personality disorder, patients with obsessive-compulsive disorder and healthy controls. *European Archives of Psychiatry and Clinical Neuroscience*, *258*(3), 137-43.

Hegerl, U., Wilk, K., Olbrich, S., Schoenknecht, P., & Sander, C. (In press). Hyperstable regulation of vigilance in patients with major depressive disorder. *The World Journal of Biological Psychiatry.*

Heinrich, H., Gevensleben, H., Freisleder, F. J., Moll, G. H., & Rothenberger, A. (2004). Training of slow cortical potentials in attention-deficit/hyperactivity disorder: Evidence for positive behavioral and neurophysiological effects. *Biological Psychiatry*, *55*(7), 772-5.

Hemmer, S. A., Pasternak, J. F., Zecker, S. G., & Trommer, B. L. (2001). Stimulant therapy and seizure risk in children with ADHD. *Pediatric Neurology*, *24*(2), 99-102.

Henriques, J. B. & Davidson, R. J. (1990). Regional brain electrical asymmetries discriminate between previously depressed and healthy control subjects. *Journal of Abnormal Psychology*, *99*(1), 22-31.

Henriques, J. B. & Davidson, R. J. (1991). Left frontal hypoactivation in depression. *Journal of Abnormal Psychology*, *100*(4), 535-545.

Henry, J. D. & Crawford, J. R. (2005). The short-form version of the depression anxiety stress scales (DASS-21): Construct validity and normative data in a large non-clinical sample. *The British Journal of Clinical Psychology*, *44*(Pt 2), 227-39.

Hermens, D. F., Cooper, N. J., Kohn, M., Clarke, S., & Gordon, E. (2005). Predicting stimulant medication response in ADHD: Evidence from an integrated profile of neuropsychological, psychophysiological and clinical factors. *Journal of Integrative Neuroscience*, *4*(1), 107-21.

Hermens, D. F., Kohn, M. R., Clarke, S. D., Gordon, E., & Williams, L. M. (2005). Sex differences in adolescent ADHD: Findings from concurrent EEG and EDA. *Clinical Neurophysiology*, *116*(6), 1455-63.

Hermens, D. F., Rowe, D. L., Gordon, E., & Williams, L. M. (2006). Integrative neuroscience approach to predict ADHD stimulant response. *Expert Review of Neurotherapeutics*, *6*(5), 753-63.

Hermens, D. F., Soei, E. X., Clarke, S. D., Kohn, M. R., Gordon, E., & Williams, L. M. (2005a). Resting EEG theta activity predicts cognitive performance in attention-deficit hyperactivity disorder. *Pediatric Neurology*, *32*(4), 248-56.

Hermens, D. F., Williams, L. M., Clarke, S., Kohn, M., Cooper, N., & Gordon, E. (2005b). Responses to methylphenidate in adolescent AD/HD: Evidence from concurrently recorded autonomic (EDA) and central (EEG and ERP) measures. *International Journal of Psychophysiology, 58*(1), 21-33.

Herrera-Guzmán, I., Gudayol-Ferré, E., Lira-Mandujano, J., Herrera-Abarca, J., Herrera-Guzmán, D., Montoya-Pérez, K., et al. (2008). Cognitive predictors of treatment response to bupropion and cognitive effects of bupropion in patients with major depressive disorder. *Psychiatry Research*, *160*(1), 72-82.

Hervey, A. S., Epstein, J. N., Curry, J. F., Tonev, S., Eugene Arnold, L., Keith Conners, C., et al. (2006). Reaction time distribution analysis of neuropsychological performance in an ADHD sample. *Child Neuropsychology*, *12*(2), 125-40.

Herwig, U., Padberg, F., Unger, J., Spitzer, M., & Schönfeldt-Lecuona, C. (2001). Transcranial magnetic stimulation in therapy studies: Examination of the reliability of "standard" coil positioning by neuronavigation. *Biological Psychiatry*, *50*(1), 58-61.

Hickie, I. B., Davenport, T. A., Naismith, S. L., & Scott, E. M. (2001). SPHERE: A national depression project. SPHERE national secretariat. *The Medical Journal of Australia*, *175 Suppl*, S4-5.

Himani, A., Tandon, O. P., & Bhatia, M. S. (1999). A study of p300-event related evoked potential in the patients of major depression. *Indian Journal of Physiology and Pharmacology*, *43*(3), 367-72.

Hoebert, M., van der Heijden, K. B., van Geijlswijk, I. M., & Smits, M. G. (2009). Long-Term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia. *Journal of Pineal Research*, *47*(1), 1-7.

Hoedlmoser, K., Pecherstorfer, T., Gruber, G., Anderer, P., Doppelmayr, M., Klimesch, W., et al. (2008). Instrumental conditioning of human sensorimotor rhythm (12-15 Hz) and its impact on sleep as well as declarative learning. *Sleep*, *31*(10), 1401-8.

Hoflich G, Kasper S, Hufnagel A, Ruhrmann S, Moller HJ (1993). Application of transcranial magnetic stimulation in the treatment of drug-resistant major depression: A report of two cases.

Holtmann, M. & Stadler, C. (2006). Electroencephalographic biofeedback for the treatment of attention-deficit hyperactivity disorder in childhood and adolescence. *Expert Review of Neurotherapeutics*, *6*(4), 533-40.

Holtmann, M., Grasmann, D., Cionek-Szpak, E., Hager, V., Panzner, N., Beyer, A., et al. (2009). Spezifische wirksamkeit von neurofeedback auf die impulsivität bei ADHS. *Kindheit Und Entwicklung*, *18*(2), 95-204.

Howe, R. C. & Sterman, M. B. (1972). Cortical-Subcortical EEG correlates of suppressed motor behavior during sleep and waking in the cat. *Electroencephalography and Clinical Neurophysiology*, *32*(6), 681-95.

Huang, Y. Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron*, *45*(2), 201-6.

Huang, Y. Z., Rothwell, J. C., Lu, C. S., Wang, J., Weng, Y. H., Lai, S. C., et al. (2009). The effect of continuous theta burst stimulation over premotor cortex on circuits in primary motor cortex and spinal cord. *Clinical Neurophysiology*, *120*(4), 796-801.

Hughes, J. R., DeLeo, A. J., & Melyn, M. A. (2000). The electroencephalogram in attention deficit-hyperactivity disorder: Emphasis on epileptiform discharges. *Epilepsy & Behavior*, *1*(4), 271-277.

Husain, M. M., Rush, A. J., Fink, M., Knapp, R., Petrides, G., Rummans, T., et al. (2004). Speed of response and remission in major depressive disorder with acute electroconvulsive therapy (ECT): A consortium for research in ECT (CORE) report. *The Journal of Clinical Psychiatry*, *65*(4), 485-91.

Hyman, S. E. (2007). Can neuroscience be integrated into the DSM-V? *Nature Reviews. Neuroscience*, *8*(9), 725-32.

Ikeda, T., Kurosawa, M., Uchikawa, C., Kitayama, S., & Nukina, N. (2005). Modulation of monoamine transporter expression and function by repetitive transcranial magnetic stimulation. *Biochemical and Biophysical Research Communications*, *327*(1), 218-24.

Iosifescu, D. V. (2008). Prediction of response to antidepressants: Is quantitative EEG (QEEG) an alternative? *CNS Neuroscience & Therapeutics*, *14*(4), 263-265.

Iosifescu, D. V., Greenwald, S., Devlin, P., Mischoulon, D., Denninger, J. W., Alpert, J. E., et al. (2009). Frontal EEG predictors of treatment outcome in major depressive disorder. *European Neuropsychopharmacology, 19*(11), 772-7.

Isenberg, K., Downs, D., Pierce, K., Svarakic, D., Garcia, K., Jarvis, M., et al. (2005). Low frequency rTMS stimulation of the right frontal cortex is as effective as high frequency rTMS stimulation of the left frontal cortex for antidepressant-free, treatment-resistant depressed patients. *Annals of Clinical Psychiatry, 17*(3), 153-9.

Ishii, R., Shinosaki, K., Ukai, S., Inouye, T., Ishihara, T., Yoshimine, T., et al. (1999). Medial prefrontal cortex generates frontal midline theta rhythm. *Neuroreport*, *10*(4), 675-9.

Ishikawa, S., Matsunaga, K., Nakanishi, R., Kawahira, K., Murayama, N., Tsuji, S., et al. (2007). Effect of theta burst stimulation over the human sensorimotor cortex on motor and somatosensory evoked potentials. *Clinical Neurophysiology*, *118*(5), 1033-43.

Itil, T. M. (1983). The discovery of antidepressant drugs by computer-analyzed human cerebral bio-electrical potentials (CEEG). *Progress in Neurobiology*, *20*(3-4), 185-249.

Itil, T. M. & Rizzo, A. E. (1967). Behavior and quantitative EEG correlations during treatment of behavior-disturbed adolescents. *Electroencephalography and Clinical Neurophysiology*, *23*(1), 81.

Itil, T. M., Marasa, J., Saletu, B., Davis, S., & Mucciardi, A. N. (1975). Computerized EEG: Predictor of outcome in schizophrenia. *The Journal of Nervous and Mental Disease*, *160*(3), 118-203.

Iyer, M. B., Schleper, N., & Wassermann, E. M. (2003). Priming stimulation enhances the depressant effect of low-frequency repetitive transcranial magnetic stimulation. *The Journal of Neuroscience, 23*(34), 10867-72.

Jann, K., Koenig, T., Dierks, T., Boesch, C., & Federspiel, A. (2010). Association of individual resting state EEG alpha frequency and cerebral blood flow. *Neuroimage*, *51*(1), 365-72.

Januel, D., Dumortier, G., Verdon, C. M., Stamatiadis, L., Saba, G., Cabaret, W., et al. (2006). A double-blind sham controlled study of right prefrontal repetitive transcranial magnetic stimulation (rTMS): Therapeutic and cognitive effect in medication free unipolar depression during 4 weeks. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *30*(1), 126-30.

Janzen, T., Graap, K., Stephanson, S., Marshall, W., & Fitzsimmons, G. (1995). Differences in baseline EEG measures for ADD and normally achieving preadolescent males. *Biofeedback and Self-Regulation*, *20*(1), 65-82.

Jasper, H. & Shagass, C. (1941a). Conditioning the occipital alpha rhythm in man. *Journal of Experimental Psychology*, *28*(5), 373-87.

Jasper, H. & Shagass, C. (1941b). Conscious time judgments related to conditioned time intervals and voluntary control of the alpha rhythm. *Journal of Experimental Psychology*, *28*(6), 503-508.

Jasper, H. H., Solomon, P., & Bradley, C. (1938). Electroencephalographic analyses of behavior problem children. *American Journal of Psychiatry*, *95*(3), 641.

Jensen, O., & Mazaheri, A. (2010). Shaping functional architecture by oscillatory alpha activity: Gating by inhibition. *Front Hum Neurosci*, *4*, 186. doi:10.3389/fnhum.2010.00186

Jensen, O., Gelfand, J., Kounios, J., & Lisman, J. E. (2002). Oscillations in the alpha band (9-12 Hz) increase with memory load during retention in a short-term memory task. *Cerebral Cortex (New York, N.Y. : 1991)*, *12*(8), 877-82.

Jepson, B., Granpeesheh, D., Tarbox, J., Olive, M. L., Stott, C., Braud, S., et al. (2010). Controlled evaluation of the effects of hyperbaric oxygen therapy on the behavior of 16 children with autism spectrum disorders. *Journal of Autism and Developmental Disorders.*

*J*in, Y., O'Halloran, J. P., Plon, L., Sandman, C. A., & Potkin, S. G. (2006). Alpha EEG predicts visual reaction time. *The International Journal of Neuroscience*, *116*(9), 1035-44.

Jin, Y., Potkin, S. G., Kemp, A. S., Huerta, S. T., Alva, G., Thai, T. M., et al. (2006). Therapeutic effects of individualized alpha frequency transcranial magnetic stimulation (alphatms) on the negative symptoms of schizophrenia. *Schizophrenia Bulletin*, *32*(3), 556-61.

John, B. & Lewis, K. R. (1966). Chromosome variability and geographic distribution in insects. *Science*, *152*(3723), 711.

John, E. R., Prichep, L. S., & Almas, M. (1992). Subtyping of psychiatric patients by cluster analysis of QEEG. *Brain Topography*, *4*(4), 321-6.

Johnson, J. S., Hamidi, M., & Postle, B. R. (2009). Using EEG to explore how rTMS produces its effects on behavior. *Brain Topography.*

Johnstone, J., Gunkelman, J., & Lunt, J. (2005). Clinical database development: Characterization of EEG phenotypes. *Clinical EEG and Neuroscience*, *36*(2), 99-107.

Juckel, G., Hegerl, U., Giegling, I., Mavrogiorgou, P., Gallinat, J., Augustin, H., et al. (2007). Loudness dependence of auditory evoked potentials is not associated with polymorphisms or haplotypes in the serotonin transporter gene in a community-based sample of german healthy volunteers. *Psychiatry Research*, *153*(2), 183-7.

Juckel, G., Mendlin, A., & Jacobs, B. L. (1999). Electrical stimulation of rat medial prefrontal cortex enhances forebrain serotonin output: Implications for electroconvulsive therapy and transcranial magnetic stimulation in depression. *Neuropsychopharmacology, 21*(3), 391-8.

Kaiser, D. A. & Othmer, S. (2000). Effect of neurofeedback on variables of attention in a large multi-center trial. *Journal of Neurotherapy*, *4*(1), 5-15.

Kalayam, B. & Alexopoulos, G. S. (1999). Prefrontal dysfunction and treatment response in geriatric depression. *Archives of General Psychiatry*, *56*(8), 713.

Kamiya, J. (1968). Conscious control of brain waves. *Psychology Today*, *1*(11), 56-60.

Kamiya, J. (2011). The first communications about operant conditioning of the EEG. *Journal of Neurotherapy*, *15*(1), 65-73.

Kaneko, S., Iwasa, H., Okada, M., & Hirose, S. (2002). [Autosomal dominant nocturnal frontal lobe epilepsy(ADNFLE)]. *Ryoikibetsu Shokogun Shirizu*, (37 Pt 6), 315-7.

Kanoh, S., Murayama, Y. M., Miyamoto, K., Yoshinobu, T., & Kawashima, R. (2009). A nirs-based brain-computer interface system during motor imagery: System development and online feedback training. *Conference Proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference*, *2009*, 594-7.

Kavale, K. (1982). The efficacy of stimulant drug treatment for hyperactivity. *Journal of Learning Disabilities*, *15*(5), 280.

Keck, M. E., Sillaber, I., Ebner, K., Welt, T., Toschi, N., Kaehler, S. T., et al. (2000). Acute transcranial magnetic stimulation of frontal brain regions selectively modulates the release of vasopressin, biogenic amines and amino acids in the rat brain. *The European Journal of Neuroscience*, *12*(10), 3713-20.

Keck, M. E., Welt, T., Müller, M. B., Erhardt, A., Ohl, F., Toschi, N., et al. (2002). Repetitive transcranial magnetic stimulation increases the release of dopamine in the mesolimbic and mesostriatal system. *Neuropharmacology*, *43*(1), 101-9.

Keller, M. B., McCullough, J. P., Klein, D. N., Arnow, B., Dunner, D. L., Gelenberg, A. J., et al. (2000). A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *The New England Journal of Medicine*, *342*(20), 1462-70.

Kemp, A. H., Gordon, E., Rush, A. J., & Williams, L. M. (2008). Improving the prediction of treatment response in depression: Integration of clinical, cognitive, psychophysiological, neuroimaging, and genetic measures. *CNS Spectrums*, *13*(12), 1066-86; quiz 1087-8.

Kenemans, J. L. & Kähkönen, S. (2011). How human electrophysiology informs psychopharmacology: From bottom-up driven processing to top-down control. *Neuropsychopharmacology, 36*(1), 26-51.

Kennedy, S. H., Evans, K. R., Krüger, S., Mayberg, H. S., Meyer, J. H., McCann, S., et al. (2001). Changes in regional brain glucose metabolism measured with positron emission tomography after paroxetine treatment of major depression. *The American Journal of Psychiatry*, *158*(6), 899-905.

Kessler, R. C., Adler, L., Barkley, R., Biederman, J., Conners, C. K., Demler, O., et al. (2006). The prevalence and correlates of adult ADHD in the united states: Results from the national comorbidity survey replication. *The American Journal of Psychiatry*, *163*(4), 716-23.

Kimbrell, T. A., Little, J. T., Dunn, R. T., Frye, M. A., Greenberg, B. D., Wassermann, E. M., et al. (1999). Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. *Biological Psychiatry*, *46*(12), 1603-13.

Kirsch, I., Deacon, B. J., Huedo-Medina, T. B., Scoboria, A., Moore, T. J., & Johnson, B. T. (2008). Initial severity and antidepressant benefits: A meta-analysis of data submitted to the food and drug administration. *Plos Medicine*, *5*(2), e45.

Kito, S., Fujita, K., & Koga, Y. (2008a). Changes in regional cerebral blood flow after repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in treatment-resistant depression. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *20*(1), 74-80.

Kito, S., Fujita, K., & Koga, Y. (2008b). Regional cerebral blood flow changes after low-frequency transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in treatment-resistant depression. *Neuropsychobiology*, *58*(1), 29-36.

Klein, E., Kreinin, I., Chistyakov, A., Koren, D., Mecz, L., Marmur, S., et al. (1999). Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: A double-blind controlled study. *Archives of General Psychiatry*, *56*(4), 315-20.

Kleinnijenhuis, M., Arns, M. W., Spronk, D. B., Breteler, M. H. M., & Duysens, J. E. J. (2008). Comparison of discrete-trial based SMR and SCP training and the interrelationship between SCP and SMR networks: Implications for brain-computer interfaces and neurofeedback. *Journal of Neurotherapy*, *11*(4), 19-35.

Klimesch, W. (1996). Memory processes, brain oscillations and EEG synchronization. *International Journal of Psychophysiology*, *24*(1-2), 61-100.

Klimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: A review and analysis. *Brain Res Brain Res Rev*, *29*(2-3), 169-95.

Klimesch, W., Freunberger, R., & Sauseng, P. (2009). Oscillatory mechanisms of process binding in memory. *Neuroscience and Biobehavioral Reviews.*

*K*limesch, W., Sauseng, P., & Gerloff, C. (2003). SHORT COMMUNICATION enhancing cognitive performance with repetitive transcranial magnetic stimulation at human individual alpha frequency. *European Journal of Neuroscience*, *17*, 1129-1133.

Klingberg, T., Fernell, E., Olesen, P. J., Johnson, M., Gustafsson, P., Dahlström, K., et al. (2005). Computerized training of working memory in children with adhd--a randomized, controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry*, *44*(2), 177-86.

Knight, L. A., Rooney, M., & Chronis-Tuscano, A. (2008). Psychosocial treatments for attention-deficit/hyperactivity disorder. *Current Psychiatry Reports*, *10*(5), 412-418.

Knott, J. R. & Henry, C. E. (1941). *The Conditioning of the Blocking of the Alpha Rhythm of the Human Electroencephalogram. Exp.*

*K*nott, V., Mahoney, C., Kennedy, S., & Evans, K. (2000). Pre-Treatment EEG and it's relationship to depression severity and paroxetine treatment outcome. *Pharmacopsychiatry*, *33*(6), 201-5.

Knott, V. J. (1988). Dynamic EEG changes during cigarette smoking. *Neuropsychobiology*, *19*(1), 54-60.

Knott, V. J., Telner, J. I., Lapierre, Y. D., Browne, M., & Horn, E. R. (1996). Quantitative EEG in the prediction of antidepressant response to imipramine. *Journal of Affective Disorders*, *39*(3), 175-84.

Knyazev, G. G. (2007). Motivation, emotion, and their inhibitory control mirrored in brain oscillations. *Neuroscience and Biobehavioral Reviews*, *31*(3), 377-95.

Koerselman, F., Laman, D. M., van Duijn, H., van Duijn, M. A., & Willems, M. A. (2004). A 3-month, follow-up, randomized, placebo-controlled study of repetitive transcranial magnetic stimulation in depression. *The Journal of Clinical Psychiatry*, *65*(10), 1323-8.

Kole, M. H., Fuchs, E., Ziemann, U., Paulus, W., & Ebert, U. (1999). Changes in 5-HT1A and NMDA binding sites by a single rapid transcranial magnetic stimulation procedure in rats. *Brain Research*, *826*(2), 309-12.

Kondacs, A. & Szabó, M. (1999). Long-Term intra-individual variability of the background EEG in normals. *Clinical Neurophysiology*, *110*(10), 1708-16.

Konofal, E., Lecendreux, M., & Cortese, S. (2010). Sleep and ADHD. *Sleep Medicine*, *11*(7), 652-8.

Kooij, J. J., Buitelaar, J. K., van den Oord, E. J., Furer, J. W., Rijnders, C. A., & Hodiamont, P. P. (2005). Internal and external validity of attention-deficit hyperactivity disorder in a population-based sample of adults. *Psychological Medicine*, *35*(6), 817-27.

Kozel, F. A., Tian, F., Dhamne, S., Croarkin, P. E., McClintock, S. M., Elliott, A., et al. (2009). Using simultaneous repetitive transcranial magnetic stimulation/functional near infrared spectroscopy (rTMS/fNIRS) to measure brain activation and connectivity. *Neuroimage*, *47*(4), 1177-84.

Kozel, F. A., Trivedi, M. H., Wisniewski, S. R., Miyahara, S., Husain, M. M., Fava, M., et al. (2008). Treatment outcomes for older depressed patients with earlier versus late onset of first depressive episode: A sequenced treatment alternatives to relieve depression (STAR*D) report. *The American Journal of Geriatric Psychiatry, 16*(1), 58-64.

Kraaier, V., Van Huffelen, A. C., & Wieneke, G. H. (1988). Quantitative EEG changes due to hypobaric hypoxia in normal subjects. *Electroencephalography and Clinical Neurophysiology*, *69*(4), 303-12.

Kraemer, H. C., Mintz, J., Noda, A., Tinklenberg, J., & Yesavage, J. A. (2006). Caution regarding the use of pilot studies to guide power calculations for study proposals. *Archives of General Psychiatry*, *63*(5), 484-9.

Kropotov, J. D., Grin-Yatsenko, V. A., Ponomarev, V. A., Chutko, L. S., Yakovenko, E. A., & Nikishena, I. S. (2005). Erps correlates of EEG relative beta training in ADHD children. *International Journal of Psychophysiology, 55*(1), 23-34.

Kuperman, S., Johnson, B., Arndt, S., Lindgren, S., & Wolraich, M. (1996). Quantitative EEG differences in a nonclinical sample of children with ADHD and undifferentiated ADD. *Journal of the American Academy of Child and Adolescent Psychiatry*, *35*(8), 1009-17.

Lakatos, P., Karmos, G., Mehta, A. D., Ulbert, I., & Schroeder, C. E. (2008). Entrainment of neuronal oscillations as a mechanism of attentional selection. *Science, 320*(5872), 110-3.

Lander, E. S. (2011). Initial impact of the sequencing of the human genome. *Nature*, *470*(7333), 187-97.

Lang, U. E., Bajbouj, M., Gallinat, J., & Hellweg, R. (2006). Brain-Derived neurotrophic factor serum concentrations in depressive patients during vagus nerve stimulation and repetitive transcranial magnetic stimulation. *Psychopharmacology*, *187*(1), 56-9.

Langguth, B., Wiegand, R., Kharraz, A., Landgrebe, M., Marienhagen, J., Frick, U., et al. (2007). Pre-Treatment anterior cingulate activity as a predictor of antidepressant response to repetitive transcranial magnetic stimulation (rTMS). *Neuro Endocrinology Letters*, *28*(5), 633-8.

Lansbergen, M., Arns, M., van Dongen-Boomsma, M., Spronk, D., & Buitelaar, J. K. (2011). The increase in theta/beta ratio on resting state EEG in boys with attention-deficit/hyperactivity disorder is mediated by slow alpha peak frequency. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *35*, 47-52.

Lansbergen, M. M., van Dongen-Boomsma, M., Buitelaar, J. K., & Slaats-Willemse, D. (2011). ADHD and EEG-neurofeedback: A double-blind randomized placebo-controlled feasibility study. *Journal of Neural Transmission, 118*(2), 275-284.

La Vaque, T. J., Hammond, D. C., Trudeau, D., Monastra, V., Perry, J., Lehrer, P., et al. (2002). Template for developing guidelines for the evaluation of the clinical efficacy of psychophysiological interventions. *Applied Psychophysiology and Biofeedback*, *27*(4), 273-281.

Lazzaro, I., Gordon, E., Li, W., Lim, C. L., Plahn, M., Whitmont, S., et al. (1999). Simultaneous EEG and EDA measures in adolescent attention deficit hyperactivity disorder. *International Journal of Psychophysiology, 34*(2), 123-34.

Lazzaro, I., Gordon, E., Whitmont, S., Plahn, M., Li, W., Clarke, S., et al. (1998). Quantified EEG activity in adolescent attention deficit hyperactivity disorder. *Clinical EEG (Electroencephalography)*, *29*(1), 37-42.

Leins, U., Goth, G., Hinterberger, T., Klinger, C., Rumpf, N., & Strehl, U. (2007). Neurofeedback for children with ADHD: A comparison of SCP and theta/beta protocols. *Applied Psychophysiology and Biofeedback*, *32*(2), 73-88.

Lemere, F. (1936). The significance of individual differences in the berger rhythm. *Brain: A Journal of Neurology.*

*L*ennox-Buchtal, M., Buchtal, F., & Rosenfalck, P. (1960). Correlation of electroencephalographic findings with crash rate of military jet pilots. *Epilepsia*, *1*, 366-72.

Leon, A. C., Davis, L. L., & Kraemer, H. C. (2011). The role and interpretation of pilot studies in clinical research. *Journal of Psychiatric Research*, *45*(5), 626-9.

Lerner, M. & Wigal, T. (2008). Long-Term safety of stimulant medications used to treat children with ADHD. *Psychiatric Annals*, *38*(1), 43.

Leth-Steensen, C., Elbaz, Z. K., & Douglas, V. I. (2000). Mean response times, variability, and skew in the responding of ADHD children: A response time distributional approach. *Acta Psychologica*, *104*(2), 167-90.

Leuchter, A. F., Cook, I. A., Gilmer, W. S., Marangell, L. B., Burgoyne, K. S., Howland, R. H., et al. (2009). Effectiveness of a quantitative electroencephalographic biomarker for predicting differential response or remission with escitalopram and bupropion in major depressive disorder. *Psychiatry Research*, *169*(2), 132-8.

Leuchter, A. F., Cook, I. A., Hamilton, S. P., Narr, K. L., Toga, A., Hunter, A. M., et al. (2010). Biomarkers to predict antidepressant response. *Current Psychiatry Reports*, 1-10.

Leuchter, A. F., Cook, I. A., Lufkin, R. B., Dunkin, J., Newton, T. F., Cummings, J. L., et al. (1994). Cordance: A new method for assessment of cerebral perfusion and metabolism using quantitative electroencephalography. *Neuroimage*, *1*(3), 208-19.

Leuchter, A. F., Cook, I. A., Marangell, L. B., Gilmer, W. S., Burgoyne, K. S., Howland, R. H., et al. (2009). Comparative effectiveness of biomarkers and clinical indicators for predicting outcomes of SSRI treatment in major depressive disorder: Results of the BRITE-MD study. *Psychiatry Research*, *169*(2), 124-31.

Leuchter, A. F., Cook, I. A., Mena, I., Dunkin, J. J., Cummings, J. L., Newton, T. F., et al. (1994). Assessment of cerebral perfusion using quantitative EEG cordance. *Psychiatry Research*, *55*(3), 141-52.

Leuchter, A. F., Cook, I. A., Witte, E. A., Morgan, M., & Abrams, M. (2002). Changes in brain function of depressed subjects during treatment with placebo. *American Journal of Psychiatry*, *159*(1), 122-129.

Leuchter, A. F., Uijtdehaage, S. H., Cook, I. A., O'Hara, R., & Mandelkern, M. (1999). Relationship between brain electrical activity and cortical perfusion in normal subjects. *Psychiatry Research*, *90*(2), 125-40.

Levkovitz, Y., Roth, Y., Harel, E. V., Braw, Y., Sheer, A., & Zangen, A. (2007). A randomized controlled feasibility and safety study of deep transcranial magnetic stimulation. *Clinical Neurophysiology*, *118*(12), 2730-44.

Lévesque, J., Beauregard, M., & Mensour, B. (2006). Effect of neurofeedback training on the neural substrates of selective attention in children with attention-deficit/hyperactivity disorder: A functional magnetic resonance imaging study. *Neuroscience Letters*, *394*(3), 216-21.

Li, C. T., Wang, S. J., Hirvonen, J., Hsieh, J. C., Bai, Y. M., Hong, C. J., et al. (2010a). Antidepressant mechanism of add-on repetitive transcranial magnetic stimulation in medication-resistant depression using cerebral glucose metabolism. *Journal of Affective Disorders*, *127*(1-3), 219-29.

Li, N., Lee, B., Liu, R. J., Banasr, M., Dwyer, J. M., Iwata, M., et al. (2010b). Mtor-Dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science, 329*(5994), 959-64.

Linden, M., Habib, T., & Radojevic, V. (1996). A controlled study of the effects of EEG biofeedback on cognition and behavior of children with attention deficit disorder and learning disabilities. *Biofeedback and Self-Regulation*, *21*(1), 35-49.

Lindgren, M., Molander, L., Verbaan, C., Lunell, E., & Rosén, I. (1999). Electroencephalographic effects of intravenous nicotine--a dose-response study. *Psychopharmacology*, *145*(3), 342-50.

Logemann, H. N., Lansbergen, M. M., Os, T. W., Böcker, K. B., & Kenemans, J. L. (2010). The effectiveness of EEG-feedback on attention, impulsivity and EEG; a sham feedback controlled study. *Neuroscience Letters*, *479*(1), 49-53.

Loo, C. K., Sachdev, P. S., Haindl, W., Wen, W., Mitchell, P. B., Croker, V. M., et al. (2003). High (15 Hz) and low (1 Hz) frequency transcranial magnetic stimulation have different acute effects on regional cerebral blood flow in depressed patients. *Psychological Medicine*, *33*(06), 997-1006.

Loo, S. K. & Barkley, R. A. (2005). Clinical utility of EEG in attention deficit hyperactivity disorder. *Applied Neuropsychology*, *12*(2), 64-76.

Loo, S. K. & Smalley, S. L. (2008). Preliminary report of familial clustering of EEG measures in ADHD. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics, 147B*(1), 107-9.

Loo, S. K., Hale, T. S., Macion, J., Hanada, G., McGough, J. J., McCracken, J. T., et al. (2009). Cortical activity patterns in ADHD during arousal, activation and sustained attention. *Neuropsychologia*, *47*(10), 2114-9.

Loomis, A. L., Harvey, E. N., & Hobart, G. A. (1937). Harvey EN, hobart GA. Cerebral states during sleep as studied by human brain potentials. *J Exp Psvchol*, *21*, 127-144.

Lopes da Silva, F. (1991). Neural mechanisms underlying brain waves: From neural membranes to networks. *Electroencephalography and Clinical Neurophysiology*, *79*(2), 81-93.

Losier, B. J., McGrath, P. J., & Klein, R. M. (1996). Error patterns on the continuous performance test in non-medicated and medicated samples of children with and without ADHD: A meta-analytic review. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *37*(8), 971-87.

Lubar, J. F. (1991). Discourse on the development of EEG diagnostics and biofeedback for attention-deficit/hyperactivity disorders. *Applied Psychophysiology and Biofeedback*, *16*(3), 201-225.

Lubar, J. F. & Shouse, M. N. (1976). EEG and behavioral changes in a hyperkinetic child concurrent with training of the sensorimotor rhythm (SMR): A preliminary report. *Biofeedback and Self-Regulation*, *1*(3), 293-306.

Lubar, J. F., Swartwood, M. O., Swartwood, J. N., & O'Donnell, P. H. (1995). Evaluation of the effectiveness of EEG neurofeedback training for ADHD in a clinical setting as measured by changes in T.O.V.A. Scores, behavioral ratings, and WISC-R performance. *Biofeedback and Self-Regulation*, *20*(1), 83-99.

Luborzewski, A., Schubert, F., Seifert, F., Danker-Hopfe, H., Brakemeier, E. L., Schlattmann, P., et al. (2007). Metabolic alterations in the dorsolateral prefrontal cortex after treatment with high-frequency repetitive transcranial magnetic stimulation in patients with unipolar major depression. *Journal of Psychiatric Research*, *41*(7), 606-615.

Manes, F., Jorge, R., Morcuende, M., Yamada, T., Paradiso, S., & Robinson, R. G. (2001). A controlled study of repetitive transcranial magnetic stimulation as a treatment of depression in the elderly. *International Psychogeriatrics / IPA*, *13*(2), 225-31.

Mann, C. A., Lubar, J. F., Zimmerman, A. W., Miller, C. A., & Muenchen, R. A. (1992). Quantitative analysis of EEG in boys with attention-deficit-hyperactivity disorder: Controlled study with clinical implications. *Pediatric Neurology*, *8*(1), 30-6.

Marie-Mitchell, A., Leuchter, A. F., Chou, C. P., James Gauderman, W., & Azen, S. P. (2004). Predictors of improved mood over time in clinical trials for major depression. *Psychiatry Research*, *127*(1-2), 73-84.

Matsuura, M., Okubo, Y., Toru, M., Kojima, T., He, Y., Hou, Y., et al. (1993). A cross-national EEG study of children with emotional and behavioral problems: A WHO collaborative study in the western pacific region. *Biological Psychiatry*, *34*(1-2), 59-65.

Mazaheri, A., Nieuwenhuis, I. L., van Dijk, H., & Jensen, O. (2009). Prestimulus alpha and mu activity predicts failure to inhibit motor responses. *Human Brain Mapping*, *30*(6), 1791-800. doi:10.1002/hbm.20763

McMahon, F. J., Buervenich, S., Charney, D., Lipsky, R., Rush, A. J., Wilson, A. F., et al. (2006). Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment. *American Journal of Human Genetics*, *78*(5), 804-14.

Millan, M. J. (2006). Multi-Target strategies for the improved treatment of depressive states: Conceptual foundations and neuronal substrates, drug discovery and therapeutic application. *Pharmacol Ther*, *110*(2), 135-370.

Miller, G. (2010). Is pharma running out of brainy ideas? *Science*, *329*(5991), 502.

Miller, J. C. (1995). Batch processing of 10,000 h of truck driver EEG data. *Biological Psychology*, *40*(1-2), 209-22.

Miniussi, C., Bonato, C., Bignotti, S., Gazzoli, A., Gennarelli, M., Pasqualetti, P., et al. (2005). Repetitive transcranial magnetic stimulation (rTMS) at high and low frequency: An efficacious therapy for major drug-resistant depression? *Clinical Neurophysiology*, *116*(5), 1062-71.

Mintz, M., Legoff, D., Scornaienchi, J., Brown, M., Levin-Allen, S., Mintz, P., & Smith, C. (2009). The underrecognized epilepsy spectrum: The effects of levetiracetam on neuropsychological functioning in relation to subclinical spike production. *Journal of Child Neurology*, *24*(7), 807-15. doi:10.1177/0883073808330762

Mizumasa, T., Hirakata, H., Yoshimitsu, T., Hirakata, E., Kubo, M., Kashiwagi, M., . . . Iida, M. (2004). Dialysis-Related hypotension as a cause of progressive frontal lobe atrophy in chronic hemodialysis patients: A 3-year prospective study. *Nephron. Clinical Practice*, *97*(1), c23-30.

Mogg, A., Pluck, G., Eranti, S. V., Landau, S., Purvis, R., Brown, R. G., et al. (2008). A randomized controlled trial with 4-month follow-up of adjunctive repetitive transcranial magnetic stimulation of the left prefrontal cortex for depression. *Psychological Medicine*, *38*(3), 323-33.

Molina, B. S., Hinshaw, S. P., Swanson, J. M., Arnold, L. E., Vitiello, B., Jensen, P. S., et al. (2009). The MTA at 8 years: Prospective follow-up of children treated for combined-type ADHD in a multisite study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *48*(5), 484-500.

Monastra, V. J., Lubar, J. F., Linden, M., VanDeusen, P., Green, G., Wing, W., et al. (1999). Assessing attention deficit hyperactivity disorder via quantitative electroencephalography: An initial validation study. *Neuropsychology*, *13*(3), 424-33.

Monastra, V. J., Lynn, S., Linden, M., Lubar, J. F., Gruzelier, J., & LaVaque, T. J. (2005). Electroencephalographic biofeedback in the treatment of attention-deficit/hyperactivity disorder. *Applied Psychophysiology and Biofeedback*, *30*(2), 95-114.

Monastra, V. J., Monastra, D. M., & George, S. (2002). The effects of stimulant therapy, EEG biofeedback, and parenting style on the primary symptoms of attention-deficit/hyperactivity disorder. *Applied Psychophysiology and Biofeedback*, *27*(4), 231-49.

Moreines, J. L., McClintock, S. M., & Holtzheimer, P. E. (2011). Neuropsychologic effects of neuromodulation techniques for treatment-resistant depression: A review. *Brain Stimulation*, *4*(1), 17-27.

Mosmans, P. C. M., Jonkman, E. J., & Veering, M. M. (1983). CBF measured by the xenon-133 inhalation technique and quantified EEG (qeeg) investigations in patients with unilateral internal carotid artery occlusion. *Clinical Neurology and Neurosurgery*, *85*(3), 155-164.

Möller, A. L., Hjaltason, O., Ivarsson, O., & Stefánsson, S. B. (2006). The effects of repetitive transcranial magnetic stimulation on depressive symptoms and the P(300) event-related potential. *Nordic Journal of Psychiatry*, *60*(4), 282-5.

Mulert, C., Juckel, G., Brunnmeier, M., Karch, S., Leicht, G., Mergl, R., et al. (2007). Prediction of treatment response in major depression: Integration of concepts. *Journal of Affective Disorders*, *98*(3), 215-25.

Murata, M., Suzuki, M., Hasegawa, Y., Nohara, S., & Kurachi, M. (2005). Improvement of occipital alpha activity by repetitive hyperbaric oxygen therapy in patients with carbon monoxide poisoning: A possible indicator for treatment efficacy. *Journal of the Neurological Sciences*, *235*(1-2), 69-74.

Murawski, B. J. & Burns, S. K. (1966). Daily correlation of adrenal steroids and alpha frequency in the EEG: A demonstration. *Journal of Applied Physiology*, *21*(2), 549-53.

Murray, C. J. & Lopez, A. D. (1997). Global mortality, disability, and the contribution of risk factors: Global burden of disease study. *Lancet*, *349*(9063), 1436-42.

Müller, M. B., Toschi, N., Kresse, A. E., Post, A., & Keck, M. E. (2000). Long-Term repetitive transcranial magnetic stimulation increases the expression of brain-derived neurotrophic factor and cholecystokinin mrna, but not neuropeptide tyrosine mrna in specific areas of rat brain. *Neuropsychopharmacology, 23*(2), 205-15.

Myslobodsky, M. S., Coppola, R., & Weinberger, D. R. (1991). EEG laterality in the era of structural brain imaging. *Brain Topography*, *3*(3), 381-90.

Myslobodsky, M. S., Coppola, R., Bar-Ziv, J., Karson, C., Daniel, D., van Praag, H., et al. (1989). EEG asymmetries may be affected by cranial and brain parenchymal asymmetries. *Brain Topography*, *1*(4), 221-8.

Nahas, Z., Kozel, F. A., Li, X., Anderson, B., & George, M. S. (2003). Left prefrontal transcranial magnetic stimulation (TMS) treatment of depression in bipolar affective disorder: A pilot study of acute safety and efficacy. *Bipolar Disorders*, *5*(1), 40-7.

Näätänen, R. & Picton, T. W. (1986). N2 and automatic versus controlled processes. *Electroencephalography and Clinical Neurophysiology. Supplement*, *38*, 169-86.

Niedermeyer, E. (1997). Alpha rhythms as physiological and abnormal phenomena. *International Journal of Psychophysiology, 26*(1-3), 31-49.

Niedermeyer, E. & Da Silva, F. H. L. (2004). *Electroencephalography: Basic principles, clinical applications, and related fields.* Lippincott Williams & Wilkins.

Nierenberg, A. A. (2010). The perfect storm: CNS drug development in trouble. *CNS Spectrums*, *15*(5), 282-3.

Nigg, J. T. (2005). Neuropsychologic theory and findings in attention-deficit/hyperactivity disorder: The state of the field and salient challenges for the coming decade. *Biological Psychiatry*, *57*(11), 1424-35.

Nir, R. R., Sinai, A., Raz, E., Sprecher, E., & Yarnitsky, D. (2010). Pain assessment by continuous EEG: Association between subjective perception of tonic pain and peak frequency of alpha oscillations during stimulation and at rest. *Brain Research*, *1344*, 77-86.

O'Connell, R. G., Dockree, P. M., Robertson, I. H., Bellgrove, M. A., Foxe, J. J., & Kelly, S. P. (2009). Uncovering the neural signature of lapsing attention: Electrophysiological signals predict errors up to 20 s before they occur. *The Journal of Neuroscience 29*(26), 8604-11.

Okamura, H., Jing, H., & Takigawa, M. (2001). EEG modification induced by repetitive transcranial magnetic stimulation. *Journal of Clinical Neurophysiology, 18*(4), 318-25.

Olbrich, S., Mulert, C., Karch, S., Trenner, M., Leicht, G., Pogarell, O., et al. (2009). Eeg-Vigilance and BOLD effect during simultaneous EEG/fmri measurement. *Neuroimage*, *45*(2), 319-32.

O'Reardon, J. P., Solvason, H. B., Janicak, P. G., Sampson, S., Isenberg, K. E., Nahas, Z., et al. (2007). Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: A multisite randomized controlled trial. *Biological Psychiatry*, *62*(11), 1208-16.

Orlandi, M. A. & Greco, D. (2005). A randomized, double-blind clinical trial of EEG neurofeedback treatment for attention deficit/hyperactivity disorder (ADHD). In *ISNR conference.*

Osipova, D., Takashima, A., Oostenveld, R., Fernández, G., Maris, E., & Jensen, O. (2006). Theta and gamma oscillations predict encoding and retrieval of declarative memory. *The Journal of Neuroscience*, *26*(28), 7523-31.

*P*adberg, F., di Michele, F., Zwanzger, P., Romeo, E., Bernardi, G., Schüle, C., et al. (2002). Plasma concentrations of neuroactive steroids before and after repetitive transcranial magnetic stimulation (rTMS) in major depression. *Neuropsychopharmacology, 27*(5), 874-8.

Padberg, F., Zwanzger, P., Thoma, H., Kathmann, N., Haag, C., Greenberg, B. D., et al. (1999). Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: Comparative study of fast, slow and sham rTMS. *Psychiatry Research*, *88*(3), 163-71.

Paige, S. R., Fitzpatrick, D. F., Kline, J. P., Balogh, S. E., & Hendricks, S. E. (1994). Event-Related potential amplitude/intensity slopes predict response to antidepressants. *Neuropsychobiology*, *30*(4), 197-201.

Paige, S. R., Hendricks, S. E., Fitzpatrick, D. F., Balogh, S., & Burke, W. J. (1995). Amplitude/intensity functions of auditory event-related potentials predict responsiveness to bupropion in major depressive disorder. *Psychopharmacology Bulletin*, *31*(2), 243-8.

Pallanti, S., Bernardi, S., Rollo, A. D., Antonini, S., & Quercioli, L. (2010). Unilateral low frequency versus sequential bilateral repetitive transcranial magnetic stimulation: Is simpler better for treatment of resistant depression? *Neuroscience.*

Parmeggiani, A., Barcia, G., Posar, A., Raimondi, E., Santucci, M., & Scaduto, M. C. (2010). Epilepsy and EEG paroxysmal abnormalities in autism spectrum disorders. *Brain & Development*, *32*(9), 783-9.

Pascual-Leone, A., Tarazona, F., Keenan, J., Tormos, J. M., Hamilton, R., & Catala, M. D. (1999). Transcranial magnetic stimulation and neuroplasticity. *Neuropsychologia*, *37*(2), 207-17.

Pascual-Leone, A., Valls-Solé, J., Wassermann, E. M., & Hallett, M. (1994). Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. *Brain, 117 (Pt 4)*, 847-58.

Paul, R. H., Gunstad, J., Cooper, N., Williams, L. M., Clark, C. R., Cohen, R. A., et al. (2007). Cross-Cultural assessment of neuropsychological performance and electrical brain function measures: Additional validation of an international brain database. *The International Journal of Neuroscience*, *117*(4), 549-68.

Paul, R. H., Lawrence, J., Williams, L. M., Richard, C. C., Cooper, N., & Gordon, E. (2005). Preliminary validity of "integneuro": A new computerized battery of neurocognitive tests. *The International Journal of Neuroscience*, *115*(11), 1549-67.

Paulus, W. (2005). Toward establishing a therapeutic window for rTMS by theta burst stimulation. *Neuron*, *45*(2), 181-3.

Paus, T. & Barrett, J. (2004). Transcranial magnetic stimulation (TMS) of the human frontal cortex: Implications for repetitive TMS treatment of depression. *Journal of Psychiatry & Neuroscience : JPN*, *29*(4), 268-79.

Paus, T., Jech, R., Thompson, C. J., Comeau, R., Peters, T., & Evans, A. C. (1997). Transcranial magnetic stimulation during positron emission tomography: A new method for studying connectivity of the human cerebral cortex. *The Journal of Neuroscience, 17*(9), 3178-84.

Perreau-Linck, E., Lessard, N., Levesque, J., & Beauregard, M. (2010). Effects of neurofeedback training on inhibitory capacities in adhdchildren: A single-blind, randomized, placebo-controlled study. *Journal of Neurotherapy*, *14*(3), 229-242.

Peters, E. J., Slager, S. L., Jenkins, G. D., Reinalda, M. S., Garriock, H. A., Shyn, S. I., et al. (2009). Resequencing of serotonin-related genes and association of tagging snps to citalopram response. *Pharmacogenet Genomics*, *19*(1), 1-10.

Petty, F., Kramer, G. L., Gullion, C. M., & Rush, A. J. (1992). Low plasma gamma-aminobutyric acid levels in male patients with depression. *Biological Psychiatry*, *32*(4), 354-63.

Picard, B. A. (2006). Double blind sham study of neurofeedback treatment for children with ADHD. In *ISNR conference, atlanta, GA, USA.*

*P*iccart-Gebhart, M. J., Procter, M., Leyland-Jones, B., Goldhirsch, A., Untch, M., Smith, I., et al. (2005). Trastuzumab after adjuvant chemotherapy in her2-positive breast cancer. *The New England Journal of Medicine*, *353*(16), 1659-72.

Pine, I., & Pine, H. M. (1953). Clinical analysis of patients with low voltage EEG. *The Journal of Nervous and Mental Disease*, *117*(3), 191

Pineda, J. A., Brang, D., Hecht, E., Edwards, L., Carey, S., Bacon, M., et al. (2008). Positive behavioral and electrophysiological changes following neurofeedback training in children with autism. *Research in Autism Spectrum Disorders*, *2*(3), 557-581.

Pivik, R. T. & Harman, K. (1995). A reconceptualization of EEG alpha activity as an index of arousal during sleep: All alpha activity is not equal. *Journal of Sleep Research*, *4*(3), 131-137.

Pizzagalli, D., Pascual-Marqui, R. D., Nitschke, J. B., Oakes, T. R., Larson, C. L., Abercrombie, H. C., et al. (2001). Anterior cingulate activity as a predictor of degree of treatment response in major depression: Evidence from brain electrical tomography analysis. *The American Journal of Psychiatry*, *158*(3), 405-15.

Pizzagalli, D. A. (2011). Frontocingulate dysfunction in depression: Toward biomarkers of treatment response. *Neuropsychopharmacology, 36*, 183-206.

Plichta, M. M., Herrmann, M. J., Baehne, C. G., Ehlis, A. C., Richter, M. M., Pauli, P., et al. (2006). Event-Related functional near-infrared spectroscopy (fnirs): Are the measurements reliable? *Neuroimage*, *31*(1), 116-24.

Pliszka, S. R. (2007). Pharmacologic treatment of attention-deficit/hyperactivity disorder: Efficacy, safety and mechanisms of action. *Neuropsychol Rev*, *17*(1), 61-72.

Pogarell, O., Koch, W., Pöpperl, G., Tatsch, K., Jakob, F., Mulert, C., et al. (2007). Acute prefrontal rTMS increases striatal dopamine to a similar degree as d-amphetamine. *Psychiatry Research*, *156*(3), 251-5.

Pogarell, O., Koch, W., Pöpperl, G., Tatsch, K., Jakob, F., Zwanzger, P., et al. (2006). Striatal dopamine release after prefrontal repetitive transcranial magnetic stimulation in major depression: Preliminary results of a dynamic [123I] IBZM SPECT study. *Journal of Psychiatric Research*, *40*(4), 307-14.

Pollock, V. E. & Schneider, L. S. (1990). Quantitative, waking EEG research on depression. *Biological Psychiatry*, *27*(7), 757-780.

Porjesz, B., Almasy, L., Edenberg, H. J., Wang, K., Chorlian, D. B., Foroud, T., . . . Begleiter, H. (2002). Linkage disequilibrium between the beta frequency of the human EEG and a GABAA receptor gene locus. *Proceedings of the National Academy of Sciences of the United States of America*, *99*(6), 3729-33.

Porter, R. J., Gallagher, P., Thompson, J. M., & Young, A. H. (2003). Neurocognitive impairment in drug-free patients with major depressive disorder. *The British Journal of Psychiatry, 182*, 214-20.

Post, A. & Keck, M. E. (2001). Transcranial magnetic stimulation as a therapeutic tool in psychiatry: What do we know about the neurobiological mechanisms? *Journal of Psychiatric Research*, *35*(4), 193-215.

Posthuma, D., Neale, M. C., Boomsma, D. I., & de Geus, E. J. (2001). Are smarter brains running faster? Heritability of alpha peak frequency, IQ, and their interrelation. *Behavior Genetics*, *31*(6), 567-79.

Poulet, E., Brunelin, J., Boeuve, C., Lerond, J., D'Amato, T., Dalery, J., et al. (2004). Repetitive transcranial magnetic stimulation does not potentiate antidepressant treatment. *European Psychiatry, 19*(6), 382-3.

Price, G. W., Lee, J. W., Garvey, C., & Gibson, N. (2008). Appraisal of sessional EEG features as a correlate of clinical changes in an rTMS treatment of depression. *Clinical EEG and Neuroscience*, *39*(3), 131-8.

Prichep, L. S., Mas, F., Hollander, E., Liebowitz, M., John, E. R., Almas, M., . . . Levine, R. H. (1993). Quantitative electroencephalographic subtyping of obsessive-compulsive disorder. *Psychiatry Research*, *50*(1), 25-32.

Pridmore, S., Bruno, R., Turnier-Shea, Y., Reid, P., & Rybak, M. (2000). Comparison of unlimited numbers of rapid transcranial magnetic stimulation (rTMS) and ECT treatment sessions in major depressive episode. *The International Journal of Neuropsychopharmacology, 3*(2), 129-134.

Rechtschaffen, A. & Kales, A. (1968). *A manual of standardized terminology technics and scoring systems for sleep of human subjects.* Washington, DC: US Government Printing Office.

Reid, S. A., Duke, L. M., & Allen, J. J. (1998). Resting frontal electroencephalographic asymmetry in depression: Inconsistencies suggest the need to identify mediating factors. *Psychophysiology*, *35*(4), 389-404.

Riccio, C. A., Waldrop, J. J., Reynolds, C. R., & Lowe, P. (2001). Effects of stimulants on the continuous performance test (CPT): Implications for CPT use and interpretation. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *13*(3), 326-35.

Richard Clark, C., Veltmeyer, M. D., Hamilton, R. J., Simms, E., Paul, R., Hermens, D., et al. (2004). Spontaneous alpha peak frequency predicts working memory performance across the age span. *International Journal of Psychophysiology, 53*(1), 1-9.

Richter, P. L., Zimmerman, E. A., Raichle, M. E., & Liske, E. (1971). Electroencephalograms of 2,947 united states air force academy cadets (1965-1969). *Aerospace Medicine*, *42*(9), 1011-4.

De Ridder, D., De Mulder, G., Verstraeten, E., Van der Kelen, K., Sunaert, S., Smits, M., et al. (2006). Primary and secondary auditory cortex stimulation for intractable tinnitus. *ORL; Journal for Oto-Rhino-Laryngology and Its Related Specialties*, *68*(1), 48-54; discussion 54-5.

Ridding, M. C. & Rothwell, J. C. (2007). Is there a future for therapeutic use of transcranial magnetic stimulation? *Nature Reviews. Neuroscience*, *8*(7), 559-67.

Riedel, M., Möller, H. J., Obermeier, M., Schennach-Wolff, R., Bauer, M., Adli, M., . . . Seemüller, F. (2010). Response and remission criteria in major depression--a validation of current practice. *Journal of Psychiatric Research*, *44*(15), 1063-8.

Rodriguez, G., Copello, F., Vitali, P., Perego, G., & Nobili, F. (1999). EEG spectral profile to stage alzheimer's disease. *Clinical Neurophysiology*, *110*(10), 1831-7.

Romani, A., Callieco, R., & Cosi, V. (1988). Prestimulus spectral EEG patterns and the evoked auditory vertex response. *Electroencephalogr Clin Neurophysiol*, *70*(3), 270-2

Rosa, M. A., Gattaz, W. F., Pascual-Leone, A., Fregni, F., Rosa, M. O., Rumi, D. O., et al. (2006). Comparison of repetitive transcranial magnetic stimulation and electroconvulsive therapy in unipolar non-psychotic refractory depression: A randomized, single-blind study. *The International Journal of Neuropsychopharmacology, 9*(6), 667-76.

Rosenberg, M. S., Adams, D. C., & Gurevitch, J. (2000). Metawin: Statistical software for meta-analysis, version 2.1. *Sinauer, Sunderland, MA.*

*R*ossi, S. & Rossini, P. M. (2004). TMS in cognitive plasticity and the potential for rehabilitation. *Trends in Cognitive Sciences*, *8*(6), 273-9.

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., & The Safety of TMS Consensus Group (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*, *120*(12), 2008-39.

Rossignol, D. A., Rossignol, L. W., Smith, S., Schneider, C., Logerquist, S., Usman, A., et al. (2009). Hyperbaric treatment for children with autism: A multicenter, randomized, double-blind, controlled trial. *BMC Pediatr*, *9*, 21.

Rossini, D., Lucca, A., Zanardi, R., Magri, L., & Smeraldi, E. (2005). Transcranial magnetic stimulation in treatment-resistant depressed patients: A double-blind, placebo-controlled trial. *Psychiatry Research*, *137*(1-2), 1-10.

Rossiter, T. (2004). The effectiveness of neurofeedback and stimulant drugs in treating AD/HD: Part I. Review of methodological issues. *Applied Psychophysiology and Biofeedback*, *29*(2), 95-112.

Rostain, A. L. (2008). Attention-Deficit/hyperactivity disorder in adults: Evidence-Based recommendations for management. *Postgraduate Medicine*, *120*(3), 27-38.

Roth, B. (1961). The clinical and theoretical importance of EEG rhythms corresponding to states of lowered vigilance. *Electroencephalography and Clinical Neurophysiology*, *13*, 395-9.

Roth, M., Kay, D. W., Shaw, J., & Green, J. (1957). Prognosis and pentothal induced electroencephalographic changes in electro-convulsive treatment; an approach to the problem of regulation of convulsive therapy. *Electroencephalography and Clinical Neurophysiology*, *9*(2), 225-37.

Rowland, A. S., Lesesne, C. A., & Abramowitz, A. J. (2002). The epidemiology of attention-deficit/hyperactivity disorder (ADHD): A public health view. *Ment Retard Dev Disabil Res Rev*, *8*(3), 162-70

Rumi, D. O., Gattaz, W. F., Rigonatti, S. P., Rosa, M. A., Fregni, F., Rosa, M. O., et al. (2005). Transcranial magnetic stimulation accelerates the antidepressant effect of amitriptyline in severe depression: A double-blind placebo-controlled study. *Biological Psychiatry*, *57*(2), 162-6.

Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., et al. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *The American Journal of Psychiatry*, *163*(11), 1905-17.

Russell, G. B., Vance, W. T., & Graybeal, J. M. (1995). Attenuation of midazolam-induced EEG activation in rats by both flumazenil and hyperbaric oxygen. *J Neurosurg Anesthesiol*, *7*(4), 271-9.

Saletu, B., Grünberger, J., Linzmayer, L., & Stöhr, H. (1984). Encephalotropic and psychotropic effects of intravenous buflomedil in the elderly: Double-Blind, placebo-controlled pharmaco-eeg and psychometric studies. *Int J Clin Pharmacol Res*, *4*(2), 95-107.

Sanacora, G., Rothman, D. L., Mason, G., & Krystal, J. H. (2003). Clinical studies implementing glutamate neurotransmission in mood disorders. *Annals of the New York Academy of Sciences*, *1003*, 292-308.

Sander, C., Arns, M., Olbrich, S., & Hegerl, U. (2010). Eeg-Vigilance and response to stimulants in paediatric patients with attention deficit/hyperactivity disorder. *Clinical Neurophysiology*, *121*, 1511-1518.

Sarnthein, J., Stern, J., Aufenberg, C., Rousson, V., & Jeanmonod, D. (2006). Increased EEG power and slowed dominant frequency in patients with neurogenic pain. *Brain, 129*(Pt 1), 55-64.

Satterfield, J. H., Cantwell, D. P., Saul, R. E., Lesser, L. I., & Podosin, R. L. (1973). Response to stimulant drug treatment in hyperactive children: Prediction from EEG and neurological findings. *J Autism Child Schizophr*, *3*(1), 36-48.

Satterfield, J. H., Lesser, L. I., & Podosin, R. L. (1971). Evoked cortical potentials in hyperkinetic children. *California Medicine*, *115*(3), 48.

Sauseng, P., Griesmayr, B., Freunberger, R., & Klimesch, W. (2010). Control mechanisms in working memory: A possible function of EEG theta oscillations. *Neuroscience and Biobehavioral Reviews*, *34*(7), 1015-22.

Schafer, J. L. (1997). *Analysis of incomplete multivariate data.* Chapman & Hall/CRC.

Schaffer, C. E., Davidson, R. J., & Saron, C. (1983). Frontal and parietal electroencephalogram asymmetry in depressed and nondepressed subjects. *Biological Psychiatry*, *18*(7), 753-62.

Schoenknecht, P., Olbrich, S., Sander, C., Spindler, P., & Hegerl, U. (2010). Treatment of acute mania with modafinil monotherapy. *Biological Psychiatry.*

*S*chutter, D. (2009a). Transcraniale magnetische stimulatie en cerebrale fysiologische processen bij psychiatrische stoornissen. *Tijdschrift Voor Psychiatrie*, *51*(2), 97-105.

Schutter, D. J. (2009b). Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: A meta-analysis. *Psychological Medicine*, *39*(1), 65-75.

Schutter, D. J. (2010). Quantitative review of the efficacy of slow-frequency magnetic brain stimulation in major depressive disorder. *Psychological Medicine*, 1-7.

Schutter, D. J., Peper, J. S., Koppeschaar, H. P., Kahn, R. S., & van Honk, J. (2005). Administration of testosterone increases functional connectivity in a cortico-cortical depression circuit. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *17*(3), 372-7.

Schwartz, J., Feldstein, S., Fink, M., Shapiro, D. M., & Itil, T. M. (1971). Evidence for a characteristic EEG frequency response to thiopental. *Electroencephalography and Clinical Neurophysiology*, *31*(2), 149-53.

Segrave, R. A., Cooper, N. R., Thomson, R. H., Croft, R. J., Sheppard, D. M., & Fitzgerald, P. B. (2011). Individualized alpha activity and frontal asymmetry in major depression. *Clinical EEG and Neuroscience*, *42*(1), 45-52.

Sherlin, L., Arns, M., Lubar, J., Heinrich, H., Kerson, C., Strehl, U., & Sterman, M. B. (2011). Neurofeedback and basic learning theory: Implications for research and practice. *Journal of Neurotherapy*, *15*(4).

Sherlin, L., Arns, M., Lubar, J. F., & Sokhadze, E. (2010). A position paper on neurofeedback for the treatment of ADHD. *Journal of Neurotherapy*, *14*(2), 66-78.

Shimizu, E., Hashimoto, K., Okamura, N., Koike, K., Komatsu, N., Kumakiri, C., et al. (2003). Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. *Biological Psychiatry*, *54*(1), 70-5.

Shouse, M. N. & Lubar, J. F. (1979). Operant conditioning of EEG rhythms and ritalin in the treatment of hyperkinesis. *Biofeedback and Self-Regulation*, *4*(4), 299-312.

Siebner, H. R., Bergmann, T. O., Bestmann, S., Massimini, M., Johansen-Berg, H., Mochizuki, H., et al. (2009). Consensus paper: Combining transcranial stimulation with neuroimaging. *Brain Stimulation*, *2*(2), 58-80.

Silva, R. R., Munoz, D. M., & Alpert, M. (1996). Carbamazepine use in children and adolescents with features of attention-deficit hyperactivity disorder: A meta-analysis. *Journal of the American Academy of Child and Adolescent Psychiatry*, *35*(3), 352-8.

Simeon , J. G., Ferguson, H. B., & Fleet, J. V. W. (1986). Buproprion effects in attention deficit and conduct disorders. *Canadian Journal of Psychiatry*, *31*, 581-585.

Simon, G. E. & Perlis, R. H. (2010). Personalized medicine for depression: Can we match patients with treatments? *The American Journal of Psychiatry*, *167*(12), 1445-55.

Small, J. G., Milstein, V., & Medlock, C. E. (1997). Clinical EEG findings in mania. *Clinical EEG (Electroencephalography)*, *28*(4), 229-35.

Smit, D. J., Boersma, M., van Beijsterveldt, C. E., Posthuma, D., Boomsma, D. I., Stam, C. J., & de Geus, E. J. (2010). Endophenotypes in a dynamically connected brain. *Behavior Genetics*, *40*(2), 167-77.

Smit, D. J., Posthuma, D., Boomsma, D. I., & De Geus, E. J. (2007). The relation between frontal EEG asymmetry and the risk for anxiety and depression. *Biological Psychology*, *74*(1), 26-33.

Smit, D. J., Posthuma, D., Boomsma, D. I., & Geus, E. J. (2005). Heritability of background EEG across the power spectrum. *Psychophysiology*, *42*(6), 691-7.

Snyder, S. M. & Hall, J. R. (2006). A meta-analysis of quantitative EEG power associated with attention-deficit hyperactivity disorder. *Journal of Clinical Neurophysiology, 23*(5), 440-55.

Soileau Jr, E. J. (2008). Medications for adolescents with attention-deficit/hyperactivity disorder. *Adolescent Medicine: State of the Art Reviews*, *19*(2), 254.

Soreni, N., Crosbie, J., Ickowicz, A., & Schachar, R. (2009). Stop signal and conners' continuous performance tasks: Test--Retest reliability of two inhibition measures in ADHD children. *Journal of Attention Disorders*, *13*(2), 137-43.

Speer, A. M., Benson, B. E., Kimbrell, T. K., Wassermann, E. M., Willis, M. W., Herscovitch, P., et al. (2009). Opposite effects of high and low frequency rTMS on mood in depressed patients: Relationship to baseline cerebral activity on PET. *Journal of Affective Disorders*, *115*(3), 386-94.

Speer, A. M., Kimbrell, T. A., Wassermann, E. M., D Repella, J., Willis, M. W., Herscovitch, P., et al. (2000). Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. *Biological Psychiatry*, *48*(12), 1133-41.

Spronk, D. & Arns, M. (2009). rTMS bij depressie. *Tijdschrift Voor Neuropsychiatrie & Gedragsneurologie*, (Juli-Augustus).

Spronk, D., Arns, M., Barnett, K. J., Cooper, N. J., & Gordon, E. (2011). An investigation of EEG, genetic and cognitive markers of treatment response to antidepressant medication in patients with major depressive disorder: A pilot study. *Journal of Affective Disorders* , *128*, 41-48.

Spronk, D., Arns, M., Bootsma, A., van Ruth, R., & Fitzgerald, P. B. (2008). Long-Term effects of left frontal rTMS on EEG and erps in patients with depression. *Clinical EEG and Neuroscience*, *39*(3), 118-24.

Steriade, M., Gloor, P., Llinás, R. R., Lopes de Silva, F. H., & Mesulam, M. M. (1990). Report of IFCN committee on basic mechanisms. Basic mechanisms of cerebral rhythmic activities. *Electroencephalography and Clinical Neurophysiology*, *76*(6), 481-508.

Sterman, M. B., Howe, R. C., & Macdonald, L. R. (1970). Facilitation of spindle-burst sleep by conditioning of electroencephalographic activity while awake. *Science*, *167*(921), 1146-8.

Sterman, M. B., LoPresti, R. W., & Fairchild, M. D. (2010). Electroencephalographic and behavioral studies of monomethylhydrazine toxicity in the cat. *Journal of Neurotherapy*, *14*(4), 293-300.

Sterman, M. B., Macdonald, L. R., & Stone, R. K. (1974). Biofeedback training of the sensorimotor electroencephalogram rhythm in man: Effects on epilepsy. *Epilepsia*, *15*(3), 395-416.

Stern, J. M. & Engel, J. (2004). *Atlas of EEG patterns.* Lippincott Williams & Wilkins.

Stevens, J. R., Sachdev, K., & Milstein, V. (1968). Behavior disorders of childhood and the electroencephalogram. *Archives of Neurology*, *18*(2), 160.

Strafella, A. P., Paus, T., Barrett, J., & Dagher, A. (2001). Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *The Journal of Neuroscience, 21*(15), RC157.

Strehl, U., Leins, U., Goth, G., Klinger, C., Hinterberger, T., & Birbaumer, N. (2006). Self-Regulation of slow cortical potentials: A new treatment for children with attention-deficit/hyperactivity disorder. *Pediatrics*, *118*(5), e1530-40.

Strijkstra, A. M., Beersma, D. G., Drayer, B., Halbesma, N., & Daan, S. (2003). Subjective sleepiness correlates negatively with global alpha (8-12 Hz) and positively with central frontal theta (4-8 Hz) frequencies in the human resting awake electroencephalogram. *Neuroscience Letters*, *340*(1), 17-20.

Stubbeman, W. F., Leuchter, A. F., Cook, I. A., Shurman, B. D., Morgan, M., Gunay, I., et al. (2004). Pretreatment neurophysiologic function and ECT response in depression. *The Journal of ECT*, *20*(3), 142-4.

Suffin, S. C. & Emory, W. H. (1995). Neurometric subgroups in attentional and affective disorders and their association with pharmacotherapeutic outcome. *Clinical EEG (Electroencephalography)*, *26*(2), 76-83.

Sumich, A., Matsudaira, T., Gow, R. V., Ibrahimovic, A., Ghebremeskel, K., Crawford, M., et al. (2009). Resting state electroencephalographic correlates with red cell long-chain fatty acids, memory performance and age in adolescent boys with attention deficit hyperactivity disorder. *Neuropharmacology*, *57*(7-8), 708-714.

Swanson, J., McBurnett, K., Wigal, T., Pfiffner, L. J., Lerner, M. A., Williams, L., et al. (1993). Effect of stimulant medication on children with attention deficit disorder: A “review of reviews”. *Exceptional Children* , *60*, 154-162.

Swanson, J. M. (1985). Measures of cognitive functioning appropriate for use in pediatric psychopharmacological research studies. *Psychopharmacology Bulletin*, *21*(4), 887-90.

Swanson, J. M., Hinshaw, S. P., Arnold, L. E., Gibbons, R. D., Marcus, S., Hur, K., . . . Wigal, T. (2007). Secondary evaluations of MTA 36-month outcomes: Propensity score and growth mixture model analyses. *Journal of the American Academy of Child and Adolescent Psychiatry*, *46*(8), 1003-14.

Swartwood, J. N., Swartwood, M. O., Lubar, J. F., & Timmermann, D. L. (2003). EEG differences in adhd-combined type during baseline and cognitive tasks. *Pediatric Neurology*, *28*(3), 199-204.

Swartwood, M. O., Swartwood, J. N., Lubar, J. F., Timmermann, D. L., Zimmerman, A. W., & Muenchen, R. A. (1998). Methylphenidate effects on EEG, behavior, and performance in boys with ADHD. *Pediatric Neurology*, *18*(3), 244-50.

Szegedi, A., Rujescu, D., Tadic, A., Müller, M. J., Kohnen, R., Stassen, H. H., et al. (2005). The catechol-o-methyltransferase val108/158met polymorphism affects short-term treatment response to mirtazapine, but not to paroxetine in major depression. *The Pharmacogenomics Journal*, *5*(1), 49-53.

Tanaka, H., Hayashi, M., & Hori, T. (1996). Statistical features of hypnagogic EEG measured by a new scoring system. *Sleep(New York, NY)*, *19*(9), 731-738.

Tanaka, H., Hayashi, M., & Hori, T. (1997). Topographical characteristics and principal component structure of the hypnagogic EEG. *Sleep*, *20*(7), 523-34.

Taylor, B. P., Bruder, G. E., Stewart, J. W., McGrath, P. J., Halperin, J., Ehrlichman, H., et al. (2006). Psychomotor slowing as a predictor of fluoxetine nonresponse in depressed outpatients. *The American Journal of Psychiatry*, *163*(1), 73-8.

Teicher, M. H., Lowen, S. B., Polcari, A., Foley, M., & McGreenery, C. E. (2004). Novel strategy for the analysis of CPT data provides now insight into the effects of methylphenidate on attentional states in children with ADHD. *Journal of Child and Adolescent Psychopharmacology*, *14*(2), 219-232.

Teneback, C. C., Nahas, Z., Speer, A. M., Molloy, M., Stallings, L. E., Spicer, K. M., et al. (1999). Changes in prefrontal cortex and paralimbic activity in depression following two weeks of daily left prefrontal TMS. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *11*(4), 426-35.

Todd, R. D., Huang, H., Todorov, A. A., Neuman, R. J., Reiersen, A. M., Henderson, C. A., et al. (2008). Predictors of stability of attention-deficit/hyperactivity disorder subtypes from childhood to young adulthood. *Journal of the American Academy of Child and Adolescent Psychiatry*, *47*(1), 76-85.

Tomarken, A. J., Davidson, R. J., Wheeler, R. E., & Kinney, L. (1992). Psychometric properties of resting anterior EEG asymmetry: Temporal stability and internal consistency. *Psychophysiology*, *29*(5), 576-92.

Toplak, M. E., Connors, L., Shuster, J., Knezevic, B., & Parks, S. (2008). Review of cognitive, cognitive-behavioral, and neural-based interventions for attention-deficit/hyperactivity disorder (ADHD). *Clinical Psychology Review*, *28*(5), 801-23.

Trivedi, M. H., Rush, A. J., Wisniewski, S. R., Nierenberg, A. A., Warden, D., Ritz, L., et al. (2006). Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice. *The American Journal of Psychiatry*, *163*(1), 28-40.

Tsai, S. J., Cheng, C. Y., Yu, Y. W., Chen, T. J., & Hong, C. J. (2003). Association study of a brain-derived neurotrophic-factor genetic polymorphism and major depressive disorders, symptomatology, and antidepressant response. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics, 123B*(1), 19-22.

Tsai, S. J., Gau, Y. T., Hong, C. J., Liou, Y. J., Yu, Y. W., & Chen, T. J. (2009). Sexually dimorphic effect of catechol-o-methyltransferase val158met polymorphism on clinical response to fluoxetine in major depressive patients. *Journal of Affective Disorders*, *113*(1-2), 183-7.

Tsuda, N., Hayashi, K., Hagihira, S., & Sawa, T. (2007). Ketamine, an nmda-antagonist, increases the oscillatory frequencies of alpha-peaks on the electroencephalographic power spectrum. *Acta Anaesthesiol Scand*, *51*(4), 472-81.

Uclés, P., Almarcegui, C., Lorente, S., Romero, F., & Marco, M. (1997). Evaluation of cerebral function after carotid endarterectomy. *Journal of Clinical Neurophysiology*, *14*(3), 242.

Ulrich, G. (1994). *Psychiatrische elektroenzephalographie.* Gustav Fischer Verl.

Ulrich, G. & Frick, K. (1986). A new quantitative approach to the assessment of stages of vigilance as defined by spatiotemporal EEG patterning. *Perceptual and Motor Skills*, *62*(2), 567-76.

Ulrich, G. & Fürstenberg, U. (1999). Quantitative assessment of dynamic electroencephalogram (EEG) organization as a tool for subtyping depressive syndromes. *European Psychiatry, 14*(4), 217-29.

Ulrich, G., Haug, H. J., & Fähndrich, E. (1994). Acute vs. Chronic EEG effects in maprotiline- and in clomipramine-treated depressive inpatients and the prediction of therapeutic outcome. *Journal of Affective Disorders*, *32*(3), 213-7.

Ulrich, G., Renfordt, E., & Frick, K. (1986). The topographical distribution of alpha-activity in the resting EEG of endogenous-depressive in-patients with and without clinical response to pharmacotherapy. *Pharmacopsychiatry*, *19*, 272-273.

Ulrich, G., Renfordt, E., Zeller, G., & Frick, K. (1984). Interrelation between changes in the EEG and psychopathology under pharmacotherapy for endogenous depression. A contribution to the predictor question. *Pharmacopsychiatry*, *17*(6), 178-83.

van Beijsterveldt, C. E., & van Baal, G. C. (2002). Twin and family studies of the human electroencephalogram: A review and a meta-analysis. *Biological Psychology*, *61*(1-2), 111-38.

Van der Heijden, K. B., Smits, M. G., Van Someren, E. J., & Gunning, W. B. (2005). Idiopathic chronic sleep onset insomnia in attention-deficit/hyperactivity disorder: A circadian rhythm sleep disorder. *Chronobiology International*, *22*(3), 559-70.

Van der Heijden, K. B., Smits, M. G., Van Someren, E. J., Ridderinkhof, K. R., & Gunning, W. B. (2007). Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. *Journal of the American Academy of Child and Adolescent Psychiatry*, *46*(2), 233-41.

Van der Worp, H. B., Kraaier, V., Wieneke, G. H., & Van Huffelen, A. C. (1991). Quantitative EEG during progressive hypocarbia and hypoxia. Hyperventilation-Induced EEG changes reconsidered. *Electroencephalography and Clinical Neurophysiology*, *79*(5), 335-41.

van Dijk, H., Schoffelen, J. M., Oostenveld, R., & Jensen, O. (2008). Prestimulus oscillatory activity in the alpha band predicts visual discrimination ability. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *28*(8), 1816-23.

Vandoolaeghe, E., van Hunsel, F., Nuyten, D., & Maes, M. (1998). Auditory event related potentials in major depression: Prolonged P300 latency and increased P200 amplitude. *Journal of Affective Disorders*, *48*(2-3), 105-13.

van Luijtelaar, G., Verbraak, M., van den Bunt, M., Keijsers, G., & Arns, M. (2010). EEG findings in burnout patients. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *22*(2), 208-17.

Van Sweden, B. (1986). Disturbed vigilance in mania. *Biological Psychiatry*, *21*(3), 311-3.

Van Veen, M. M., Kooij, J. J., Boonstra, A. M., Gordijn, M. C., & Van Someren, E. J. (2010). Delayed circadian rhythm in adults with attention-deficit/hyperactivity disorder and chronic sleep-onset insomnia. *Biological Psychiatry*, *67*(11), 1091-6.

Vogel, F. (1970). The genetic basis of the normal human electroencephalogram (EEG). *Human Genetics*, *10*(2), 91-114.

Vriens, E. M., Wieneke, G. H., Van Huffelen, A. C., Visser, G. H., & Eikelboom, B. C. (2000). Increase in alpha rhythm frequency after carotid endarterectomy. *Clinical Neurophysiology*, *111*(8), 1505-13.

Walters, A. S., Silvestri, R., Zucconi, M., Chandrashekariah, R., & Konofal, E. (2008). Review of the possible relationship and hypothetical links between attention deficit hyperactivity disorder (ADHD) and the simple sleep related movement disorders, parasomnias, hypersomnias, and circadian rhythm disorders. *Journal of Clinical Sleep Medicine, 4*(6), 591-600.

Wangler, S., Gevensleben, H., Albrecht, B., Studer, P., Rothenberger, A., Moll, G. H., et al. (2011). Neurofeedback in children with ADHD: Specific event-related potential findings of a randomized controlled trial. *Clinical Neurophysiology*, *122*(5), 942-950.

Wassermann, E. M. (1998). Risk and safety of repetitive transcranial magnetic stimulation: Report and suggested guidelines from the international workshop on the safety of repetitive transcranial magnetic stimulation, june 5-7, 1996. *Electroencephalography and Clinical Neurophysiology*, *108*(1), 1-16.

Wassermann, E. M. & Lisanby, S. H. (2001). Therapeutic application of repetitive transcranial magnetic stimulation: A review. *Clinical Neurophysiology*, *112*(8), 1367-77.

Wassermann, E. M., Epstein, C. M., & Ziemann, U. (2008). *The oxford handbook of transcranial stimulation.* Oxford University Press, USA.

Wehr, T. A. (1992). Improvement of depression and triggering of mania by sleep deprivation. *JAMA : The Journal of the American Medical Association*, *267*(4), 548-51.

Weiland-Fiedler, P., Erickson, K., Waldeck, T., Luckenbaugh, D. A., Pike, D., Bonne, O., et al. (2004). Evidence for continuing neuropsychological impairments in depression. *Journal of Affective Disorders*, *82*(2), 253-8.

Wienbruch, C., Paul, I., Bauer, S., & Kivelitz, H. (2005). The influence of methylphenidate on the power spectrum of ADHD children - an MEG study. *BMC Psychiatry*, *5*, 29.

Williams, J. B. (1988). A structured interview guide for the hamilton depression rating scale. *Archives of General Psychiatry.*

*W*illiams, L. M., Hermens, D. F., Thein, T., Clark, C. R., Cooper, N. J., Clarke, S. D., et al. (2010a). Using brain-based cognitive measures to support clinical decisions in ADHD. *Pediatric Neurology*, *42*(2), 118-26.

Williams, L. M., Hermens, D. F., Thein, T., Clark, C. R., Cooper, N. J., Clarke, S. D., et al. (2010b). Using brain-based cognitive measures to support clinical decisions in ADHD. *Pediatric Neurology*, *42*(2), 118-126.

Williams, L. M., Rush, A. J., Koslow, S. H., Wisniewski, S. R., Cooper, N. J., Nemeroff, C. B., et al. (2011). International study to predict optimized treatment for depression (ispot-d), a randomized clinical trial: Rationale and protocol. *Trials*, *12*, 4.

Williams, L. M., Simms, E., Clark, C. R., Paul, R. H., Rowe, D., & Gordon, E. (2005). The test-retest reliability of a standardized neurocognitive and neurophysiological test battery: "Neuromarker". *The International Journal of Neuroscience*, *115*(12), 1605-30.

Winterer, G., Mahlberg, R., Smolka, M. N., Samochowiec, J., Ziller, M., Rommelspacher, H. P., . . . Sander, T. (2003). Association analysis of exonic variants of the GABA b-receptor gene and alpha electroencephalogram voltage in normal subjects and alcohol-dependent patients. *Behavior Genetics*, *33*(1), 7-15.

Wood, J. G., Crager, J. L., Delap, C. M., & Heiskell, K. D. (2007). Beyond methylphenidate: Nonstimulant medications for youth with ADHD. *Journal of Attention Disorders*, *11*(3), 341-50.

Wright, C. & Gunkelman, J. (1998, September 10). *QEEG evaluation doubles the rate of clinical success. Series data and case studies*. Austin, TX: *Society for the Study of Neuronal Regulation, 6th Annual Conference*.

Wundt, W. M. (1896). *Lectures on human and animal psychology.* S. Sonnenschein.

Xiong, Z., Shi, S., & Xu, H. (2005). A controlled study of the effectiveness of EEG biofeedback training on-children with attention deficit hyperactivity disorder. *Journal of Huazhong University of Science and Technology. Medical Sciences = Hua Zhong Ke Ji Da Xue Xue Bao. Yi Xue Ying De Wen Ban = Huazhong Keji Daxue Xuebao. Yixue Yingdewen Ban*, *25*(3), 368-70.

Yasuhara, A. (2010). Correlation between EEG abnormalities and symptoms of autism spectrum disorder (ASD). *Brain & Development*, *32*(10), 791-8.

Young, J. (2008). Common comorbidities seen in adolescents with attention-deficit/hyperactivity disorder. *Adolesc Med State Art Rev*, *19*(2), 216-228, vii.

Yue, L., Xiao-Lin, H., & Tao, S. (2009). The effects of chronic repetitive transcranial magnetic stimulation on glutamate and gamma-aminobutyric acid in rat brain. *Brain Research*, *1260*, 94-99.

Yukimasa, T., Yoshimura, R., Tamagawa, A., Uozumi, T., Shinkai, K., Ueda, N., et al. (2006). High-Frequency repetitive transcranial magnetic stimulation improves refractory depression by influencing catecholamine and brain-derived neurotrophic factors. *Pharmacopsychiatry*, *39*(2), 52-9.

Zahn, T. P., Abate, F., Little, B. C., & Wender, P. H. (1975). Minimal brain dysfunction, stimulant drugs, and autonomic nervous system activity. *Archives of General Psychiatry*, *32*, 381-387.

Zahodne, L. B., Okun, M. S., Foote, K. D., Fernandez, H. H., Rodriguez, R. L., Wu, S. S., et al. (2009). Greater improvement in quality of life following unilateral deep brain stimulation surgery in the globus pallidus as compared to the subthalamic nucleus. *Journal of Neurology*, *256*(8), 1321-9.

Zaidel, E. & Barnea, A. (2006). Symposium IV: Quantitative EEG and neurofeedback. *Brain and Cognition*, *60*(3), 329-330.

Zanardi, R., Magri, L., Rossini, D., Malaguti, A., Giordani, S., Lorenzi, C., et al. (2007). Role of serotonergic gene polymorphisms on response to transcranial magnetic stimulation in depression. *European Neuropsychopharmacology, 17*(10), 651-7.

Zanardini, R., Gazzoli, A., Ventriglia, M., Perez, J., Bignotti, S., Rossini, P. M., et al. (2006). Effect of repetitive transcranial magnetic stimulation on serum brain derived neurotrophic factor in drug resistant depressed patients. *Journal of Affective Disorders*, *91*(1), 83-6.

Zangen, A. & Hyodo, K. (2002). Transcranial magnetic stimulation induces increases in extracellular levels of dopamine and glutamate in the nucleus accumbens. *Neuroreport*, *13*(18), 2401-5.

Zangen, A., Roth, Y., Voller, B., & Hallett, M. (2005). Transcranial magnetic stimulation of deep brain regions: Evidence for efficacy of the h-coil. *Clinical Neurophysiology*, *116*(4), 775-9.

Zoefel, B., Huster, R. J., & Herrmann, C. S. (2010). Neurofeedback training of the upper alpha frequency band in EEG improves cognitive performance. *Neuroimage.*

*Z*ou, Y. F., Ye, D. Q., Feng, X. L., Su, H., Pan, F. M., & Liao, F. F. (2010). Meta-Analysis of BDNF val66met polymorphism association with treatment response in patients with major depressive disorder. *European Neuropsychopharmacology, 20*(8), 535-544.

Zuckerman, M. (1985). Sensation seeking, mania, and monoamines. *Neuropsychobiology*, *13*(3), 121-8.

Summary in Dutch / Samenvatting in het Nederlands

Samenvatting

De primaire doelstelling van deze thesis is om de mogelijkheden van neurofysiologische technieken zoals het EEG en ERPs te onderzoeken bij het voorspellen van behandeleffecten bij ADHD en depressie. In deze thesis zijn veelbelovende aanwijzingen gevonden voor het gebruik van deze technieken en de mogelijkheid deze toe te passen om te komen tot een gepersonaliseerde behandeling bij ADHD en depressie. Hiermee kan de behandelaffectiviteit vergroot worden. De behandelmodaliteiten die aan bod zijn gekomen in deze thesis zijn medicatie (psychostimulantia en antidepressiva), neurofeedback bij ADHD en rTMS bij de behandeling van depressie. De resultaten laten zien dat er een aantal duidelijke EEG en ERP predictoren bestaan die voorspellen dat patiënten niet zullen reageren op een behandeling, zogenaamde predictoren voor non-response. Deze lijken 'generiek' te zijn, en lijken non-response te voorspellen voor enerzijds antidepressieve behandelingen bij depressie (voor zowel antidepressiva als rTMS). Anderzijds, is er een endofenotype gevonden dat non-response voorspelt op de meeste gangbare behandelingen bij zowel antidepressieve behandelingen (antidepressiva en rTMS) als ADHD (psychostimulantia).

De belangrijkste bevindingen gerelateerd aan het voorspellen van non-respons, zijn hieronder samengevat.

Verminderde vigilantie regulatie

Verzwakte vigilantie regulatie (overmatige EEG thèta activiteit) bleek een kernprobleem bij ADHD te zijn. Op basis hiervan kunnen de symptomen van ADHD verklaard worden vanuit het EEG vigilantie model. Ook kan verklaard worden waarom psychostimulantia een klinisch effect hebben bij ADHD: Door de vigilantie stabiliserende werking van psychostimulantia. In dit geval betreft het dus een predictor voor een goede response.

Een subgroep van non-responders op verschillende antidepressieve behandelingen (antidepressiva en rTMS) lieten een vergelijkbaar patroon van verminderde vigilantie regulatie zien (hoofdstuk 10; Prichep et al., 1993; Suffin & Emory 1995; Debattista et al., 2010). Enkele onderzoeken hebben laten zien dat deze subgroep van depressieve patiënten (met overmatige thèta) goed reageren op psychostimulantia welke normaal gesproken bij ADHD worden voorgeschreven (Depressie: Suffin & Emory 1995; Debattista et al. 2010; Manische depressiviteit: Bschor et al. 2001; Schoenknecht 2010).

In deze thesis wordt beargumenteerd dat mogelijk de kern-pathofysiologie voor dit subtype van verminderde vigilantie regulatie ligt in slaapproblemen (zoals inslaapproblemen) en een vertraagde circadiane fase, wat resulteert in verminderde vigilantie regulatie overdag. Psychostimulantia lijken een effectieve behandelmodaliteit te zijn bij dit EEG subtype bij zowel ADHD als depressie. Echter, dit effect wordt bereikt door het verhogen van de vigilantie overdag, hetgeen resulteert in 'symptoom onderdrukking,' maar grijpt niet in op de veronderstelde kern-pathofysiologie, namelijk de slaapproblemen en circadiane fase. Toekomstige onderzoeken zullen daarom moeten uitwijzen of behandelingen die zich richten op het verbeteren van inslaapproblemen en de circadiane fase, inderdaad tot een klinische verbetering van de ADHD en depressie klachten leiden zoals reeds gedemonstreerd door melatonine bij ADHD (Hoebert et al., 2009) of SMR neurofeedback bij slaap (Cortoos et

al., 2010; Hoedlmoser et al., 2008; Sterman et al., 1970). Zulke behandelmethoden zouden zich met name moeten richten op het vinden van behandelingen met een gunstiger lange termijn-effect gezien de effecten van psychostimulantia en melatonine beperkt zijn op de lange-termijn.

Individuele alfa piek frequentie (iAPF)

Een eigenschap van het EEG die vaak over het hoofd wordt gezien, is de aanwezigheid van een vertraagde iAPF. Deze maat is een solide predictor gebleken voor het niet-reageren op verschillende behandelingen zoals psychostimulantia bij ADHD (hoofdstuk 2), rTMS bij depressie (hoofdstuk 9 en 10 en Conca et al. (2000)) evenals antidepressiva (Ulrich et al., 1984). Een vertraagde iAPF is duidelijke geassocieerd met een verlaagde cerebrale doorbloeding. Methoden zoals carotide endarterectomie (Uclés et al., 1997; Vriens et al., 2000) en hyperbare zuurstof therapie (Murata et al., 2005) hebben laten zien te resulteren in een snellere iAPF. Beide procedures verhogen ook de beschikbare zuurstof in de hersenen en/of doorbloeding. Gezien de hoge mate van erfelijkheid van de iAPF (van Beijsterveldt & van Baal, 2002), de stabiliteit van deze maat over tijd (Kondacs & Szabó, 1999), de duidelijke relatie met cerebrale doorbloeding en het substantiële voorkomen ervan bij ADHD en depressie, stellen we voor dat deze maat als een endofenotype gezien kan worden, geassocieerd met non-respons op conventionele behandelingen bij ADHD en depressie. Toekomstig onderzoek moet zich richten op de vraag welke behandelingen wel een klinisch effect zullen hebben in deze substantiële subgroep, en of dit endofenotype geschikt is om patiënten op voorhand te selecteren en hen huidige beschikbare behandelingen te ontraden. Mogelijk kan dit endofenotype nieuw onderzoek stimuleren naar een biomarker-gebaseerde behandeling.

Discussie

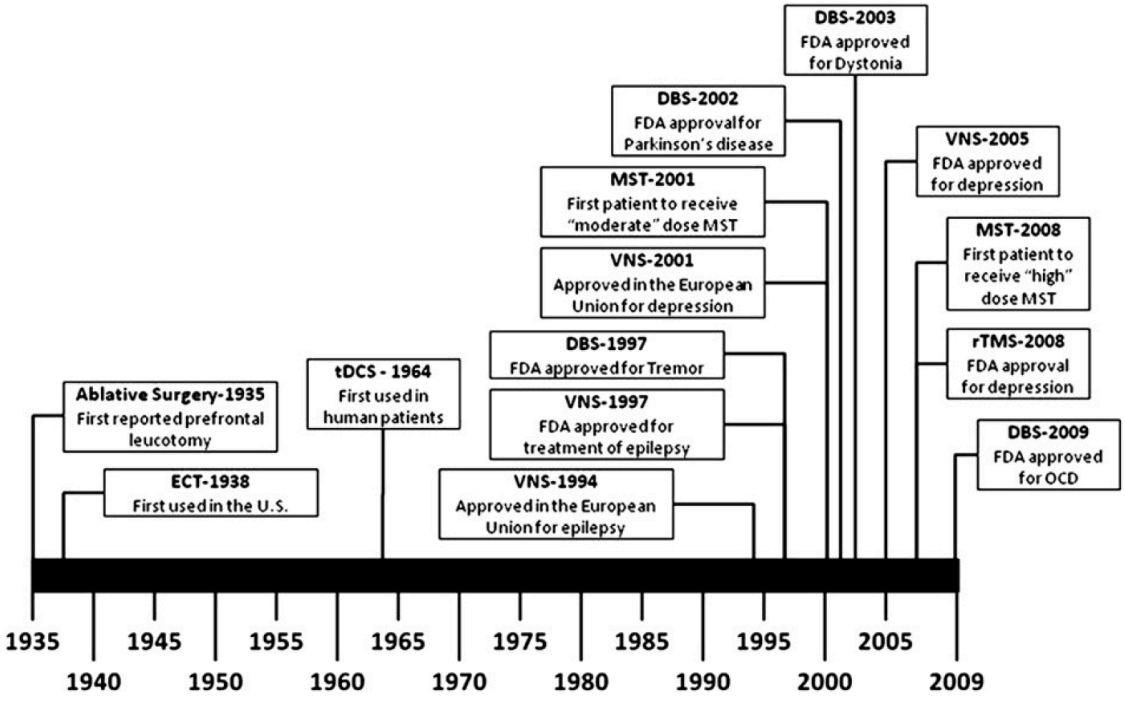
Het landschap in de psychiatrie ondergaat de laatste tijd aanzienlijke veranderingen. Enkele grootschalige onderzoeken hebben recentelijk laten zien dat de conventionele behandelingen bij ADHD en depressie *op groeps-niveau* beperkingen hebben. Duidelijke voorbeelden hiervan zijn de beperkte effectiviteit van antidepressiva en cognitieve gedragstherapie bij depressie (STAR*D: Rush et al., 2006), een overschatting van de klinische effecten van cognitieve gedragstherapie bij depressie het gevolg van een publicatie-bias (Cuijpers, 2010) en beperkte lange termijn effecten van psychostimulantia, gedragstherapie en een combinatie van beiden bij ADHD (NIMH-MTA onderzoek: Molina et al., 2009). Een aantal grote farmaceutische bedrijven waaronder GlaxoSmithKline (GSK) en AstraZeneca hebben recentelijk tevens aangekondigd om de stekker uit de ontwikkelingen van verschillende psychiatrische geneesmiddelen te trekken of zoals Miller in Science aangeeft: *'…pull the plug on drug discovery in some areas of neuroscience….'* (Miller, 2010). Dit is een zorgelijke ontwikkeling, gezien er nog zoveel te verbeteren valt in de behandeling van ADHD en depressie. Vandaar dat het belangrijk is om niet langer meer naar de effectiviteit op groepsniveau te kijken, maar te concentreren op het identificeren van de meest effectieve behandeling voor een individuele patiënt (Simon & Perlis, 2010) ofwel het personaliseren van behandeling. Bij een gepersonaliseerde behandeling (ook wel Personalized Medicine genoemd) is het doel om de juiste behandeling, voor de juiste persoon, op het juiste moment voor te schrijven. Dit in tegenstelling tot de huidige 'trial-and-error' aanpak. Hierbij spelen biomarkers of endofenotypen een belangrijke rol.

Tevens is recentelijk ook sprake van een verschuiving in het behandelaanbod van psychiatrische aandoeningen van een 'systemische behandelaanpak' (dat wil zeggen systemisch toepassen van medicatie, waardoor een stof in het gehele lichaam verhoogd wordt) naar een meer 'lokale behandelaanpak'. Deze nieuwe ontwikkelingen worden ook wel onder de noemer 'Neuromodulatie' geschaard. In het vakgebied van de neuromodulatie zijn er momenteel veel nieuwe ontwikkelingen gaande zoals de toepassing van diepe-hersenstimulatie bij depressie (Hamani et al., 2011.), parkinsonisme (Zahodne et al., 2009.), intracraniële stimulering van de primaire en secundaire auditieve schors bij tinnitus (De Ridder et al., 2006.), rTMS bij depressie (Schutter 2010, Schutter 2009a), fMRI neurofeedback bij pijn (deCharms et al., 2005.), neurofeedback bij ADHD (Arns, de Ridder, Strehl, Breteler & Coenen, 2009), Nervus Vagus Stimulatie (VNS) bij depressie (Daban, Martinez-Aran, Cruz & Vieta, 2008) enz.

In figuur 1 is een overzicht van bereikte mijlpalen voor een aantal niet-farmacologische neuromodulatie toepassingen terug te vinden, zoals toelatingen tot de markt, FDA approval en introductie van nieuwe technieken (ontleend aan: Moreines, McClintock & Holtzheimer, 2011). Verder laat deze figuur goed de toename van bereikte mijlpalen in de laatste 10-15 jaar zien.

Parallel aan de ontwikkeling van deze nieuwe technieken is het interessant op te merken dat de toepassing van sommige van deze neuromodulatie technieken niet langer meer afhangen van enkel een DSM-IV diagnose. Ze richten zich meer op het identificeren van disfunctionele neurale netwerken, waarbij de neuromodulatie zich richt op het ingrijpen en normaliseren van deze neurale netwerken. Voorbeelden hiervan zijn: diepe hersenstimulatie specifiek

gericht voor het moduleren van de hersenactiviteit in de subcallosal cingulate gyrus (Hamani et al., 2011), fMRI neurofeedback specifiek gericht op het leren reguleren van activiteit in de rostral anterior cingulate bij pijn-patiënten (deCharms et al., 2005) en de mogelijkheid van het personaliseren van de neurofeedback behandeling bij ADHD op basis van het individuele QEEG zoals beschreven in hoofdstuk 6.



Figuur 1: Een historisch overzicht van bereikte mijlpalen voor diverse neuromodulatie technieken. Het aantal bereikte mijlpalen is in de afgelopen 10-15 jaar enorm toegenomen. Ontleend van: Moreines, McClintock & Holtzheimer (2011).

Zoals betoogt in de inleiding van dit proefschrift is een focus op biomarkers en endofenotypen die een voorspellende waarde hebben voor behandeleffecten, cruciaal bij het verbeteren van de behandelingen bij ADHD en depressie, teneinde tot een doelmatigere behandeling te komen. In dat opzicht is de ontwikkeling van personalized medicine dus een cruciale ontwikkeling in de psychiatrie. Het voornaamste doel van dit proefschrift is om te onderzoeken of het mogelijk is om gebruikmakend van neurofysiologische technieken, zoals het EEG en ERPs, te kunnen voorspellen wie wel en wie niet op een specifieke behandeling zal gaan reageren. Hierbij is de focus gelegd op voorspellers voor een niet-succesvolle behandeling.

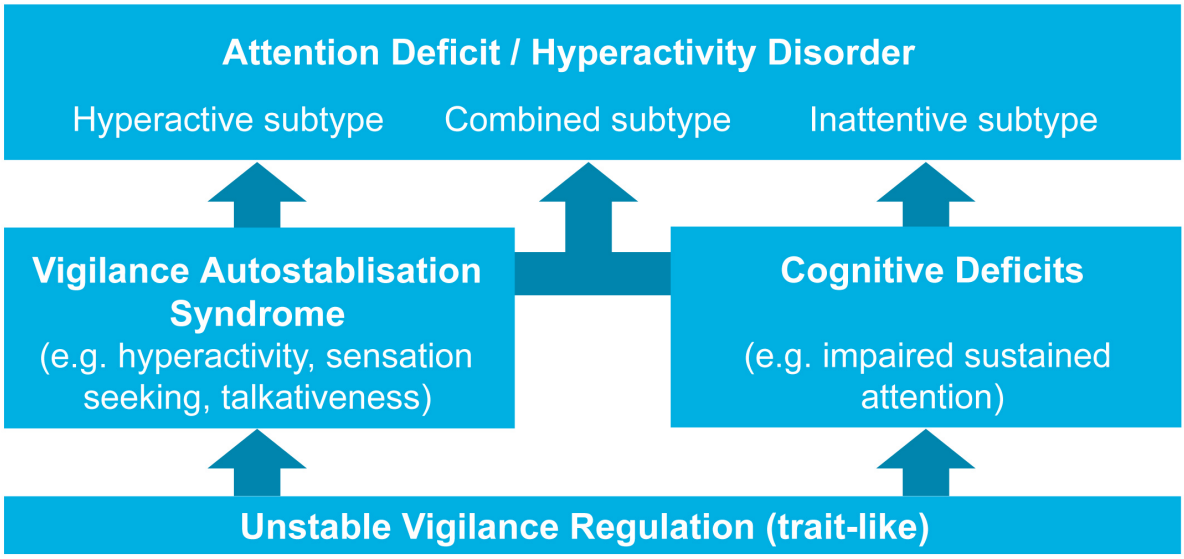
In het hiernavolgende zullen we een overzicht van de belangrijkste bevindingen en conclusies van de verschillende studies in dit proefschrift bespreken en bediscussiëren, alsmede het bespreken van de implicaties van deze bevindingen voor de toekomst van gepersonaliseerde geneeskunde ofwel personalized medicine.

ADHD

Op basis van de voorgaande hoofdstukken zijn een aantal neurofysiologische subgroepen van ADHD naar voren gekomen met relevantie voor behandelsucces. Hieronder worden deze subgroepen in meer detail behandeld en ingebed in een meer theoretisch kader, alsmede aanbevelingen voor toekomstig onderzoek en de implicaties voor de behandeling.

Verminderde regulatie van de waakzaamheid ('vigilantie regulatie')

De belangrijkste bevinding uit de ADHD onderzoeken is dat een specifieke subgroep van de ADHD-patiënten gekenmerkt wordt door een verlaagde waakzaamheid of alertheid en een verminderde regulatie van de waakzaamheid. In het hiernavolgende wordt in dit verband gesproken over 'vigilantie' wat vergelijkbaar is met waakzaamheid of alertheid. Deze groep reageert goed op psychostimulantia, wat te begrijpen is door het feit dat dit type medicatie tot een stabilisering en versterking van de vigilantie leidt. In hoofdstuk 2 werd gerapporteerd dat kinderen met ADHD die gekenmerkt worden door frontale alfa en frontale thèta EEG activiteit – wat een weerspiegeling is van een verlaagd vigilantie niveau - goed reageerden op psychostimulantia. Bovendien konden we dit in hoofdstuk 3 verder bevestigen op basis van het 'EEG Vigilantie model' dat ADHD-patiënten worden gekenmerkt door een lagere vigilantie en een meer onstabiele vigilantie regulatie. Er was ook een tendens die liet zien dat ADHD-patiënten met verlaagde EEG vigilantie voor behandeling de slechtste scores lieten zien op een CPT taak, een reflectie van onoplettendheid en impulsiviteit, en dat deze patiënten beter leken te reageren op psychostimulantia. Deze bevindingen zijn in lijn met het EEG vigilantie model, oorspronkelijk ontwikkeld door Bente (1964) en recent verder ontwikkeld door Hegerl (2010) en bieden op die manier ook een adequate verklaring voor de ADHD-symptomen en subtypen. Zoals te zien is in figuur 2, ligt een onstabiele en verlaagde vigilantie regulatie aan de basis van de cognitieve problemen die kenmerkend zijn voor ADHD en ADD, zoals een verminderde volgehouden aandacht. Bovendien is er sprake van vigilantie autostabilisatie gedrag waaruit de hyperactiviteit bij ADHD verklaard kan worden als compensatoir gedrag om de vigilantie omhoog te reguleren.



Figuur 2: Deze figuur geeft een overzicht van de relatie tussen een onstabiele vigilantie regulatie en de verschillende gedragssymptomen van ADHD (ontleend aan Hegerl et al. 2009.).

Het EEG vigilantie model is meer gericht op het onderzoeken van de temporele dynamiek van het EEG in plaats van het analyseren van het EEG door een gemiddelde *over* tijd te maken. De verschillende vigilantie stadia zijn allen een indicatie van hetzelfde onderliggende proces namelijk vigilantie ofwel waakzaamheid. Derhalve zijn verschillen in alleen de alfa of thèta band niet informatief in het beschrijven van de relatie met gedrag of psychiatrische aandoening. Het EEG vigilantie model verklaart de relatie tussen EEG verschijnselen en gedrag middels vigilantie regulatie. Een interessante implicatie van dit model is dat de relatie tussen gedrag en EEG niet als een lineair verband verklaard kan worden, daarmee ook verklarend waarom we in hoofdstuk 4 geen (lineaire) correlaties konden vinden tussen de verschillende EEG maten en neuropsychologische prestaties. Het volgende voorbeeld illustreert dit verder.

Na een vermoeiende dag zal de EEG vigilantie regulatie van een gezond persoon steeds instabieler worden en meer van de lagere vigilantie stadia laten zien, beter bekend als ‘vermoeidheid’ of ‘slaperigheid’. Dit proces heeft ook een duidelijke signatuur zichtbaar in het EEG zoals een toename van frontale alfa (Broughton & Hasan, 1995;. Connemann et al., 2005;. De Gennaro et al., 2001; De Gennaro et al. , 2004; De Gennaro et al., 2005;. Pivik & Harman, 1995) en een toename in frontale trage golven, zoals thèta (Strijkstra et al., 2003;. Tanaka et al., 1996; Tanaka et al., 1997). In het EEG vigilantie model worden deze stadia respectievelijk aangeduid als stadium A2-A3 en B2-B, waarbij de B stadia lagere vigilantie niveau’s zijn dan de A stadia. Bij jonge kinderen zien we vaak het hyperactieve, levendige gedrag als kinderen oververmoeid worden. Dit is een duidelijk voorbeeld van vigilantie autostablisatie gedrag (dat wil zeggen: het zichzelf wakker houden). Bij een gezonde volwassene die dit type EEG laat zien – er vanuit gaande dat deze thuis op de bank zit en het bijna bedtijd is – zal zich slaperig voelen en besluiten naar bed te gaan (dat wil zeggen: de volwassene besluit om zich 'terug te trekken' en te zoeken naar een omgeving met weinig externe stimulatie om daarmee de kans te verhogen om in slaap te vallen).

Echter, wanneer diezelfde gezonde volwassene deze hersenactiviteit laat zien als hij aan het autorijden is, dus eigenlijk versuft is, dan zal hij: …het volume van de muziek harder zetten ... het raam openen ... de airconditioning kouder zetten ... het raam weer dichtdoen... en ga zo maar door. Deze gezonde volwassene laat op dat moment dus ook vigilantie autostabilisatie gedrag zien om daarmee zichzelf wakker te houden Bovendien, als de auto vóór hem onverwacht gaat remmen, zal hij hoogstwaarschijnlijk trager reageren (verminderde volgehouden aandacht) met een grotere kans te resulteren in een auto-ongeluk als gevolg van een lagere vigilantie ofwel vermoeidheid (Miller, 1995). Dit voorbeeld toont aan dat dezelfde EEG toestand – afhankelijk van de omgeving – kan resulteren in volkomen ander gedrag (slaap vs. 'hyperactief' gedrag), hetgeen verklaart waarom de relatie tussen EEG en gedrag geen lineaire relatie is, maar eerder een 'binaire relatie.' Daarnaast, zoals hierboven aangeduid, verschaffen veranderingen in alfa en thèta weinig informatie aangezien beiden een afspiegeling zijn van hetzelfde proces – namelijk vigilantie.

Voor toekomstig onderzoek dat de relatie tussen rust EEG en cognitie onderzoeken is het daarom aan te raden een algemene EEG vigilantie maat toe te passen in plaats van de gemiddelde spectrale inhoud van het EEG tijdens een taak te onderzoeken. Zo willen we in een toekomstig onderzoek de EEG vigilantie bij patiënten met ADHD onderzoeken tijdens een CPT taak en onderzoeken of het optreden van een lagere vigilantie stadium voorafgaand aan een stimulus die een reactie vereist, vaker resulteert in het uitblijven van een reactie wat een maat voor onoplettendheid is (false negative errors). Verschillende onderzoeken hebben de relatie tussen alfa en thèta EEG activiteit en cognitieve processen reeds onderzocht en laten zien dat *tijdens* een taak een toename van alfa is gerelateerd aan geheugencapaciteit (Jensen & Mazaheri, 2010; Jensen et al., 2002) en een toename van thèta aan het korte termijngeheugen (Klimesch, 1996; Osipova et al., 2006). Deze onderzoeken laten dus taak-geïnduceerde synchronisatie in de thèta en alfa band zien, die verband houdt met verbeterde cognitieve functies. Echter, onderzoeken die het pre-stimulus EEG onderzochten hebben laten zien dat een toename van pre-stimulus alfa geassocieerd is met een afname in visuele discriminatie (van Dijk et al., 2008), met impulsiviteitsfouten tijdens een Go-NoGo taak (Mazaheri et al., 2009) en een verzwakte aandacht (O'Connell et al., 2009). Laatstgenoemde studie vond dat alfa al tot 20 seconden voorafgaande aan een gemist doel begon toe te nemen (O'Connell et al., 2009). Romani et al (1988) lieten zien dat er een verband is tussen vigilantie, geclassificeerd middels het EEG, en de amplitude en latentietijd van ERPs. Zij vonden dat een verlaagde vigilantie voordat de stimulus gepresenteerd werd, geassocieerd was met een vertraagde N100 latentietijd. Zij vonden ook dat proefpersonen met een meer onstabiele vigilantie (grotere fluctuaties) gekarakteriseerd waren door langzamere N100 latentietijden en verlaagde N100 amplituden tijdens 'minder vigilante' stadia (Romani et al., 1988). Deze resultaten suggereren dat EEG vigilantie stadia inderdaad momenten van onoplettendheid kunnen verklaren (in tegenstelling tot de interpretatie van Van Dijk et al. (2008)). Echter, al deze onderzoeken zijn uitgevoerd met gezonde vrijwilligers en allen onderzochten de gemiddelde EEG power in een specifieke frequentie band, terwijl, zoals hierboven reeds uitgelegd, men beter EEG vigilantie stadia van afnemende vigilantie kan onderzoeken in relatie tot momenten van onoplettendheid, waar frontale alfa en thèta een continuüm vormen.

Slaapproblemen als de kern-pathofysiologie van de verlaagde vigilante subgroep bij ADHD

De verminderde EEG vigilantie zoals beschreven in bovenstaand voorbeeld kan voortkomen uit vermoeidheid door het 's avonds laat besturen van een auto, maar het kan ook worden veroorzaakt door slaapgebrek of aandoeningen van de alertheidsregulatie. Zoals uitgelegd in (Hegerl et al., 2010): '*slaapstoornissen of andere factoren die een onstabiele vigilantie induceren veroorzaken een autoregulatie gedragssyndroom met hyperactiviteit, spanningsbehoefte en afleidbaarheid. Dit gedragssyndroom helpt de vigilantie te stabiliseren door het creëren van een zeer stimulerende omgeving. In kwetsbare individuen domineert het auto-regulatie mechanisme de fysiologische neiging te gaan slapen, verergert het slaapprobleem en de vigilante onstabiliteit en begint hierdoor een vicieuze cirkel.*'

Bij ADHD worden klachten als slaperigheid, verkorte slaaplatentie (Golan et al., 2004), primaire slaapstoornissen, slaap-gerelateerde bewegingsstoornissen, parasomnieën (Chervin et al., 2002; Konofal et al., 2010; Walters et al., 2008) vaak gerapporteerd en op ADHD gelijkend gedrag kan bij kinderen worden opgewekt door slaaptekort (Fallone et al., 2001; Golan et al., 2004). Dit op ADHD lijkend gedrag verbetert door het normaliseren van slaapstoornissen (Dahl et al., 1991). Recentelijk raporteerde Van Veen et al. (2010) in een onderzoek bij volwassen met ADHD dat 78% last had van inslaapproblemen, bevestigd door actigrafie en in verband gebracht met een vertraagde nachtelijke melatonine-afgifte. Een gelijksoortige percentage van 73% inslaapproblemen werd gerapporteerd bij kinderen met ADHD (Van der Heijden et al., 2005). Deze data suggereert dat in ieder geval een substantiële subgroep van patiënten met ADHD wordt gekenmerkt door een vertraagde endogene circadiane fase geassocieerd met inslaapproblemen (Van Veen et al., 2010). Verscheidene studies hebben de effecten van melatonine als een hulpmiddel om deze circadiane fase te verschuiven onderzocht en de meeste hebben duidelijke verbeteringen van inslaapproblemen gemeld (Hoebert et al., 2009; Van der Heijden et al., 2007); na vier weken was er echter nog geen verbeteringen van de ADHD-symptomen en cognitie opgetreden (Van der Heijden et al., 2007). Na deze behandeling op lange termijn voort te zetten werd er wel vooruitgang geboekt op het gebied van gedrag en stemming, met name bij de kinderen die nog steeds melatonine gebruikten. Het staken van de melatonine leidde meestal tot een terugval van inslaapproblemen (Hoebert et al., 2009). Dit impliceert dat in deze subgroep normalisatie van inslaapproblemen bereikt kan worden door bijvoorbeeld melatonine te gebruiken; zij het met een vertraagd effect op ADHD symptomen. De effecten van psychostimulantia op slaapparameters laten een discrepantie zien tussen objectieve en subjectieve maten, behalve voor een de tijd tot inslapen en een langere duur tot de eerste REM cyclus (Cohen-Zion & Ancoli-Israel, 2004; Corkum et al., 1998). Deze resultaten wijzen er tenminste op dat psychostimulantia de slaap niet verbeteren bij ADHD. Vandaar moet de werkzaamheid van psychostimulantia gezocht worden in de vigilantie stabiliserende eigenschappen overdag.

Hoofstukken 5 en 6 hebben laten zien dat neurofeedback behandeling bij ADHD goed onderzocht is en dat deze behandeling veelbelovende resultaten bij de behandeling van ADHD laat zien. Het is niet geheel duidelijk wat het werkingsmechanisme van deze behandeling is, maar de huidige opvatting is dat neurofeedback een proces is waarbij gebruik wordt gemaakt van operante conditionering van hersenactiviteit, zoals het EEG

(Sherlin et al., 2011). De meest gebruikte protocollen bij de behandeling van ADHD zijn Thèta/Bèta neurofeedback en SMR neurofeedback en, zoals vermeld in hoofdstuk 5, werden er geen differentiële effecten van deze beide protocollen gevonden op groepsniveau. Hoofdstuk 6 liet echter zien dat de selectie van een deze protocollen gebaseerd op het EEG voorafgaande aan de behandeling, tot betere resultaten leidde, met name voor onoplettendheid.

Verscheidene studies hebben aangetoond dat SMR neurofeedback resulteert in een toename van slaapspoeltjes tijdens slaap die vaak in verband zijn gebracht met een betere slaap (Hoedlmoser et al., 2008; Sterman et al., 1970). Verder leidt SMR neurofeedback ook direct tot een verbetering van slaap, zoals insomnia patiënten die langer slapen of het sneller in slaap vallen (Cortoos et al., 2010; Hoedlmoser et al., 2008). Dit suggereert dat dit type neurofeedback mogelijk de specifieke kernpathofysiologie van ADHD beïnvloedt, zoals hierboven uitgelegd, namelijk de inslaapproblemen, resulterend in vigilante stabilisatie (zie ook figuur 2). Uiteindelijk resulteert dit ook in een verbetering van de onoplettendheid en hyperactiviteit/impulsiviteit bij ADHD. Interessant in dit perspectief is dat we in hoofdstuk 6 zagen dat een subgroep die was behandeld met SMR neurofeedback duidelijke neurofysiologische verbeteringen lieten zien na neurofeedback behandeling (zoals een toename van de N200 en P300 amplitude tijdens de oddball ERP) vergezeld van een duidelijke klinische verbetering van ADHD symptomen. Deze verbeteringen zijn hoogstwaarschijnlijk het directe effect van neurofeedback, maar dit kan niet bevestigd worden door het ontbreken van een controle groep. In deze hoedanigheid is het interessant om op te merken dat bij alle patiënten een duidelijke verbetering optrad van de slaapkwaliteit zoals gemeten met de Pittsburgh Sleep Quality Inventory (PSQI; unpublished observation). Dit is in overeenstemming met deze hypothese.

Het thèta/bèta neurofeedback protocol richt zich op het reduceren van fronto-centrale thèta en een toename van bèta activiteit. In termen van het vigilantiemodel kan men veronderstellen dat patiënten door deze behandeling leren hun vigilantie te stabiliseren door het verminderen van de lagere vigilantie stadia (gekenmerkt door thèta) en het toenemen van bèta activiteit, karakteristiek voor een actieve wakkere toestand. Verder onderzoek zal moeten aantonen wat het exacte werkingsmechanisme is van deze thèta/bèta neurofeedback.

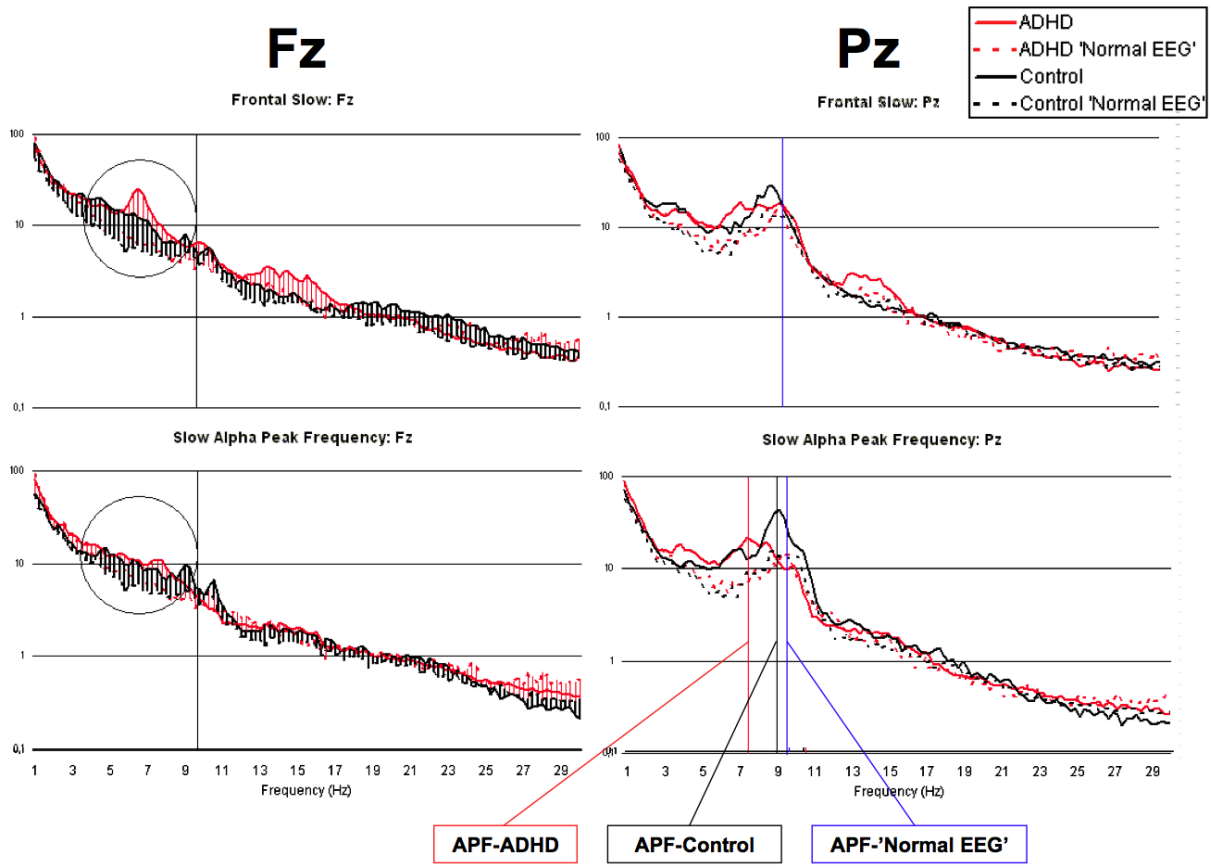
Samenvattend: er lijkt sprake van een subgroep van ADHD patiënten die een verminderde vigilantie regulatie hebben, welke hoogstwaarschijnlijk veroorzaakt worden door inslaapproblemen. Op basis van hoofdstuk 1, waarbij de ‘frontal slow’ (B2-3), ‘frontal alpha’ (A3) en ‘low voltage EEG’ (B1) als staten van lagere EEG vigilantie beschouwd kunnen worden, kan de prevalentie geschat worden op 55%. Gebaseerd op de hierboven besproken studies naar inslaapproblemen kan de prevalentie geschat worden op 75% (Van der Heijden et al., 2007; Van Veen et al., 2010). De inslaapproblemen bij ADHD zijn gerelateerd aan een vertraagde circadiane ritmiek (Van Veen et al., 2010). Het normaliseren van deze circadiane regulatie wordt verondersteld tot een verbetering van de vigilantie regulatie te leiden daarbij zijn effect uitoefenend op de ADHD symptomen. Deze patiënten reageren goed op psychostimulantia vanwege de vigilantie stabiliserende eigenschappen. Echter, in deze zienswijze moeten de effecten van psychostimulantia gezien worden al een symptoom-onderdrukking die geen direct effect hebben op de onderliggende pathofysiologie van

ADHD, maar slechts de vigilantie overdag verhoogt. De effecten van melatonine lijken een directere invloed te hebben op de door ons veronderstelde kern-pathofysiologie, zij het met een vertragend effect op de ADHD klachten. Op basis van dit vertragende effect van melatonine op de ADHD klachten is het een interessante gedachte die verder onderzoek verdient: Misschien zijn voor neurofeedback veel minder behandelsessies nodig, en kan de behandeling stoppen als de slaap genormaliseerd is. Deze effecten van melatonine verdwijnen echter wanneer deze wordt stopgezet. Toekomstig onderzoek zou zich dus moeten richten op hoe deze ADHD subgroep betrouwbaarder kan worden geïdentificeerd middels een EEG, polysomnografie of misschien gebruik makend van slaapparameters zoals de 'dim light melatonin onset' of DLMO maat zoals gebruikt in verschillende studies (Hoebert et al., 2009; Van der Heijden et al., 2007; Van Veen et al., 2010). Toekomstige studies zouden tevens moeten onderzoeken hoe deze slaapproblemen effectiever behandeld kunnen worden met blijvende effecten zoals bijvoorbeeld intens licht, slaaphygiëne of SMR neurofeedback.

De 'vertraagde individuele alfa piek frequentie' (iAPF) subgroep.

De meest consistente bevinding die in de meeste in deze thesis vermeldde studies naar voren is gekomen, is de aanwezigheid van de vertraagde individuele alfa piek frequentie (iAPF) subgroep bij zowel ADHD als depressie. Zoals reeds vermeld in hoofdstuk 1 is deze maat vaak gerapporteerd in de oudere EEG literatuur. Echter, deze maat is door de meeste QEEG onderzoekers niet onderzocht, waarschijnlijk vanwege de moeilijkheid om deze op een betrouwbare manier geautomatiseerd te berekenen. Eén van de bevindingen was dat ADHD patiënten met een vertraagde iAPF – in tegenstelling tot patiënten met een frontale thèta – niet goed reageren op psychostimulantia, terwijl ze op de voormeting wel degelijk de slechtste resultaten op een CPT test (onoplettendheid en impulsiviteit fouten) laten zien. Dit illustreert verder het belang van het identificeren van deze twee subgroepen (frontale thèta of een vertraagde iAPF).

In figuur 3 (overgenomen uit hoofdstuk 1 en 3) wordt dit in meer detail geïllustreerd. Deze figuur laat de spectrale EEG inhoud zien van kinderen met ADHD (rood) en van een controlegroep (zwart) voor zowel frontale (Fz) als pariëtale (Pz) locaties. De stippellijnen laten de spectraal inhoud van de groepen met een 'normaal EEG' zien en de doorgetrokken lijnen laten de spectraal inhoud zien van de subgroepen met een 'frontale thèta' (boven) of een 'vertraagde alfa piek frequentie' (onder). Zoals duidelijk te zien, is de spectraal inhoud voor de frontale thèta groep toegenomen in de thèta frequentie band, met name op Fz, zoals verwacht kon worden. De ADHD groep met de vertraagde iAPF op Pz laat een gemiddelde APF van 7.5 Hz. In de frontale locaties (linksonder) is dit ook terug te zien als een 'verhoogde thèta'. Echter dit is het gevolg van de vertraagde APF en is dus alfa, en moet dus niet als thèta gezien worden.



Figuur 3: *Deze figuur laat zien dat de subgroep met een vertraagde alfa piek frequentie (onder), op pariëtale locaties, tevens een verhoogde thèta EEG power op de frontale kanten laat zien. Dit is echter geen echte 'frontale thèta' maar simpelweg het effect van de vertraagde alfa piek frequentie. Dit geeft aan dat een verhoogde thèta/bèta ratio tenminste ook de trage APF subgroep omvat, welke neurofysiologisch gezien een andere groep is, zoals duidelijk is geworden met de effecten van psychostimulantie bij ADHD, waarbij de frontale thèta groep wel en de vertraagde APF groep niet reageerde op deze behandeling. Zie voor verdere details hoofdstuk 1.*

In hoofdstuk 4 hebben we verder laten zien middels een kwantitatieve aanpak dat de vaak gerapporteerde toename in de thèta/bèta ratio bij ADHD dus een combinatie is van de frontale thèta groep (geïnterpreteerd als de verminderde vigilantie regulatie subgroep,' zie boven) en de trage iAPF subgroep. Dit verklaart waarom de thèta/bèta ratio en de 'verhoogde thèta' groep een goed onderscheid kunnen maken tussen kinderen met een DSM-IV diagnose ADHD en een gezonde controlegroep (Boutros et al., 2005; Monastra et al., 1999; Snyder & Hall, 2006). Echter, dit is geen specifieke maat, aangezien het bestaat uit verschillende neurofysiologische subtypes. Vanuit het perspectief van gepersonaliseerde behandeling is dit niet optimaal, aangezien deze subtypes verschillend reageren op medicatie en hypothetisch gezien een andere onderliggende pathofysiologie hebben.

Dit helpt ook de tegenstrijdige bevindingen te verklaren zoals de bevindingen van Chabot et al. (1999; 2001), die vonden dat hun verhoogde thèta groep (omschreven als *'gegeneraliseerde toename van de absolute en relatieve thèta, verlaagde gemiddelde alfa frequentie, en hypercoherente frontale thèta')* een slechtere response op psychostimulantia lieten zien, suggererend dat ze patiënten met een lagere iAPF meerekenden, versus Clarke

et al. (2002a; 2002b) en Suffin en Emory (1995), die vonden dat responders op psycho-stimulantia een verhoogde thèta en een verhoogde thèta/bèta ratios lieten zien.

In hoofdstuk 6 zagen we dat er geen verband was tussen een trage iAPF en het effect van neurofeedback bij ADHD op onoplettendheid en impulsiviteit/hyperactiviteit. In dit onderzoek is waarschijnlijk de prevalentie van een vertraagde iAPF te laag geweest (iAPF < 8 Hz: N=1 voor pariëtale iAPF en N=6 voor frontale iAPF van totaal N=19) om een duidelijk verband tussen een trage iAPF en behandelresultaat op ADHD waarderingsschalen te vinden. Daarom is de conclusie dat neurofeedback een effectieve behandeling is voor patiënten met een trage iAPF, die niet reageren op psychostimulantia momenteel niet gerechtvaardigd. Verder onderzoek met grotere steekproeven zijn hiervoor vereist.

Verdere implicaties voor behandeling van dit subtype zullen worden besproken in het volgende gedeelte over depressie, aangezien dit subtype een non-specifieke predictor voor non-response op verschillende behandelingen is.

Overmatige bèta subgroep

Naast de twee hierboven beschreven subgroepen is er nog een derde subgroep die gekarakteriseerd wordt door overmatige bèta activiteit of bèta spindels bij ADHD. Het voorkomen van deze groep varieert van 13 tot 20% (Chabot & Serfontein, 1996; Clarke et al., 1998; 2001b), wat we ook terug vonden in hoofdstuk 2 en 6. Verschillende onderzoeken hebben laten zien dat deze patiënten goed reageren op psychostimulantia (Chabot et al., 1999; Clarke et al., 2003b; Hermens et al., 2005). Er is relatief weinig duidelijk over zowel deze overmatige bèta groep en bèta spindels. Ze worden over het algemeen beschouwd als een medicatie-effect na gebruik van benzodiazepines (Blume, 2006) of barbituraten (Schwartz et al., 1971). Clarke et al. (2001c) lieten verder zien dat deze ADHD subgroep gekenmerkt wordt door woedeaanvallen en humeurig gedrag. Barry et al. (2009) meldden dat de ERP's van deze subgroep substantieel verschilden van ADHD kinderen zonder overmatige bèta, daarmee suggererend dat verschillende disfunctionele netwerken de klachten verklaren. Interessant genoeg leken de ERP's van de overmatige bèta sub-groep normaler dan die van de ADHD subgroep zonder overmatige bèta.

Oorspronkelijk onderscheidden Gibbs en Gibbs (1950) twee vormen van overwegend snelle EEG activiteit: een milde toename in bèta, welke zij 'F1' noemden en een overmatige toegenomen bèta, welke zij 'F2' noemden. Het F1 type werd tot de jaren veertig van de vorige eeuw als 'abnormaal' beschouwd, waarna Gibbs en Gibbs alleen het F2 type nog als zodanig beschouwden. Echter, EEG specialisten hebben inmiddels een minder stringente houding ten opzichte van dit type EEG (Uit: Niedermeyer & Da Silva (2004) pagina 161). Momenteel is het enige abnormale EEG patroon gekenmerkt door overmatige bèta de 'paroxysmal fast activity' of het 'bèta band seizure patroon,' welke meestal tijdens de non-REM slaap plaatsvindt, maar ook in wakende toestand kan optreden (Stern & Engel, 2004). Dit patroon is erg zeldzaam (4 in 3000) en wordt meestal bij het Lennox-Gastaut syndroom gezien (Halasz et al., 2004). Vogel (1970) beschrijft tevens een EEG patroon van 'trage bètagolven' op occipitale locaties, ook bekend als 'snelle alfa variaties 16-19/sec.'. Deze reageert op dezelfde manier als alfa bij het openen van de ogen en welke eveneens een gelijke topografische distributie heeft. Dit patroon werd gevonden in enkel 0.6% van een

grote populatie van gezonde deelnemers. Gezien de lage prevalentie en occipitale dominantie ervan, is het onwaarschijnlijk dat dit subtype de verklaring is voor de 'overmatige bèta' of het 'bèta spindling' subtype dat gevonden is bij ADHD. De ADHD subgroep met overmatige bèta of bèta spindling (er van uitgaande dat de paroxysmale activiteit is uitgesloten) kan neurologisch gezien als een 'normale variant' worden beschouwd. Neurofysiologisch gezien kan dit echter worden gezien als een aparte subgroep van ADHD die wel reageert op psychostimulantia (Chabot et al., 1999; Clarke et al., 2003b; Hermens et al., 2005). Meer onderzoek is nodig om de precieze onderliggende neurofysiologie van dit subtype te achterhalen en om te zien of andere behandelingen de overmatige bèta of bèta spindling specifieker kunnen behandelen.

Depressie

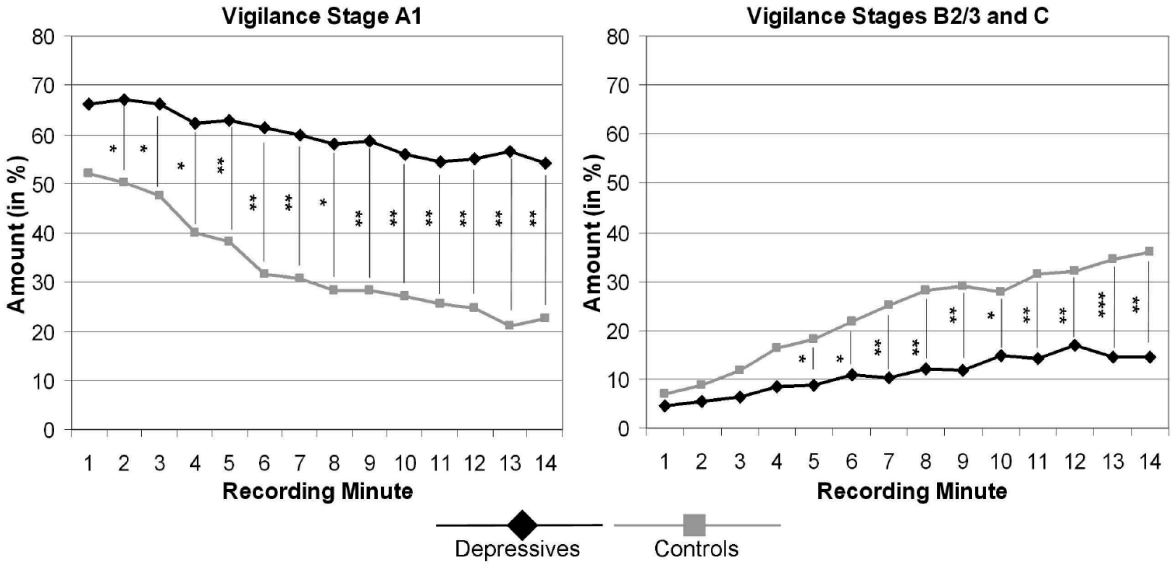
Nadat we het EEG phenotype model bij ADHD (hoofdstuk 2) hadden toegepast, is deze methode ook bij depressie toegepast. De resultaten zijn samengevat in supplement 1 van hoofdstuk 7. De resultaten lieten een grotere heterogeniteit in EEG fenotypen bij depressie zien – waardoor de steekproefgrootte, waarvoor pre- en post-behandeling data beschikbaar was, te klein was om betrouwbare uitspraken te doen over de voorspellende waarde van dit EEG fenotype model bij depressie. In een grotere steekproef van meer dan 200 patiënten die met rTMS behandeld zijn, is ook geen duidelijke voorspellende waarde van dit model gevonden (ongepubliceerde observatie). Daarom is in hoofdstuk 7 en hoofdstuk 10 een meer 'integratieve benadering' gebruikt waarbij combinaties van maten gebruikt zijn. Deze lieten betere resultaten zien. In de volgende sectie zullen de meest consistente bevindingen voor depressie samengevat worden, tevens in relatie tot reeds gepubliceerde onderzoeken.

Te hoge of te lage thèta?

De in hoofdstuk 10 gerapporteerde verhoogde thèta bij non-responders op rTMS behandeling komt overeen met eerdere studies die lieten zien dat non-responders op antidepressiva ook verhoogde thèta lieten zien (Iosifescu et al., 2009; Knott et al., 2000; Knott et al., 1996). Zoals duidelijk te zien in figuur 2 van hoofdstuk 10 (pagina 181), is thèta voornamelijk verhoogd in fronto-centrale locaties en niet specifiek in de frontale middellijn, terwijl in hoofdstuk 7 juist een verhoogde thèta op Fz (middellijn locatie) gevonden is die gerelateerd was aan een beter behandelresultaat op antidepressiva. Frontale middellijn thèta is gelokaliseerd in de mediale prefrontale cortex en de anterior cingulate (Asada et al., 1999; Ishii et al., 1999) en een recente meta-analysis heeft overtuigend laten zien dat thèta in de rostrale anterior cingulate cortex een betrouwbare maat voor een gunstige behandeluitkomst is (Pizzagalli, 2011). De resultaten uit hoofdstuk 10 wijzen dus eerder op een gegeneraliseerde verhoogde thèta in non-responders in plaats van frontale middellijn thèta die voortkomt uit de anterior cingulate, in overeenstemming met de resultaten van Knott et al. (2000; 1996) en Iosifescu et al. (2009).

Figuur 4 is ontleend aan een onderzoek van Hegerl et al. (2011) en geeft de EEG Vigilantie regulatie weer bij depressieve patiënten (N=30) vergeleken met een controlegroep (N=30). Zoals deze figuur laat zien is er een duidelijk verschil in EEG vigilantie regulatie bij

depressieve patiënten vergeleken met een controlegroep. In lijn met de EEG vigilantie theorie, laten depressieve patiënten een hyperstabiele vigilantie regulatie zien, met name te zien in het meer voorkomen van A1 stadia (pariëtale alfa) en een afname van B2/3 en C stadia (frontale thèta). Dit is in overeenstemming met een onderzoek van Ulrich and Fürstenberg (1999) en andere onderzoeken die een toename van pariëtale alfa bij depressie laten zien (Itil, 1983; Pollock & Schneider, 1990). Verder lieten de EEG fenotype resultaten uit supplement 1 van hoofdstuk 7 een trend zien dat het frontale alfa EEG fenotype minder vaak aanwezig was in de depressiegroep en suggereert minder van de lagere A3 vigilantie stadia – en dus meer verhoogde vigilantiestadia zoals A1. In zijn onderzoek beschrijft Vogel (1970) een 'Monotonous High Alpha Waves' met een autosomale dominantie van erfelijkheid. De beschrijving van dit door Vogel gerapporteerde EEG patroon ('Kontinuität') komt zeer overeen met de 'hyper-rigide' of 'hyperstabiele' EEG vigilantie bevonden door Hegerl et al. (2011) en suggereert dat dit inderdaad een stabiele EEG vigilantie regulatie reflecteert met een erfelijke component.



Figuur 4: EEG Vigilantie regulatie over een tijdspanne van 15 minuten bij depressieve patiënten en een gezonde controlegroep. Depressieve patiënten laten een hyperstabiele vigilantie regulatie zien, door een vaker voorkomen van A1 stadia (pariëtale alpha) en minder B2/3 en C stadia (frontale thèta). Uit: Hegerl et al. (2011).

Een verhoogde alfa EEG activiteit vóór behandeling is daarnaast ook geassocieerd met betere behandelresultaten van antidepressiva (Bruder et al., 2001; Ulrich et al., 1984) en de meeste antidepressiva resulteerden ook in een afname van alfa-activiteit (zie: Itil (1983) voor een overzicht). De gerapporteerde subgroep van non-responders uit hoofdstuk 10 die gekenmerkt werden door een verhoogde frontale thèta kunnen dus geïnterpreteerd worden als een subgroep met een *verlaagde* EEG vigilantie regulatie (Arns, 2010a; Hegerl et al., 2010), in tegenstelling tot de hierboven beschreven *verhoogde* vigilantie of hyperstabiele vigilantie regulatie ('hyperstabiele' pariëtale alfa). Aangezien patiënten met een verlaagde EEG vigilantie regulatie beter op psychostimulantia reageren (Manische depressiviteit: Bschor et al., 2001; Hegerl et al., 2010; Schoenknecht et al., 2010; ADHD: Arns et al., 2008; Sander et al., 2010) is te verwachten dat deze subgroep van non-responders misschien beter op psychostimulantia of andere vigilantie-stabiliserende behandelingen reageren.

Psychostimulantia zijn reeds succesvol toegepast in een subgroep van depressieve patiënten die een verhoogde thèta lieten zien door Suffin en Emory (1995), recentelijk ook gerepliceerd in een prospectief gerandomiseerde onderzoek (Debattista et al., 2010). Een recente Cochrane review toonde ook aan dat psychostimulantia klinische effecten kunnen hebben op stemming en vermoeidheid, al waren er te weinig gecontroleerde onderzoeken aanwezig om hier een steekhoudende conclusie over te trekken (Candy et al., 2008). In lijn met de speculatie dat een verstoorde circadiane ritmiek en (in)slaapproblemen mogelijk als de kern pathofysiologie bij ADHD gezien kunnen worden, zouden toekomstige onderzoeken zich moeten richten op het verder onderzoeken van EEG vigilantie regulatie en de aanwezigheid van slaapproblemen en verstoorde circadiane ritmiek in deze subgroep van non-responders bij depressie om zo een geschiktere behandeling voor deze patiënten te ontwikkelen. Figuur 4 laat ook duidelijk zien dat bij depressie tot vijftien minuten durende EEG opnamen met gesloten ogen nodig zijn om betrouwbare verschillen in EEG vigilantie regulatie aan te kunnen tonen. Dit was de voornaamste reden dat dit niet getest is met deze dataset, gezien deze beperkt was tot 2 minuten met gesloten ogen.

Samenvattend: Responders op antidepressieve-behandelingen zoals antidepressiva en rTMS worden over het algemeen gekarakteriseerd door verhoogde pariëtale alfa (ofwel een 'hyperstabiele' vigilantie regulatie) en een verhoogde thèta in de rostral anterior cingulate (Pizzagalli, 2011) in het EEG weerspiegeld als frontale-middellijn thèta (Asada et al., 1999; Ishii et al., 1999). Een subgroep van non-responders op antidepressiva is gekarakteriseerd door verhoogde frontale thèta, wijzend op een verlaagde EEG vigilantie regulatie. Er zijn aanwijzingen dat deze groep beter zouden kunnen reageren op vigilantie-stabiliserende behandelingen zoals psychostimulantia of slaap-normaliserende behandelingen zoals melatonine. In dit verband is het interessant dat recentelijk een nieuw antidepressivum op de markt is gekomen dat met name werkt op Melatonine MT1/MT2 receptor genaamd Agomelatine (Demyttenaera, In Press). Een laatste subgroep van non-responders op antidepressieve behandelingen worden gekenmerkt door een vertraagde alfa piek frequentie (iAPF), wat in het hiernavolgende verder wordt besproken.

De 'vertraagde individuele alfa piek frequentie' subgroep (iAPF): vervolgd…

Zoals duidelijk werd in de sectie over ADHD, bleken ADHD patiënten met een vertraagde iAPF niet te reageren op psychostimulantia. Daarnaast werd in hoofdstuk 6 een duidelijk verband gevonden tussen de iAPF vóór behandeling en de verbetering in comorbide depressieve symptomen als een gevolg van neurofeedback. Hoofdstukken 9 en 10 hebben verder laten zien dat deze maat duidelijk verband houdt met het niet reageren op rTMS behandeling bij depressie. Dit is in overeenstemming met andere onderzoeken die ook hebben laten zien dat deze maat verband houdt met non-response bij rTMS (Conca et al., 2000), antidepressiva (Ulrich et al., 1984) en antipsychotica (Itil et al., 1975). Dit lijkt te suggereren dat een vertraagde iAPF als een algemene biomarker voor non-response zou kunnen worden beschouwd. Deze subgroep beslaat een substantieel aantal patiënten (28% bij ADHD (hoofdstuk 2), 17% bij depressie (hoofdstuk 10)) en de vraag rijst dus: *'Op welke behandeling zouden deze patiënten wel reageren?'*

Neurofysiologie van de iAPF

Er is veel onderzoek gedaan naar de relatie tussen de iAPF en cognitieve functies; voor een uitgebreid overzicht zie Klimesch (1999). De meeste van deze onderzoeken zijn uitgevoerd bij gezonde proefpersonen en laten met name de relatie met neuropsychologisch functioneren, zoals geheugen, zien in een 'normaal functionerend' brein. In deze sectie zijn we vooral geïnteresseerd in methoden die de iAPF beïnvloeden, zodat we kunnen evalueren welke specifieke methoden mogelijk als behandeling van de hierboven besproken subgroep van patiënten met een trage iAPF kunnen dienen. Daarom beperken we ons hier met name tot onderzoeken die een verhoging of verlaging van de iAPF hebben laten zien.

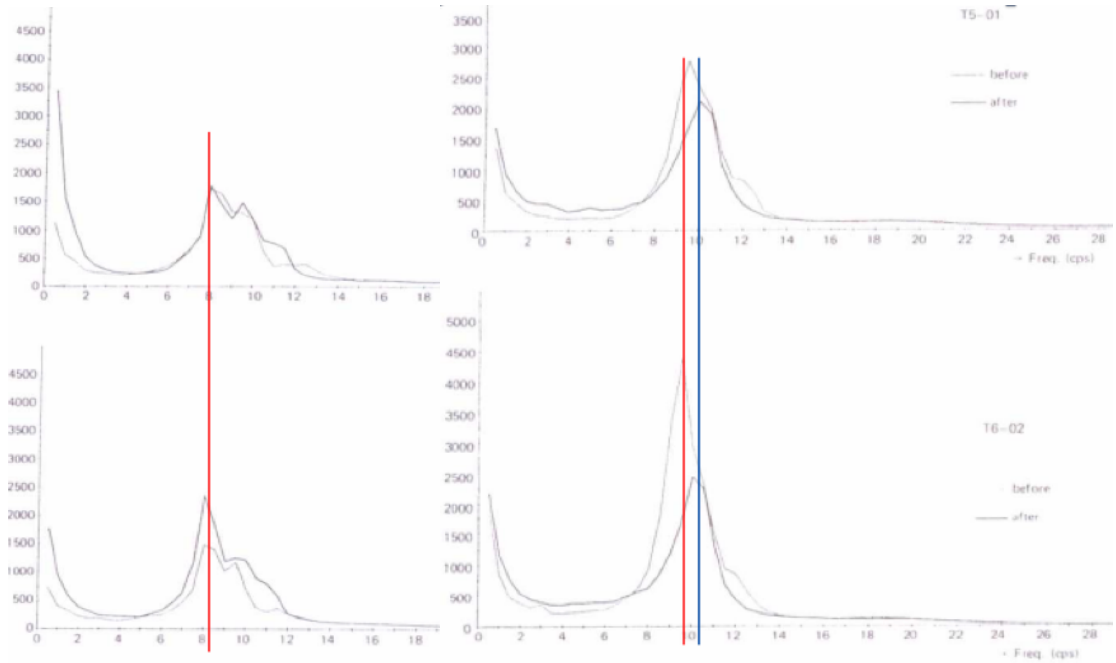
De iAPF is de meest stabiele en reproduceerbare maat van het EEG (Kondacs & Szabó, 1999) en is een erfelijke eigenschap, waarbij tussen de 71 en 83% van de variantie verklaard wordt door erfelijkheid (Posthuma et al., 2001). Daarom kan de iAPF gezien worden als een echt endofenotype in lijn met de definitie van Gotessman en Gould (2003), welke reeds is toegelicht in de introductie. Alfa activiteit wordt gegenereerd in thalamocorticale feedback loops van prikkelende en remmende zenuwcellen (Lopes da Silva, 1991; Steriade et al., 1990). Door de thalamocorticale basis van alfa, kan de iAPF gezien worden als een informatie-uitwisseling tussen de cortex en de thalamus. Een hogere iAPF zou dus een weerspiegeling zijn van snellere verwerking van informatie. Dit komt overeen met de vele studies die hebben laten zien dat een hoge iAPF verband houdt met betere cognitieve prestaties zoals werk-geheugen (Richard Clark et al., 2004), semantisch geheugen (Klimesch, 1996) en een snellere reactietijd tijdens complexe taken (Jin et al., 2006). Het meest duidelijke neurologische syndroom dat een trage iAPF laat zien, is de ziekte van Alzheimer (AD), waarbij de mate van vertraging ook verband houdt met de ernst van de ziekte (Rodriguez et al., 1999). AD wordt tevens gekenmerkt door een verminderd semantische geheugen en werk-geheugen.

In pijnonderzoek is gevonden dat in gezonde patiënten een pijnstimulus tot een directe verhoging van de iAPF leidt (Nir et al., 2010), hetgeen waarschijnlijk een reflectie is van een 'fight-flight' ofwel 'vecht-vlucht' reactie. In dit onderzoek werd ook een significante correlatie gerapporteerd tussen de iAPF voorafgaande aan de pijnprikkels en de subjectieve pijnervaring van eenzelfde pijnstimulus, waarbij patiënten met een hogere iAPF eenzelfde pijnstimulus als meer pijnlijk beoordeelden (Nir et al., 2010). Bij patiënten met chronische pijn daarentegen wordt juist een trage iAPF gerapporteerd (Boord et al., 2008; Sarnthein et al., 2006). Echter, wanneer deze patiënten behandeld worden middels 'central lateral thalectomy' (een procedure die resulteert in een pijnverlichting van 95% na 12 maanden) keert de iAPF weer terug naar normale waarden (Sarnthein et al., 2006). Ook al wordt de iAPF als een stabiele en erfelijke eigenschap gezien (Kondacs & Szabó, 1999; Posthuma et al., 2001), deze onderzoeken laten zien dat de iAPF wel degelijk sneller of trager kan worden als reactie op 'bedreigingen' zoals pijnstimuli. Speculatief kan deze aan bedreigingen-gerelateerde toename in iAPF gezien worden als een mechanisme gerelateerd aan een toename in alertheid teneinde sneller op een bedreiging te kunnen reageren. Echter, wanneer een 'dreiging' chronisch van karakter wordt, wordt juist een vertraagde iAPF gezien, zoals in de hierboven beschreven studies bij chronische pijn. Dezelfde observatie is gedaan bij burnout (van Luijtelaar et al., 2010). Mogelijk dient bij chronische 'dreiging' deze

iAPF als een ‘gating mechanisme’ waarmee de hoeveelheid prikkels die geprojecteerd worden van de thalamus naar de cortex verminderd worden, waardoor de perceptie van de pijn bij chronische pijn of de informatieverwerking/werkdruk bij burnout minder wordt. Wanneer de chronische ‘dreiging’ ofwel de pijn weggenomen wordt, treedt er interessant genoeg een complete normalisatie van de iAPF op (Sarnthein et al., 2006).

Medicatie en de iAPF

Ulrich et al. (1984) lieten zien dat non-responders op antidepressiva werden gekenmerkt door een duidelijk vertraagde iAPF (8 Hz vs. 9.5 Hz) op een voormeting, en dat alleen de responders ná medicatie een toename in de iAPF lieten zien, zie ook figuur 5. Dit suggereert dat antidepressiva de iAPF doen toenemen, maar alleen bij patiënten die in beginsel een ‘normale’ iAPF hadden.



Figuur 5: De spectraal inhoud van het EEG voor non-responders (links) en responders (rechts) op antidepressieve medicatie op posterior locaties. Let met name op de verlaagde alfa power en de vertraagde iAPF bij de non-responders (8 Hz). De rode lijn laat de iAPF voor behandeling zien, en de blauwe lijn de iAPF na behandeling. Alleen de responders laten een toename van de iAPF zien na behandeling van ongeveer 0.5 Hz. Figuur ontleend aan Ulrich et al., (1984).

Verder heeft onderzoek laten zien dat nicotine gebruik leidt tot een directe verhoging van de iAPF (Foulds et al., 1994; Knott, 1988; Lindgren et al., 1999) en hetzelfde geldt voor Piracetam (Saletu et al., 1984).

Neuromodulatie en de iAPF

Modulatie van de iAPF door neurofeedback is voor het eerst aangetoond door Joe Kamiya (1968). Latere goed gecontroleerde onderzoeken bij gezonde proefpersonen hebben laten zien dat deze proefpersonen in staat zijn om hun hoge-alfa omhoog te trainen, hetgeen gesuggereerd wordt te resulteren in een verhoging van de iAPF, met als gevolg een verbetering van hun performance op een mentale rotatie taak (Hanslmayr et al., 2005; Zoefel et al., 2010). Deze studies zijn allen uitgevoerd bij gezonde vrijwilligers met over het algemeen 'normale' iAPF's. Het is dus onduidelijk of deze techniek bruikbaar kan zijn voor patiënten met een vertraagde iAPF. Op basis van hoofdstuk 6 bleek het niet mogelijk om definitieve conclusies te trekken over het effect van neurofeedback bij deze groep op ADHD klachten. Verder onderzoek is dus benodigd om de mogelijkheden van neurofeedback bij deze groep te onderzoeken.

Slechts één studie die gebruik maakte van 10 Hz rTMS over de linker frontale cortex heeft een acute toename van de iAPF, voor de duur van twee minuten, gerapporteerd (Okamura et al., 2001). De resultaten uit hoofdstuk 9 en 10 hebben echter aangetoond dat non-responders op rTMS werden gekarakteriseerd door een trage iAPF, suggererend dat rTMS een onwaarschijnlijke behandelmodaliteit is voor deze subgroep. Eén onderzoek bij schizofrenie heeft wel betere effecten laten zien van rTMS, gebruikmakend van een rTMS stimulatie frequentie die identiek is aan de iAPF op negatieve symptomen bij schizofrenie, terwijl LF or HF rTMS gebruikmakend van 'standaard' frequenties geen effecten liet zien (Jin et al., 2006). Dit was helaas niet te repliceren bij depressie in hoofdstuk 9.

Cerebrale doorbloeding (CBF)

In 1934 beschreef Hans Berger reeds een vertraging van het EEG als gevolg van verlaagde zuurstoftoevoer naar de hersenen (from: Kraaier, Van Huffelen & Wieneke, 1988). Sindsdien wordt een vertraagde iAPF beschouwd als de meest gevoelige EEG maat om de effecten van een verlaagde zuurstofvoorziening naar de hersenen te meten, zoals in cerebrale ischemie (Kraaier et al., 1988; Van der Worp et al., 1991) en carotide arterie occlusie (Mosmans et al., 1983). Bij patiënten met geringe cerebrale ischemie, met op het oog normale EEG's, is vertraging van de iAPF gerapporteerd in de aangetaste zijde (Van der Worp et al., 1991). Carotide Endarterectomie (operatie van de halsslagader) is een ingreep die toegepast wordt om een hersenbloeding te voorkomen door middel van het corrigeren van de halsslagader en hiermee de bloedtoevoer naar de hersenen te verhogen. Onderzoek heeft laten zien dat deze procedure de cerebrale doorbloeding verbetert, en resulteert in een verhoogde iAPF (Uclés et al., 1997; Vriens et al., 2000), vooral bij patiënten met een vertraagde iAPF lager dan 9 Hz (Vriens et al., 2000). Een ander onderzoek heeft tevens laten zien dat patiënten met koolstofmonoxide vergiftiging die behandeld worden met hyperbare zuurstof therapie een duidelijke toename van meer dan 1 Hz in de iAPF lieten zien (Murata et al., 2005).

Recentelijk is ook een direct verband gelegd tussen regionale CBF en iAPF waar een hogere iAPF geassocieerd was met een hogere regionale cerebrale doorbloeding, vooral in de bilaterale inferieure frontale gyrus (BA 45) en de rechter insulaire cortex (BA 13) (Jann, Koenig, Dierks, Boesch & Federspiel, 2010). Deze structuren spelen een belangrijke rol bij het moduleren van aandacht en de bereidheid tot verwerking van externe input ofwel arousal,

relevant voor het uitvoeren van cognitieve taken. Daarmee is een directe relatie gelegd tussen de iAPF en cerebrale doorbloeding aan de ene kant, en aandacht en arousal aan de andere kant, beide aangedaan bij ADHD en depressie.

In dit opzicht is het interessant op te merken dat Midazolam (een benzodiazepine) de cerebrale doorbloeding met 30% verlaagt, terwijl een benzodiazepine antagonist dit effect opheft, maar deze benzodiazepine antagonist zelf geen effect had op de CBF (Forster et al., 1987). Een ander onderzoek heeft ook laten zien dat zowel hyperbare zuurstof therapie (welke de zuurstofbeschikbaarheid in de hersenen verhoogt) als Flumazenil (een benzodiazepine antagonist) beiden de EEG activatie zoals geïnduceerd door Midazolam opheffen (Russell et al., 1995). Aangezien de toediening van benzodiazepines vaak tot een verlaagde iAPF leiden (met name Carbamazepine en oxcarbazepine: Clemens et al., 2006), suggereren deze onderzoeken een interactie tussen het GABA-erge systeem en cerebrale doorbloeding.

Ontwikkelingen van nieuwe behandelmethoden voor deze subgroep?

Samenvattend: de subgroep met een trage iAPF, in zowel de onderzoeken uit deze thesis als wel andere onderzoeken (Conca et al., 2000; Itil et al., 1975; Ulrich et al., 1984), kunnen als een groep van non-responders op verscheidene behandelingen gezien worden. Na de samenvatting over de bekende literatuur over de iAPF, kan geconcludeerd worden dat een vertraagde iAPF duidelijk geassocieerd is met een verlaagde cerebrale doorbloeding. Verschillende typen medicatie laten een kleine toename van de iAPF zien zoals nicotine en Piracetam, maar meer onderzoek is nodig om uit te wijzen of deze medicatie-effecten specifiek zijn en een voldoende substantieel effect laten zien voor deze subgroep met een vertraagde iAPF.

Toekomstige onderzoeken zullen zich verder moeten richten op deze subgroep van patiënten en tevens uitsluiten of organische verklaringen, zoals cerebrale ischemie, stenose en zuurstoftekort tijdens de geboorte deze afwijking kunnen verklaren. Indien zulke organische verklaringen inderdaad bevestigd worden, dienen eerst deze oorzaken verder onderzocht worden en, indien dit mogelijk is, deze organische oorzaken direct behandeld worden om vast te stellen of dit resulteert in een normalisatie van de iAPF en een verbetering van de depressieve of ADHD klachten. Indien zulke factoren uitgesloten worden, zouden behandelmethoden overwogen kunnen worden die de cerebrale doorbloeding verhogen, gezien de verbeteringen in iAPF na procedures zoals carotid endarterectomie (Uclés et al., 1997; Vriens et al., 2000) of hyperbare zuurstoftherapie (Murata et al., 2005).

Andere potentiele technieken die in dit opzicht verder onderzoek verdienen zijn:

1) Near-infrared spectroscopie (NIRS) biofeedback. Deze techniek meet de bloedoxygenatie en de-oxygenatie in de onderliggende cortex (Plichta et al., 2006); real-time applicaties van deze techniek voor brain-computer interfaces (BCI) zijn reeds ontwikkeld (Kanoh et al., 2009). Momenteel wordt een eerste onderzoek dat deze techniek toepast bij kinderen met ADHD al uitgevoerd in Tübingen (Strehl, personal communication).

2) Transcraniële Doppler Sonografie Biofeedback: Deze techniek meet de snelheid van de bloeddoorstroming in de cerebrale bloedvaten en kan hier in real-time feedback op geven. De haalbaarheid van deze aanpak is recentelijk aangetoond (Duschek et al., 2010).

3) Hyperbare zuurstoftherapie: Deze techniek bestaat uit het blootstellen van mensen aan hogere zuurstofconcentraties in een atmosferische druk-kamer om daarmee de zuurstofbeschikbaarheid in het lichaam te verhogen en inflammatoire reacties te verminderen (Granpeesheh et al., 2010). Deze techniek is een goed onderzochte behandeling voor decompressieziekte, wordt onderzocht voor de toepassing bij het beter helen van wonden, en wordt reeds toegepast bij de behandeling van autisme (Granpeesheh et al., 2010). Echter, waar aanvankelijk onderzoek gunstige resultaten bij autisme boekte (Rossignol et al., 2009), bleken recente goed gecontroleerde onderzoeken niet in staat dit te repliceren (Granpeesheh et al., 2010; Jepson et al., 2010). In plaats van deze behandeling bij een DSM-IV gebaseerde groep patiënten te onderzoeken, zouden toekomstige studies moeten vaststellen of deze behandeling gunstige resultaten kan boeken bij enkel patiënten met een vertraagde iAPF.

De vraag rijst of voor de behandeling van patiënten met dit EEG patroon het afdoende is om een normalisatie van hun iAPF te bereiken, of dat deze normalisatie van de iAPF patiënten meer vatbaar maakt voor reguliere behandelingen. Deze vraag zal tevens verder onderzocht moeten worden.

Laatste opmerkingen

In overeenstemming met de recente ontwikkelingen zoals geschetst aan het begin van dit hoofdstuk, zijn in dit hoofdstuk verschillende biomarkers voor non-response op verschillende behandelmethoden bij ADHD en depressie beschreven. De iAPF is een solide marker voor non-response gebleken voor verschillende behandelmethoden zoals psychostimulantia, antidepressiva en rTMS. Gegeven het feit dat deze maat de meest reproduceerbare en stabiele maat van het EEG is en in hoge mate erfelijk is (Posthuma et al., 2001; van Beijsterveldt et al., 2002; Smit et al., 2005), geassocieerd is met het COMT gen (Bodenmann et al., 2009) en een duidelijke relatie met cerebrale doorbloeding laat zien, wordt voorgesteld dat deze maat een endofenotype voor non-response is, die verder onderzoek verdient. Dit endofenotype kan in onderzoek als verder uitgangspunt gebruikt worden om nieuwe behandelingen te ontwikkelen en te toetsen waarmee deze substantiële subgroep van patiënten beter geholpen kunnen worden.

Tenslotte kan geconcludeerd worden dat het vooral binnen het vakgebied van elektro-encefalografie belangrijk is om bewust te zijn van de lange, rijke historie van onderzoek in plaats van ons enkel te richten op recent onderzoek. Het voorbeeld van de iAPF toont immers duidelijk aan dat met de introductie van nieuwe technieken zoals het QEEG, oudere, reeds bekende feiten over het hoofd gezien worden, hetgeen resulteert in blind-spots zoals aangetoond met het voorbeeld van de overmatige thèta bij ADHD die eigenlijk een combinatie van een trage iAPF *en* echte theta is en de robuuste status van de iAPF als endofenotype voor non-response.

Dankwoord

(acknowledgements)

Na eindelijk op pagina 276 beland te zijn, is het tijd om een aantal mensen te bedanken…

Allereerst, Dirk de Ridder voor je motiverende betoog om toch echt eens *'mijn rijbewijs voor de wetenschap'* te gaan halen, zonder die motivatie waren deze pagina's er niet gekomen!

Leon Kenemans, voor je kritische inbreng waar ik een hoop van geleerd heb.

Pim Drinkenburg, dank voor de 'tweede kans' na ons Schotland avontuur.

En natuurlijk, collega's en oud-collega's, dank voor jullie samenwerking: Mathanje Huisman, Hanneke Friesen, Rosalinde van Ruth, Niels Veth, Dianne Winkelmolen, Vera Kruiver, Rien Breteler, Aukje Bootsma, Sabine de Ridder, Desirée Spronk, Anne Schreiber en Dagmar Timmers en collega's.

Oud-collega's van de Radboud Universiteit voor de voortgaande samenwerking: Gilles van Luijtelaar, Marijtje Jongsma, Ton Coenen en Tineke van Rijn.

Furthermore, I would also like to thank some of my international colleagues and collaborators:

Evian Gordon, thanks for your continuing trust and support and our inspiring interactions.

Jay Gunkelman, for teaching me how to look at an EEG and your continuous support.

Paul Fitzgerald, for your inspiring collaboration in several of the rTMS projects.

Ulrich Hegerl, Sebastian Olbrich and Christian Sander for your support and input into understanding and testing the EEG Vigilance model further.

Ute Strehl, for your collaboration and many wise comments.

Many current and previous colleagues at Brainnet and BRC, thanks: Lea Williams, Dan Segal, Michelle Wang, Adam Chimes, Kylie Barnett, Louis Yang, Patrick Hopkinson and Deborah Kargl.

Niels Klein Lankhorst, dank voor de inspirerende avonden in de kroeg, dit was vaak een erg welkome afwisseling van weer een dag tussen de cijfers.

Wim en Coby, dank dat jullie me altijd de vrijheid hebben gegund om mijn eigen pad te kiezen, me daarin gesteund hebben en daar altijd vertrouwen in hebben gehad. Jullie zijn de meest geweldige ouders die ik me kan wensen!

En tenslotte natuurlijk Nicole, Rumo en Sia, dank dat jullie er altijd voor me zijn, jullie ondersteuning en jullie geduld met 'papa's hobby'. Nicole – alias mijn 'spellingscontrole' – dank voor het altijd klaar voor me staan en het continu 'aanhoren' van wat er weer in mijn hoofd rondgaat. Rumo en Sia – levendige voorbeelden van 'vigilantie auto-stabilisatie gedrag' – alleen al de gedachte aan jullie bezorgd me een glimlach!

Curriculum Vitae

Martijn Arns was born on December 4th, 1974 in Apeldoorn, the Netherlands. He finished his pre-university education (VWO) in 1994 (state exam) and started the Psychology program at the Radboud University in Nijmegen in the same year. He obtained a Master's degree in Biological Psychology in 1998. In 2001 Martijn founded Research Institute Brainclinics specializing in applied neuroscience research and personalized medicine with a focus on ADHD and depression. In 2004 he also started implementing new treatments such as neurofeedback and later rTMS which resulted in a separate psychology practice Brainclinics Treatment in 2007. Martijn was chairman of the Applied Neuroscience Foundation in the Netherlands which organised the succesful international conference 'Applied Neuroscience for Healthy Brain Function' in 2007, was International member at Large for the International Society for Neurofeedback and Research (ISNR) form 2009 to 2011 and was Senior Editor for the Journal of Neurotherapy from 2009 to 2011 and is currently treasurer of the International Pharmaco EEG Group (IPEG).

Publications

Alexander, D. M., Arns, M. W., Paul, R. H., Rowe, D. L., Cooper, N., Esser, A. H., et al. (2006). EEG markers for cognitive decline in elderly subjects with subjective memory complaints. *Journal of Integrative Neuroscience*, *5*(1), 49-74.

Arns, M. (2008). Personalized medicine: Nieuwe ontwikkelingen in de diagnostiek en behandeling van ADHD en depressie. *De Psycholoog*, (September).

Arns, M. (2010a). Handboek neurofeedback bij ADHD. [Handbook Neurofeedback in ADHD] (1 ed.). SWP.

Arns, M. (2010b). Historical archives: The beginning. *Journal of Neurotherapy*, *14*(4), 291-292.

Arns, M. & de Ridder, D. (2011). Neurofeedback 2.0. *Journal of Neurotherapy*, *15*(2), 91-93.

Arns, M., de Ridder, S., Strehl, U., Breteler, M., & Coenen, A. (2009). Efficacy of neurofeedback treatment in ADHD: The effects on inattention, impulsivity and hyperactivity: A meta-analysis. *Clinical EEG and Neuroscience*, *40*(3), 180-9.

Arns, M., Drinkenburg, W. H. I. M., & Kenemans, J. L. (submitted). The effects of QEEG-*informed* neurofeedback in ADHD: An open label pilot study. *European Child & Adolescent Psychiatry*

Arns, M., Drinkenburg, W. H. I. M., Fitzgerald, P. B., & Kenemans, J. L. (submitted). Neurophysiological predictors of treatment outcome to rTMS in depression. *Brain Stimulation.*

Arns, M., Gunkelman, J., Breteler, M., & Spronk, D. (2008). EEG phenotypes predict treatment outcome to stimulants in children with ADHD. *Journal of Integrative Neuroscience*, *7*(3), 421-38.

Arns, M., Gunkelman, J., Olbrich, S., Sander, C., & Hegerl, U. (2010). EEG vigilance and phenotypes in neuropsychiatry: Implications for intervention. In: *Neuromodulation and neurofeedback: Techniques and applications* (R. Coben & J. Evans, Eds.). Elsevier.

Arns, M., Peters, S., Breteler, R., & Verhoeven, L. (2007). Different brain activation patterns in dyslexic children: Evidence from EEG power and coherence patterns for the double-deficit theory of dyslexia. *Journal of Integrative Neuroscience*, *6*(1), 175-90.

Arns, M., Sauvage, M., & Steckler, T. (1999). Excitotoxic hippocampal lesions disrupt allocentric spatial learning in mice: Effects of strain and task demands. *Behavioural Brain Research*, *106*(1-2), 151-64.

Arns, M., Spronk, D., & Fitzgerald, P. B. (2010). Potential differential effects of 9 Hz rTMS and 10 Hz rTMS in the treatment of depression. *Brain Stimulation*, (3), 124-126.

Arns, M., Van Luijtelaar, G., Sumich, A., Hamilton, R., & Gordon, E. (2007). Electroencephalographic, personality, and executive function measures associated with frequent mobile phone use. *The International Journal of Neuroscience*, *117*(9), 1341-60.

Arns, M. W., Kleinnijenhuis, M., Fallahpour, K., & Breteler, M. H. M. (2008). Golf performance enhancement by means of 'real-life neurofeedback'training based on personalized event-locked EEG profiles. *Journal of Neurotherapy*, *11(4)*, 11-18.

Breteler, M. H., Arns, M., Peters, S., Giepmans, I., & Verhoeven, L. (2010a). Erratum to: Improvements in spelling after qeeg-based neurofeedback in dyslexia: A randomized controlled treatment study. *Applied Psychophysiology and Biofeedback, 35(2), 187.*

Breteler, M. H., Arns, M., Peters, S., Giepmans, I., & Verhoeven, L. (2010b). Improvements in spelling after QEEG-based neurofeedback in dyslexia: A randomized controlled treatment study. *Applied Psychophysiology and Biofeedback*, *35*(1), 5-11.

Breteler, Van Heeswijk, Arns, & Verdellen (2008). Psychologische interventies bij het syndroom van gilles de la tourette. *Tijdschrift Voor Neuropsychiatrie & Gedragsneurologie*, (Juli/Augustus).

Clark, C. R., Paul, R. H., Williams, L. M., Arns, M., Fallahpour, K., Handmer, C., et al. (2006). Standardized assessment of cognitive functioning during development and aging using an automated touchscreen battery. *Archives of Clinical Neuropsychology*, *21*(5), 449-67.

Coben, R., Arns, M., & Kouijzer, E. J. (2010). Enduring effects of neurofeedback in children. In: *Neuromodulation and neurofeedback: Techniques and applications* (R. Coben & J. Evans, Eds.). Elsevier.

Cortoos, A., De Valck, E., Arns, M., Breteler, M. H., & Cluydts, R. (2010). An exploratory study on the effects of tele-neurofeedback and tele-biofeedback on objective and subjective sleep in patients with primary insomnia. *Applied Psychophysiology and Biofeedback*, *35*(2), 125-34.

Gunstad, J., Paul, R. H., Brickman, A. M., Cohen, R. A., Arns, M., Roe, D., et al. (2006). Patterns of cognitive performance in middle-aged and older adults: A cluster analytic examination. *Journal of Geriatric Psychiatry and Neurology*, *19*(2), 59-64.

Jongsma, M. L. A., Postma, S., Souren, P., Arns, M., Gordon, E., Vissers, K., . . . van Goor, H. (2011). Neurodegenerative properties of chronic pain: Cognitive decline in patients with chronic pancreatitis. *Plos One*, *6*(8), e23363. doi:doi:10.1371/journal.pone.0023363

Kemp, A. H., Griffiths, K., Felmingham, K. L., Shankman, S. A., Drinkenburg, W. H. I. M., Arns, M., et al. (2010). Disorder specificity despite comorbidity: Resting EEG alpha asymmetry in major depressive disorder and post-traumatic stress disorder. *Biological Psychology, 85(2), 350-354.*

Kleinnijenhuis, M., Arns, M. W., Spronk, D. B., Breteler, M. H. M., & Duysens, J. E. J. (2008). Comparison of discrete-trial based SMR and SCP training and the interrelationship between SCP and SMR networks: Implications for brain-computer interfaces and neurofeedback. *Journal of Neurotherapy, 11(4), 19-35.*

Lansbergen, M., Arns, M., van Dongen-Boomsma, M., Spronk, D., & Buitelaar, J. K. (2011). The increase in theta/beta ratio on resting state EEG in boys with attention-deficit/hyperactivity disorder is mediated by slow alpha peak frequency. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *35*, 47-52.

Liddell, B. J., Paul, R. H., Arns, M., Gordon, N., Kukla, M., Rowe, D., et al. (2007). Rates of decline distinguish alzheimer's disease and mild cognitive impairment relative to normal aging: Integrating cognition and brain function. *Journal of Integrative Neuroscience*, *6*(1), 141-74.

Sander, C., Arns, M., Olbrich, S., & Hegerl, U. (2010). EEG-Vigilance and response to stimulants in paediatric patients with attention deficit/hyperactivity disorder. *Clinical Neurophysiology*, *121*, 1511-1518.

Sherlin, L., Arns, M., Lubar, J., Heinrich, H., Kerson, C., Strehl, U., & Sterman, M. B. (In Press). Neurofeedback and basic learning theory: Implications for research and practice. *Journal of Neurotherapy*, *15*(4).

Sherlin, L., Arns, M., Lubar, J., & Sokhadze, E. (2010a). A reply to Lofthouse, Arnold, and Hurt (2010). *Journal of Neurotherapy*, *14*(4), 307-311.

Sherlin, L., Arns, M., Lubar, J. F., & Sokhadze, E. (2010b). A position paper on neurofeedback for the treatment of ADHD. *Journal of Neurotherapy*, *14*(2), 66-78.

Spronk, D. & Arns, M. (2009). rTMS bij depressie. *Tijdschrift Voor Neuropsychiatrie & Gedragsneurologie*, (Juli-Augustus).

Spronk, D., Arns, M., & Fitzgerald, P. B. (2010). Repetitive transcranial magnetic stimulation in depression: Protocols, mechanisms and new developments. In: *Neuromodulation and neurofeedback: Techniques and applications* (R. Coben & J. Evans, Eds.). Elsevier.

Spronk, D., Arns, M., Barnett, K. J., Cooper, N. J., & Gordon, E. (2011). An investigation of EEG, genetic and cognitive markers of treatment response to antidepressant medication in patients with major depressive disorder: A pilot study. *Journal of Affective Disorders*, *128*, 41-48.

Spronk, D., Arns, M., Bootsma, A., van Ruth, R., & Fitzgerald, P. B. (2008). Long-Term effects of left frontal rTMS on EEG and ERP's in patients with depression. *Clinical EEG and Neuroscience*, *39*(3), 118-24.

Spronk, D., Kleinnijenhuis, M., Luijtelaar, G., & Arns, M. (2010). Discrete-Trial SCP and GSR training and the interrelationship between central and peripheral arousal. *Journal of Neurotherapy*, *14*(3), 217-228.

Thomassen, F. & Arns, M. (2010). Are the effects of rTMS in parkinson's disease clinically relevant? *Journal of Neurotherapy*, *14*(2), 96-101.

van den Bunt, M., Arns, M., Verbraak, M., Keijsers, G., & van Luijtelaar, G. (2010). Biomarkers bij burn-outpatiënten. *Neuropraxis*, *14*, 165-173.

van Luijtelaar, G., Verbraak, M., van den Bunt, M., Keijsers, G., & Arns, M. (2010). EEG findings in burnout patients. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *22*(2), 208-17.

Williams, L. M., Gatt, J. M., Hatch, A., Palmer, D. M., Nagy, M., Rennie, C., Cooper, N.J., Morris, C., Grieve, S., Dobson-Stone, C., Schofield, P., Clark, C.R., Gordon, E., Arns, M. & Paul, R. (2008). The integrate model of emotion, thinking and self regulation: An application to the "paradox of aging". *Journal of Integrative Neuroscience*, *7*(3), 367-404.