

Neurofeedback and Neuromodulation Techniques and Applications

Edited by Robert Coben • James R. Evans



NEUROFEEDBACK AND NEUROMODULATION TECHNIQUES AND APPLICATIONS

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Edited by

ROBERT COBEN

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CONTENTS

<i>Contributors</i>	xi
<i>Preface</i>	xv
Part One: Neuromodulation: Analysis Techniques	1
1. Use of Quantitative EEG to Predict Therapeutic Outcome in Neuropsychiatric Disorders	3
Jack Johnstone and Joy Lunt	
Introduction	3
Foundations of Clinical EEG: Reliability	4
Quantitative EEG	5
Quantitative EEG/ERP and Medication Management	7
Prediction of Neurofeedback Protocol Efficacy	12
Using EEG to Guide Transcranial Magnetic Stimulation	17
Conclusion	19
References	20
2. EEG Source Analysis: Methods and Clinical Implications	25
Marco Congedo and Leslie Sherlin	
Introduction	25
Method	27
Clinical Examples	39
Discussion	43
References	44
3. ERP-Based Endophenotypes: Application in Diagnosis and Neurotherapy	47
Juri D. Kropotov, Andreas Mueller, and Valery A. Ponomarev	
Introduction	47
Event-Related Potentials (ERPs)	48
Theoretical Considerations	49
New Methods in ERP Analysis	52

HBI Reference Database	53
GO/NO-GO Task	53
Methodology of Decomposition of Collection of ERPs into Independent Components	56
Methodology of Decomposition of Individual ERPs into Independent Components	57
Independent Components in GO/NO-GO Task	58
Application of ERP/ICA Methodology for ADHD — Response Inhibition	65
ERPs as Indexes of Neurofeedback Efficacy	66
ERPs as Index of tDCS effect	70
References	73
4. EEG Vigilance and Phenotypes in Neuropsychiatry: Implications for Intervention	79
Martijn Arns, Jay Gunkelman, Sebastian Olbrich, Christian Sander, and Ulrich Hegerl	
Introduction	79
History of EEG Research in ADHD and Depression	83
EEG and qEEG: Models and Theory	94
EEG Vigilance Model	95
EEG Phenotype Model	105
EEG Phenotype vs. EEG Vigilance: Towards a Coherent Model?	112
Acknowledgments	115
References	115
Part Two: Endogenous Neuromodulation Strategies	125
5. Neurofeedback with Children with Attention Deficit Hyperactivity Disorder: A Randomized Double-Blind Placebo-Controlled Study	127
Roger J. deBeus and David A. Kaiser	
Introduction	128
Method	132
Results	139
Discussion	141
Conclusions	148
Acknowledgments	148
References	148

6. Emerging Empirical Evidence Supporting Connectivity-Guided Neurofeedback for Autistic Disorders	153
Robert Coben and Lori A. Wagner	
Introduction	153
Major Treatments for ASD: An Overview	155
Neurofeedback for ASD	168
qEEG Evaluation and ASD	170
Discussion	175
References	176
7. Neurofeedback and Epilepsy	183
Gabriel Tan, D. Corydon Hammond, Jonathan Walker, Ellen Broelz, and Ute Strehl	
Introduction	183
Research Synopsis	184
Clinical Protocols	186
Individualizing Neurofeedback Based on qEEG Findings	187
Low Energy Neurofeedback System (LENS)	198
Observations and Implications for Future Direction	200
References	201
8. Feedback of Slow Cortical Potentials: Basics, Application, and Evidence	205
Sarah Wyckoff and Ute Strehl	
Basics	206
Technical and Training Requirements	209
Diagnosis and Evaluation	215
Evidence Base and Indications	217
Conclusion	222
References	222
9. Real-Time Regulation and Detection of Brain States from fMRI Signals	227
Ranganatha Sitaram, Sangkyun Lee, Sergio Ruiz, and Niels Birbaumer	
Introduction	227
Historical Development of Real-Time fMRI	228

Overview of the fMRI–BCI System	232
fMRA–BCI in Research and Clinical Treatment	238
Conclusions	248
References	249
Part Three: Exogenous Neuromodulation Strategies	255
10. Repetitive Transcranial Magnetic Stimulation in Depression: Protocols, Mechanisms, and New Developments	257
Desirée Spronk, Martijn Arns, and Paul B. Fitzgerald	
Introduction	257
Protocols	261
Mechanisms of rTMS Treatment in Depression	270
New Developments	277
Acknowledgments	282
References	283
11. Transcranial Magnetic Stimulation for Tinnitus	293
Berthold Langguth and Dirk de Ridder	
Tinnitus: Introduction	293
Transcranial Magnetic Stimulation	296
Conclusion	311
References	312
12. Neurophysiological Effects of Transcranial Direct Current Stimulation	319
Jay S. Reidler, Soroush Zaghi, and Felipe Fregni	
Introduction	319
The Growing Field of Brain Stimulation	320
Electrophysiology of tDCS	323
Neurochemistry of tDCS	337
Safety Considerations for tDCS	340
Conclusions and Future Directions	341
Acknowledgment	344
References	344

Part Four: Mechanism of Change and Long-Term Consolidation: Beginning Evidence	351
13. Functional Neuroimaging Evidence Supporting Neurofeedback in ADHD	353
Johanne Lévesque and Mario Beauregard	
Introduction	353
Biological Basis of ADHD	354
Impact of Neurofeedback Training on the Neural Substrates of Selective Attention and Response Inhibition in Children with ADHD	361
Putative Neural Mechanisms Underlying the Effects of Neurofeedback in ADHD	366
Conclusion	368
References	369
14. The Immediate Effects of EEG Neurofeedback on Cortical Excitability and Synchronization	381
Tomas Ros and John H. Gruzelier	
Introduction	381
Methods	383
Results	387
Discussion	395
References	399
15. Enduring Effects of Neurofeedback in Children	403
Robert Coben, Martijn Arns, and Mirjam E.J. Kouijzer	
Introduction	403
Neurofeedback as a Treatment for Children with ADHD	405
Long-Term Effects of Neurofeedback	406
Neurofeedback as a Treatment for Children with ASD	408
Enduring Behavioral and Neuropsychological Benefits of Neurofeedback in ASD	413
Discussion	417
Acknowledgment	419
References	419
<i>Index</i>	423
<i>Color Plate Section</i>	

EEG Vigilance and Phenotypes in Neuropsychiatry: Implications for Intervention

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Contents

Introduction	79
Personalized Medicine: “Prognostics” Rather than “Diagnostics”	81
History of EEG Research in ADHD and Depression	83
ADHD	83
Depression	89
Conclusion: Averaged Group Data vs. Individual Client Data	93
Influence of Vigilance/Arousal	94
EEG and qEEG: Models and Theory	94
EEG Vigilance Model	95
EEG-Vigilance Algorithm – “VIGALL”	95
Validation of EEG Vigilance	97
EEG-Vigilance Regulation in Psychiatric Disorders	98
EEG Phenotype Model	105
Inter-rater Reliability	107
Prevalence of EEG Phenotypes in ADHD and Depression	109
EEG Phenotype vs. EEG Vigilance: Towards a Coherent Model?	112
Similarities Between EEG Phenotypes and EEG Vigilance	113
Unique Contributions of Both Methods	114
Acknowledgments	115
References	115

INTRODUCTION

Since the discovery of EEG by Hans Berger in 1929 (Berger, 1929) 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 disorders. In the early years EEG was mainly inspected visually until equipment became available that made possible Fourier analysis on EEG data to extract the spectral 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 clarify that the EEG should not only be submitted to spectral analysis but also compared to a control group and/or normative database (Kaiser, personal communication).

The group led by Ross Adey at the UCLA Brain Research Institute in the period 1961–1974 pioneered the first developments 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 4.1 for photos of the first equipment developed to measure EEG in outer space and during driving. As part of the Space



Figure 4.1 A photo from 1963 showing the equipment developed by Adey et al. to measure EEG in space. Ross Adey – who pioneered qEEG – is on the right in the top-left picture. (Courtesy of the Computer History Museum.)

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” (Kaiser, personal communication; Graham & Dietlein, 1965).

In the last 20 years, due to the increasing availability of affordable computer equipment, the field of qEEG has expanded even further and has become available for clinicians. Along with this, several different normative databases have also been developed and are available to most clinicians. Examples of such databases are Neuroguide (Thatcher), Brain Resource International Brain Database (Gordon), Neurometrics (John et al., 1992), SKIL (Serman), NeuroRep (Hudspeth) and Eureka3 (NovaTech). For a description and comparison of these databases also see Johnstone et al. (Johnstone, Gunkelman, & Lunt, 2005).

In this chapter, where we speak of qEEG we focus on normative EEG, or qEEG data that are compared to a control group or normative database. Furthermore, in this chapter we will limit the application of qEEG to neuropsychiatric conditions and will not focus on more strictly neurological applications that fall beyond the scope of the 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 could show up as an increased “relative” beta and theta power.

Personalized Medicine: “Prognostics” Rather than “Diagnostics”

Current conventional treatment methods in psychiatry are based on behavioral interventions and 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 over 3000 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 and 33% treatment resistance after four cumulative treatments (Rush et al., 2006). Some methodological issues potentially limit the generalizability of these results, 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 attention deficit hyperactivity disorder (ADHD) (the NIMH-MTA trial) also clearly showed a lack of long-term effects for stimulant medication, multicomponent behavior therapy, and multimodal treatment (Molina et al., 2009). Furthermore, in general, response rates to stimulant medication in ADHD are estimated to be 70% (see Hermens, Rowe, Gordon, & Williams, 2006 for an overview). New drug developments in psychiatry are not demonstrating major breakthroughs, but rather “refinements”, i.e. showing fewer side effects, but not a drastically improved efficacy rate. Recently it was also announced that two major pharmaceutical companies (GSK and AstraZeneca) will no longer develop psychiatric medications (Nierenberg, 2010). So what do these developments mean?

These developments suggest something might be wrong with the current approach to psychiatric treatments. Rather than blaming this on the industry, it seems more likely that something is wrong with our definitions of psychiatric disorders and hence the DSM-IV. Brain surgeons who want to remove a tumor from the brain first make sure they exactly pinpoint the location of this tumor by employing brain-imaging techniques. Of course they do not simply rely on behavior to undertake such surgery. So why do we still mainly use behavior in psychiatry to guide our treatments? Engaging in a direct interaction with the brain (e.g., medication, neurofeedback, rTMS) requires knowledge about the current status of the brain. A new development along these lines is the development of Personalized Medicine. In this area the goal is to prescribe *the right treatment, for the right person at the right time* as opposed to the current one-size-fits-all treatments. Genotypic and phenotypic information or “Biomarkers” lie at the basis of Personalized Medicine. Usually in this context genetic markers are considered that can predict effects of medication, such as the classical example of herceptin. Herceptin is a drug used for breast cancer treatment, but only for patients showing an over-expression for a specific protein better known as human epidermal growth factor receptor 2 (HER2) (Piccart-Gebhart et al., 2005). 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. Given there is no psychiatric disorder that is completely genetically determined (Hyman, 2007), a strictly genetic approach to Personalized Medicine for psychiatry seems therefore less plausible.

In this context Gordon (2007) proposed the term “neuromarker”, and Johnstone et al. (2005) the term “EEG phenotype” as examples of biomarkers. In another context EEG-vigilance regulation has also been proposed as a state-dependent trait (Hegerl, Olbrich, Schönknecht, & Sander, 2008). The underlying idea behind these concepts is that neuroimaging data such as EEG, fMRI, PET scans etc. can be considered stable phenotypes incorporating both the effects of nature and nurture. This potentially makes such markers ideal candidates as biomarkers, which could predict treatment outcome for treatments such as antidepressants or stimulants, but also for other treatments such as neurofeedback. 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, and 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. In this development the focus is hence more on “prognostics” rather than “diagnostics”. In this chapter we will review the history of EEG and qEEG findings in ADHD and depression and their limitations for this Personalized Medicine approach. Thereafter, we will present two more “theoretically” driven models, which have recently been investigated in more detail and show promise for the further development of EEG-based Personalized Medicine.

HISTORY OF EEG RESEARCH IN ADHD AND DEPRESSION

ADHD

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 et al. (1938) already described an EEG pattern we now call the Frontal Slow 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). The most predominant feature in the group of children resembling most closely the current diagnosis of

ADHD (hyperactive, impulsive, highly variable) were the occurrence of slow waves from one or more regions and an “abnormal EEG” in 83% of the cases. 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). However, it is to be noted that Stevens et al. (1968) earlier stated that the presence or absence of an “abnormal EEG” alone is of little value in predicting clinical or etiological features.

Capute et al. (1968) reported that the most common “abnormality” in MBD was excessive bilateral posterior slowing, which is similar to a slowed alpha peak frequency. In this regard it is also 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 a true slow occipital rhythm. 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 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 alpha peak frequency rather than to frontal excess slow activity.

Paroxysmal EEG Abnormalities

Part of the above mentioned “abnormal EEG findings” consist of the so-called “paroxysmal” or “epileptiform discharges”. The estimated incidences of paroxysmal EEG in some ADHD groups were around 12–13% (Capute et al., 1968; Satterfield et al., 1973) to approximately 30% (Hughes et al., 2000), which are high as compared to 1–2% in normal populations (Goodwin, 1947; Richter, Zimmerman, Raichle, & Liske, 1971). Note that these people did not suffer from epilepsy, but simply exhibited a paroxysmal EEG in the absence of seizures. The exact implications of such 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-Buchthal, Buchthal, 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. This at least suggests such an EEG pattern might have implications for behavior; however, more research is required to investigate that.

The Era of Computerized EEG Analysis

With the introduction of qEEG and computerized EEG analysis many more studies have been carried out investigating the neurophysiology of ADHD. The introduction of computerized EEG made EEG analysis much easier since many analyses could be performed in an automated fashion.

“Excess Theta” and “Theta/Beta Ratio”

The most consistent findings reported in the literature are those of increased absolute power in theta (Bresnahan, Anderson, & Barry, 1999; Chabot & Serfontein, 1996; Clarke, Barry, McCarthy, & Selikowitz, 1998;¹ Clarke, Barry, McCarthy, & Selikowitz, 2001c; 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 et al., 2001c; Kuperman, Johnson, Arndt, Lindgren, & Wolraich, 1996; Matsuura et al., 1993).

Lubar in 1991 laid the foundation for the concept of the theta/beta power ratio as a measure that could discriminate “normal” children from children with ADD, learning disorders and ADHD (Lubar, 1991). This measure was investigated further by many others, with the clearest replication from Monastra et al. (1999) who demonstrated in a multicenter study in 482 subjects and 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 by Lubar many groups have further investigated the EEG in ADHD, mainly using computerized power

¹ Clarke et al., 1998 and Clarke et al. (2001c) excluded an “excess beta group” from their analysis, which means that they excluded about 20% of children with ADHD thereby potentially biasing their results.

spectral EEG analysis (FFT) and coherence. Furthermore, Boutros, Fraenkel, & Feingold (2005), using a meta-analysis incorporating more than 1100 subjects with ADHD/ADD, concluded that increased theta activity in ADHD is a robust enough finding to warrant further development as a diagnostic test or biomarker for ADHD, with data suggesting that relative theta power is an even stronger predictor.

In contrast to the results described in the previous section, almost none of the recent studies reports on alpha peak frequency, but only on spectral power measures in ADHD, whereas from this old research clear relations have been reported between the slowing of this APF and behavioral measures such as hyperactivity (Stevens et al., 1968). As indicated by Steriade, Gloor, Linás, Lopes de Silva, and Mesulam (1990), theta may be a slowing down of alpha activity, suggesting that perhaps the often-reported excess theta consists of both a slowed alpha peak frequency and real excess slow activity. In Figure 4.2, this is illustrated in detail. This

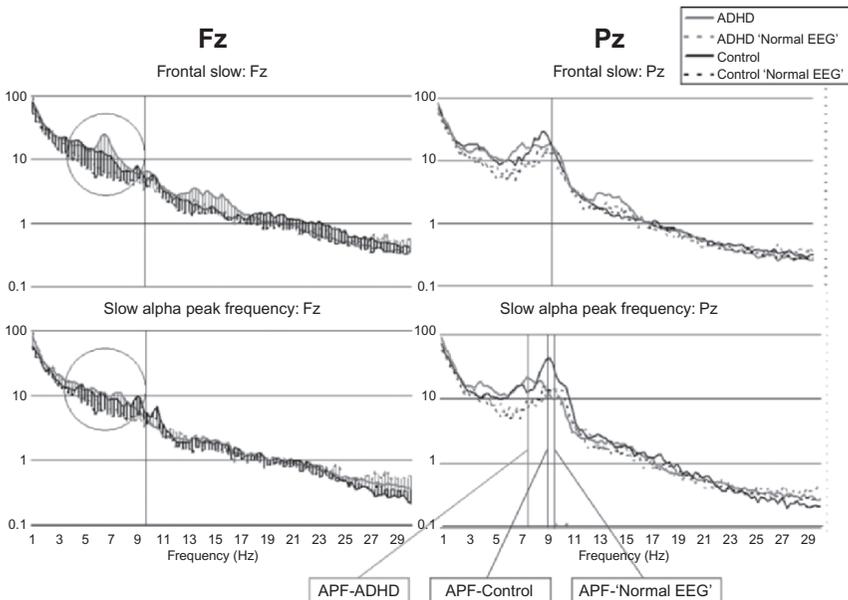


Figure 4.2 (See Color Plate Section) This figure clearly shows that the sub-group with a slowed alpha peak frequency (bottom), present parietally, also show elevated “theta EEG power” at frontal sites. However, this is not true “frontal slow”, but simply the effect of the slowed alpha peak frequency. 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 later with respect to treatment outcome to stimulant medication. (From Arns, Gunkelman, Breteler, & Spronk (2008); reproduced with permission.)

figure shows the spectral content of ADHD children and data from a control group 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 APF 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 APF.

In another study by Lansbergen, Arns, van Dongen-Boomsma, Spronk, & Buitelaar (in press) this was further tested. They calculated the theta/beta ratio in a group of 49 ADHD children and 49 matched controls using both fixed frequency bands and also using individualized EEG frequency bands based on the approach suggested by Klimesch (1999). In this study a significantly deviating theta/beta ratio was only found for the “fixed” EEG frequency bands, but there was no significant difference when the individualized EEG frequency bands were employed, further demonstrating that most of the above-reported studies have indeed been picking up both real elevated theta, but also patients with a slow APF which are two neurophysiologically very different groups. Therefore, although the theta/beta ratio and the “excess theta” can discriminate a group of children with ADHD very well from healthy controls, this measure is probably *not a specific* measure since they incorporate different subtypes of ADHD. So from a Personalized Medicine approach this is not optimal, since it is expected that these sub-types respond differentially to medication as well, which will be clearly demonstrated later.

Increased or Decreased Beta?

The literature is less consistent about the decreased absolute beta in ADHD (Callaway, Halliday, & Naylor, 1983; Dykman, Ackerman, Oglesby, & Holcomb, 1982; Mann et al., 1992; Matsuura et al., 1993). This was not found in several other studies (Barry, Clarke, Johnstone, & Brown, 2009; Clarke et al., 2001c; Lazzaro et al., 1999; Lazzaro et al., 1998) and was found actually to be increased in one study (Kuperman et al., 1996). Furthermore, some studies have also reported a specific subgroup in ADHD with excess beta ranging from 13% (Chabot, Merkin, Wood, Davenport, & Serfontein, 1996) to 20% (Clarke et al., 1998; Clarke, Barry, McCarthy & Selikowitz, 2001b), and most prevalent in

males with ADHD. Clarke et al. (2001a) also reported that about 10% of the excess beta group showed beta spindles, and Arns et al. reported that 16% had beta spindles (Arns et al., 2008). In summary, several studies point to the existence of an ADHD sub-group with excess beta.

In general, minor differences have been found in 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, Clarke & Johnstone, 2003; Chabot et al., 1996).

EEG as a Prognostic Tool: Treatment Prediction in ADHD

Satterfield and colleagues (1971, 1973) 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 generally that abnormal EEG findings could be considered a predictor for positive treatment outcome (Satterfield et al., 1973). Chabot et al. (Chabot, diMichele, 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 lower response and a higher probability of a negative 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 (emphasis added)”. Note the mention 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, Barry, McCarthy, & Selikowitz (2002a, 2002b) and Suffin and Emory (1995) showed that in ADHD and ADD good responders to stimulant medication were characterized by increased theta and theta/beta ratios. Clarke et al. (2003), however, showed that an excess beta group also responded well to stimulants, in agreement with Chabot et al. (1999). They noted, however, that there were few EEG normalizations. In line with this, Hermens et al. (2005) showed that increased beta was related to better treatment outcome in ADHD.

As pointed out earlier and demonstrated in Figure 4.2, Arns et al. (2008) separated a frontal slow wave group from a slowed alpha peak frequency group, but most importantly demonstrated that only the frontal slow group responded to stimulant medication, whereas the slowed alpha

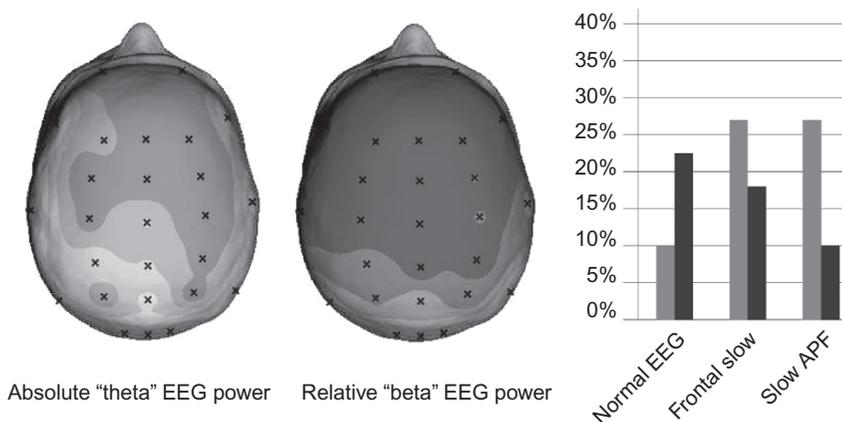


Figure 4.3 (See Color Plate Section) The averaged brain activity of 275 ADHD patients compared to a matched control group. The figure left shows the increased theta ($p < 0.0001$) and right the decreased relative beta power ($p < 0.0001$). Note the fronto-central localization. The graph on the right shows that when inspecting the individual data sets only 25% of children with ADHD (red) indeed exhibit “real frontal slow” or frontal theta. Finally, about the same percentage exhibit a slow APF pattern, which after filtering will show up as “theta” but in fact is alpha, as explained below.

peak frequency group did not respond (Arns et al., 2008). These results further demonstrate that many of the previous studies reporting on frontal theta have mixed up frontal slow and slowed alpha peak frequency groups, as illustrated in Figure 4.3. Furthermore, this finding also helps explain the above contradictory findings between Chabot et al. (1999, 2001) versus the results from Clarke et al. (2002a, 2002b) and Suffin and Emory (1995).

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 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, where they consider “approach” and “withdrawal” as the

essential basis for this asymmetry: “The approach system facilitates 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 such as those involving manipulation of frontal EEG asymmetry by neurofeedback (Allen, Harmon-Jones, & Cavender, 2001; Baehr, Rosenfeld, & Baehr, 1997). Besides these frontal deficits they 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 that require the decoding of non-verbal, expressive behavior (Henriques & Davidson, 1990).

In the often-cited Henriques and Davidson paper researchers used data from 15 depressed subjects and 13 controls (Henriques & Davidson, 1991). They reported significant differences in alpha asymmetry between depressive patients and controls, with medium *p*-values ($p = 0.2; 0.3$). As can be clearly seen in Figure 4.4, 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 in Henriques & Davidson, (1990), showing the individual data. This clearly demonstrates that these data are unusable for diagnostic and/or prognostic purposes, which is also acknowledged by Davidson (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 two occasions (separated by weeks) in their more

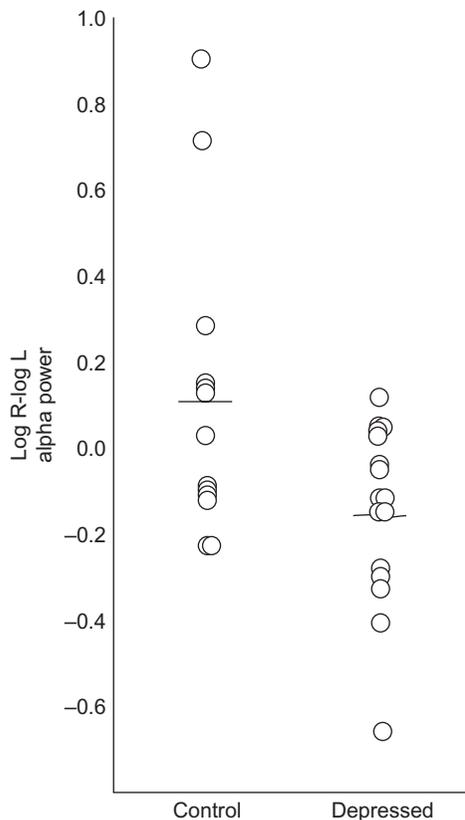


Figure 4.4 This figure shows the initial results from the Henriques and Davidson paper (1990) demonstrating the differences in “frontal alpha asymmetry” between healthy controls and depressed subjects. Note the large overlap between these two groups. They reported that 2/15 normals and 1/15 depressive differed significantly from the other group. These findings demonstrate that alpha asymmetry is not likely to be of clinical use when applied to individual patients, but only useful in group-averaged data. (From Henriques & Davidson, 1990; reproduced with permission.)

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 (Henriques & Davidson, 1991). 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).

A deviating alpha asymmetry is also found in previously depressed patients no longer meeting criteria for depression (Henriques & Davidson, 1990), suggesting that frontal alpha asymmetry could be considered a stable trait rather than a state-marker for depression. (Or, more specifically as Davidson phrased it: “that individual differences in prefrontal asymmetry are most appropriately viewed as diatheses that bias a person’s affective style, and then in turn modulate an individual’s vulnerability to develop depression ...” [Davidson, 1998].) 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). This was supported empirically by Hagemann, Naumann, & Thayer (2001), who found that about 60% of the variance was explained by a latent trait and about 40% was due to state-like fluctuations. Allen, Urry, Hitt, & Coan (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, Bar-Ziv, van Praag, & Glicksohn, 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 across different referencing procedures. 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., sex of the experimenter in relation to the sex of the subject, montages, etc.) and for a review of structural skull deviations and their potential of confounding frontal alpha asymmetry variables, see Myslobodsky, Coppola, & Weinberger (1991).

Alpha power is traditionally seen as an occipital-parietal EEG rhythm, and is most often maximal at these locations. As Hagemann et al. (2001) suggest, the above-mentioned contradictory validity ratings 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 to result into a reliable measurement 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).

EEG as a Prognostic Tool: Treatment Prediction in Depression

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 2001 Bruder et al. investigated the use of alpha asymmetry and dichotic listening tasks to predict treatment outcomes to SSRIs (selective serotonin reuptake inhibitors) and found that non-responders showed more right-frontal activation as compared to responders which seemed to be a gender specific effect (for females only). Few, if any other studies have been reported on the prognostic use of alpha asymmetry in depression. Other authors have used EEG-derived measures such as EEG cordance (Leuchter et al., 2009) and ERP-derived measures (loudness intensity dependence [LDAEP]) (Hegerl, Gallinat & Juckel, 2001) to predict treatment outcome to antidepressants; however these are beyond the scope of this chapter. In general, there are no reliable EEG-based predictors that can predict treatment outcome to antidepressants based on pre-treatment EEG and 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, 2010).

A relatively new treatment approach for depression, which is largely based on the frontal asymmetry hypothesis, is rTMS or repetitive transcranial magnetic stimulation. This treatment usually focuses on “stimulating” the left frontal cortex or “inhibiting” the right frontal cortex. For a full overview of details also see Chapter 10 by Spronk, Arns, and Fitzgerald in this volume.

Conclusion: Averaged Group Data vs. Individual Client Data

As has been clearly shown above, both the excess theta and the theta/beta ratio in ADHD and the frontal alpha asymmetry in depression, show a good correspondence to their respective DSM diagnosis, i.e., in *groups* of patients with the disorder these markers are usually found. However, it was also clearly shown that these measures have limited use for individualized or personalized approaches when the goal is to personalize treatment given their (a) non-specificity (“theta” EEG power comprised of two distinct sub-types, namely slow APF and frontal slow) or their (b) underrepresentation on the individual level (only 1 in 15 depressives differing significantly on their frontal alpha asymmetry as compared to a control group).

Influence of Vigilance/Arousal

In the above sections on the theta/beta ratio and alpha asymmetry there is another aspect, not yet addressed, which deserves more attention. Many studies use different lengths of EEG recordings. In the ADHD studies the recording lengths for EEG data vary between 2 minutes to over 20 minutes. All studies from the group of Adam Clarke (Clarke et al., 1998; Clarke et al., 2001a, 2001b, 2001d; Clarke et al., 2002a, 2002b), for example, have collected 20 minutes of eyes-closed EEG and selected a 1-minute EEG from these 20 minutes for final analysis (Clarke, personal communication). The studies by Chabot also consisted of 20–30 minutes eyes-closed EEG, whereas others have shorter recording times only during eyes-open (e.g. Bresnahan et al., 1999; Lazzaro et al., 1998, 1999).

Furthermore, for frontal alpha asymmetry it was reported that studies measuring short EEG segments (2–3 min) more often find the expected alpha asymmetry as compared to studies measuring longer EEG segments (e.g. 8 min) (Davidson, 1998; Reid et al., 1998). Bruder et al. (2001) stated:

One possibility is that hemispheric asymmetry differences between fluoxetine responders and non-responders may depend upon level of arousal. Eyes closed during resting EEG is the least arousing condition, whereas eyes open leads to an increase in arousal and dichotic listening requires active task performance ...

thus hinting at a potential role of vigilance.

In all these studies the “EEG dynamics” have not been investigated, but accumulated EEG power across a full record has been used. Therefore, we will now address the EEG Vigilance model (Bente, 1964) in more detail to demonstrate potential value of studying EEG dynamics during eyes closed conditions. This might help explain some of the contradictory findings, and, perhaps above all, provide a more coherent and personalized framework for the discovery and interpretation of EEG findings with prognostic value.

EEG AND qEEG: MODELS AND THEORY

In the following sections we will explain in more detail the EEG Vigilance model, which is a theory-driven approach, and one that has been around since the first reports by Dieter Bente (1964). It has roots in the writings of Loomis, Harvey, and Hobart (1937) and was modified by Roth (1961).

After that we will address a more recently published and employed qEEG model, namely the EEG Phenotype model by Johnstone, Gunkelman, & Lunt (2005).

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 auto-stabilization 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 as an autoregulatory behavior. The proposed concept of vigilance autostabilization behavior is related to earlier theories of brain function (Bente, 1964; Ulrich & Frick, 1986; Wundt, 1874), personality (Eysenck, 1990) and sensation-seeking (Zuckerman, 1985).

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 electroencephalogram (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. (later modified by Roth (1961), Bente et al. (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 confirmed by research:

- 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 (1937).
- Alpha power anteriorization 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).
- Low voltage EEG is increasingly observed during lower vigilance stages. The alpha rhythm disappears (alpha drop-out) and beta power increases (De Gennaro, Ferrara & Bertini, 2001; Merica & Fortune, 2004; Tanaka, Hayashi, & Hori, 1996, 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.
- Increased delta and theta activity is observed in parallel with increasing subjective drowsiness (Strijkstra, Beersma, Drayer, Halbesma, & Daan, 2003; Tanaka et al., 1996, 1997), corresponding to vigilance stages B2 and B3 (Roth, 1961).
- 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 (Figure 4.5) 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 2-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

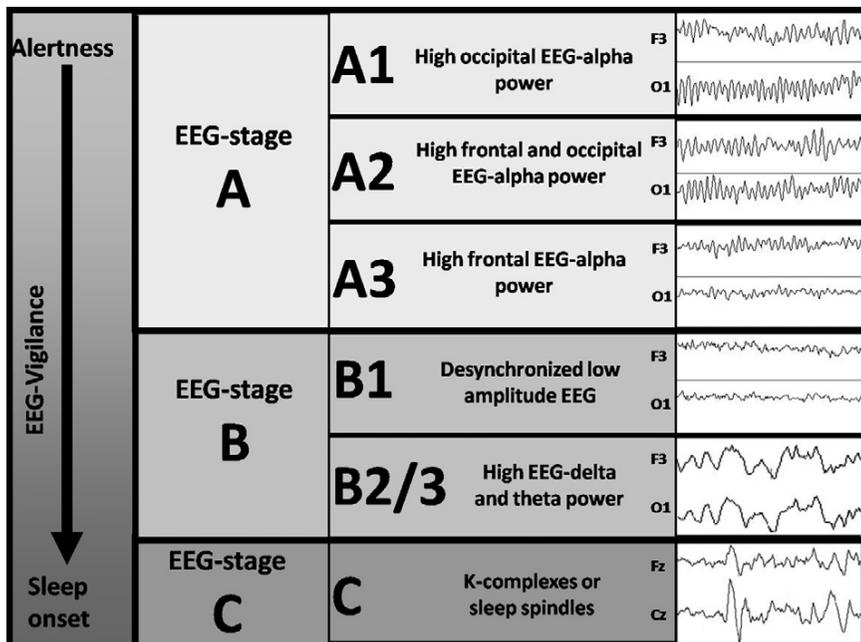


Figure 4.5 EEG-vigilance stages on the continuum from high to low vigilance levels (left column). The main criteria of the EEG-vigilance classification algorithm are given for six distinct EEG-vigilance stages (middle columns). Examples of native two-second EEG curves are presented in the right column.

different regions of interest (ROIs). The segment length is technically not restricted to a minimum duration because the power is computed by complex demodulation instead of Fourier transformation with its reciprocal relationship between segment length and usable frequency resolution.

Validation of EEG Vigilance

EEG Vigilance and the Autonomous Nervous System

Further evidence for the validity of the EEG-vigilance concept comes from results of studies concerning the functional level of the autonomic nervous system (ANS). Its two counteracting parts, the sympathetic and the parasympathetic branch, regulate homeostatic processes for adapting the organism to actual needs, e.g. increased blood flow and sweating during a fight-or-flight reaction in case of danger (increased sympathetic tone) or decreased breathing frequency and increased metabolic activity

during the resting phase (increased parasympathetic tone). It was found that average heart rates decreased from stage A1 with 67.22 beats per minute (bpm) to stage A2 with 65.31 bpm, stage A3 with 64.54 bpm, stage B1 with 63.28 bpm and stage B2/3 with 61.06 bpm. The heart beat rate related to vigilance stage A was significantly larger than that during stage B ($T = 2.90$, $p < 0.02$). Comparing the heart beat rate during the sub-stages of “vigilance stage A” and “vigilance stage B”, respectively, a significantly higher rate during B1 versus B2/3 was found ($T = 2.92$, $p < 0.02$). The comparison between sub-stages A1 and A3 failed to be significant after correction for the three multiple t-tests, but there was a trend towards a higher heart beat rate during vigilance stage A1 versus A3 ($T = 2.38$, $p < 0.04$). These results suggest that a decrease of the global functional brain levels, as assessable by VIGALL goes in parallel with decreased sympathetic and increased parasympathetic activity.

Switching Between Different EEG-Vigilance Stages

The EEG-vigilance algorithm and the underlying concept imply that decline of vigilance during rest follows a certain order from high to low vigilance stages. Hence it would be expected that switches between neighboring stages occur more often than switches to more distant stages. The analysis of 15 resting EEGs (Olbrich et al., 2009) showed that the real transition probabilities (rTP) of all switches between vigilance stages differed indeed from the expected transition probabilities (eTP) (see Figure 4.6). 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.

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 two 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 4.7 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 in the figure – namely the “rigid regulation” and the “labile regulation”. The first example of rigid regulation is characterized

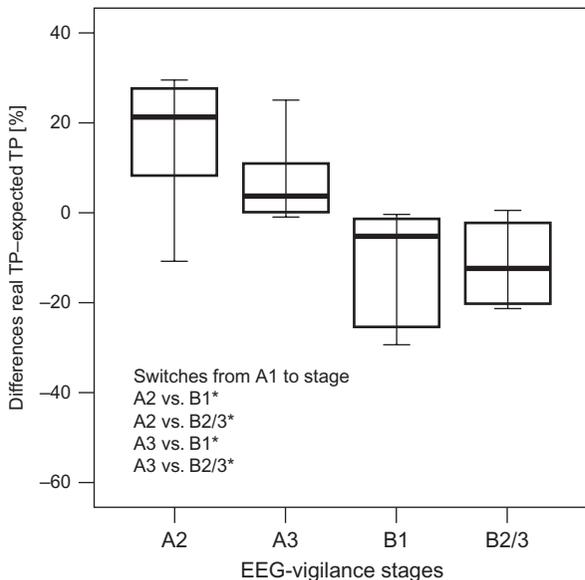


Figure 4.6 The differences between real (rTP) and expected (eTP) transition probabilities for stage A1 were significantly higher for switches to stages A2 and A3 than for switches to stages B1 and B2/3. This indicates that vigilance decline is a more or less homogeneous process with switches between neighboring EEG-vigilance stages occurring more often than switches between distant vigilance stages. (After Olbrich et al., 2009.)

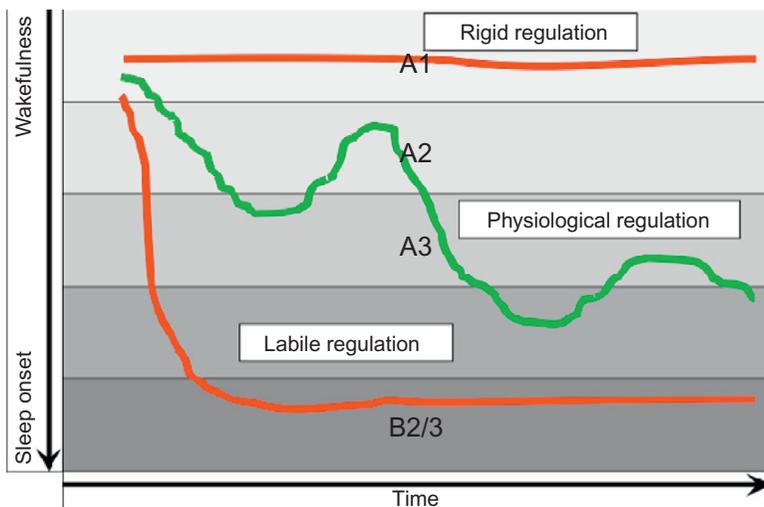


Figure 4.7 The different modes of vigilance regulation, namely the rigid regulation, a physiological or “normal” regulation, and a labile vigilance regulation.

by an inability to downregulate one's vigilance level and such individuals might avoid additional external stimulation and withdraw themselves as autoregulatory behavior. This is a behavioral pattern that 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 to 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. This behavioral pattern matches the behavior also seen in ADHD and mania.

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, 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 (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 (Barbini, Bertelli, Colombo & Smeraldi, 1996; 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 (Hegerl et al., 2008). 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 psychostimulants reported an improvement within one or two hours of

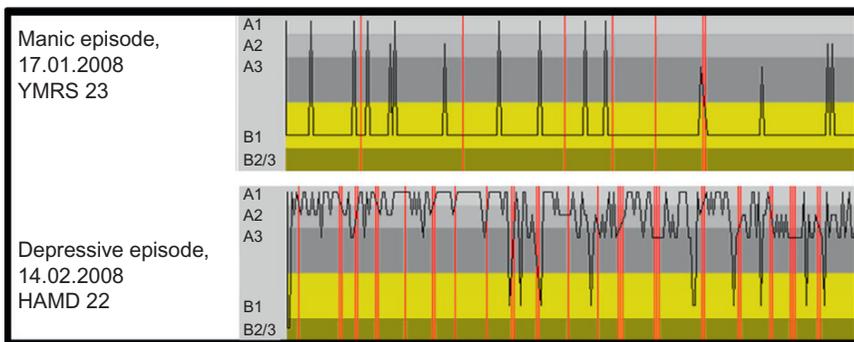


Figure 4.8 Time course of EEG-vigilance stages for consecutive 2-second segments of a 10-minute resting EEG in a patient with bipolar affective disorder during a manic episode (top: Young Mania Rating Scale 23) and during depression (bottom: Hamilton Depression Score 22). Labile vigilance regulation is found during the manic state while during depression the vigilance level does not drop to low vigilance stages. Vertical lines mark segments with artifacts.

first dose (Beckmann & Heinemann, 1976; Brown & Mueller, 1979; Bschor et al., 2001).

In contrast to the unstable vigilance regulation in mania, a hyperstable vigilance regulation may be observed during depressive episodes (Ulrich, 1994). 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 4.8 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 shows 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.

Vigilance Regulation in Attention Deficit Hyperactivity Disorder (ADHD)

Support for an unstable vigilance regulation in ADHD is provided by the fact that this disorder is associated with sleepiness and shortened mean sleep latency in the Multiple Sleep Latency Test, a finding that is not explained by differences in preceding nocturnal sleep (Golan, Shahar, Ravid, & Pillar, 2004). Furthermore, there is convincing empirical evidence that

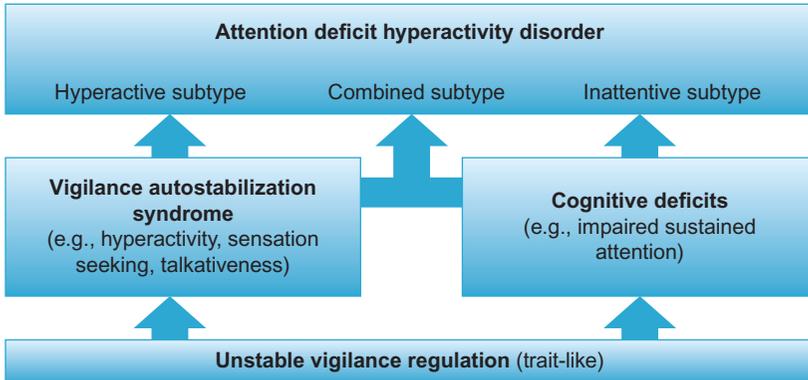


Figure 4.9 Overview of the relation between an unstable vigilance regulation and the behavioral symptoms of ADHD. (Adapted from Hegerl, Sander, Olbrich, & Schoenknecht, 2009.)

disorders affecting sleep quality (e.g. restless legs syndrome, periodic limb movement syndrome) are associated with pediatric ADHD or increased ADHD severity (e.g. Chervin et al., 2002). Also, ADHD-like behavior can be induced in children by sleep restriction (Fallone, Acebo, Arnedt, Seifer, & Carskadon, 2001; Golan et al., 2004) and improved by reducing sleep deficits (Dahl, Pelham, & Wierson, 1991).

Taken together, these data suggest that a labile vigilance regulation is a pathogenetic 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 4.9. Therefore, the well-documented effectiveness of psychostimulants in pediatric ADHD (Pliszka, 2007) could be explained by their vigilance stabilizing property.

In another study Sander et al. (2010), using the same data as Arns et al. (2008), directly investigated EEG-vigilance regulation in children with ADHD, and its relationship to treatment outcome after stimulant medication. In Figure 4.10 the amount of time spent per vigilance stage is plotted.

As hypothesized, the results show that ADHD patients spent significantly less time in A1-stages than controls, and compared to controls tended to remain longer in A2-stages, suggesting children with ADHD indeed showed lower EEG vigilance. Comparable results were found when age was included as a covariate. Furthermore, when comparing the percentage rate of stage-switches (corrected for switches into, between, and out of segments

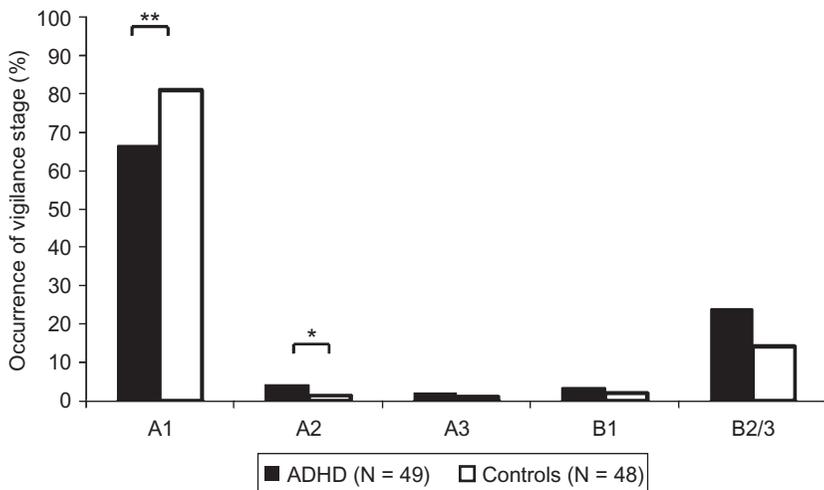


Figure 4.10 Percentage occurrence of vigilance stages A1, A2, and B2/3 in ADHD-patients (black) compared to healthy controls (white) during 2 minutes of resting EEG with closed eyes. The ADHD patients showed more A2 and less A1 stages, suggesting an unstable or labile vigilance regulation. (After Sander et al., 2010.)

containing artifacts), ADHD patients were shown to switch between different vigilance stages more often than controls (ADHD: 26.02%; Controls: 19.09%), indicating a less stable vigilance regulation in ADHD.

Subjects were also classified according to their “predominant EEG vigilance stage” over the entire recording period. Thirty-eight subjects in the ADHD group (77.6%) and 43 subjects 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 subject from both groups was classified as “B1-type”. Although the trends were in the expected direction (higher percentage of ADHD children with lower EEG vigilance), no significant differences between the ADHD and control group were found. The relationship between the “predominant EEG vigilance stage” and treatment outcome after stimulant medication was investigated as can be seen in Figure 4.11. The “low vigilance” group consisted of the ADHD children with predominantly B stages in their EEG whereas the “high vigilance” group consisted of the ADHD children with predominantly A stages in the EEG. The “low vigilance” group achieved worse pre-treatment results as compared to the “high vigilance” group on all continuous performance test (CPT) scores (slower mean reaction time with less standard deviation, more false positives, false negatives, and total errors) and, after

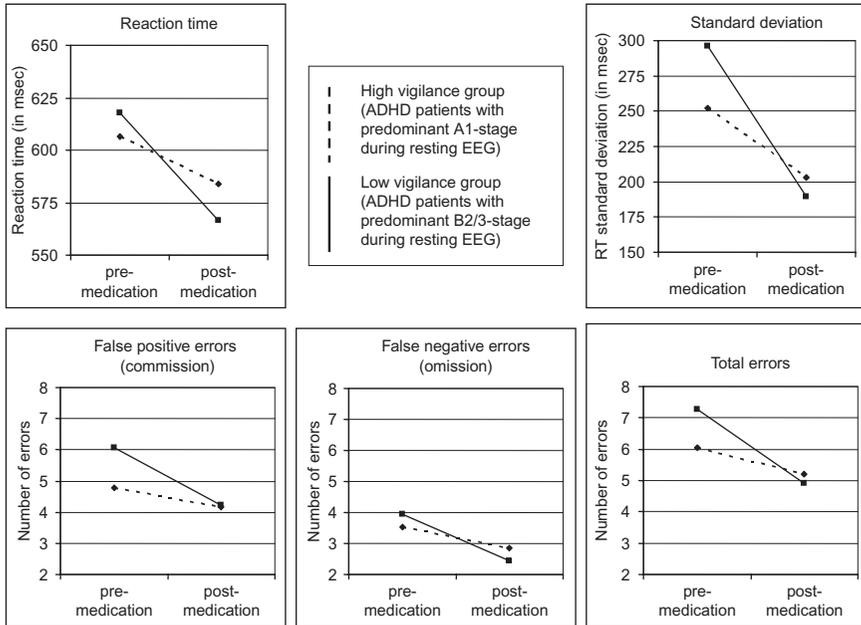


Figure 4.11 Results of the ADHD group on the continuous performance test (CPT). Subjects performed the CPT in non-medicated state (pre-treatment) and after at least 4 weeks of medication with stimulants (methylphenidate, dexamphetamine). Shown separately are the results of those ADHD patients whose resting EEG showed signs of an unstable vigilance (low vigilance group, N = 10), resulting in a greater proportion of time spent in lower vigilance stages, compared to those ADHD patients who exhibited predominantly higher A1-stages during the 2 minutes of resting EEG (high vigilance group, N = 30). (After Sander et al., 2010.)

stimulant medication, improved most on all scores, resulting in better post-treatment performance as compared to the “high vigilance” group (see Figure 4.11). 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.

In this study it was confirmed that ADHD patients spent less time in stages of higher vigilance (A1) and demonstrated more fluctuations in vigilance levels, seen as a higher number of stage switches. In general, those ADHD patients who at baseline demonstrated more signs of an unstable vigilance achieved numerically worse results on the CPT during the baseline condition. After 4 weeks of medication with methylphenidate or dexamphetamine they tended to improve better than patients who had demonstrated a

higher vigilance level at baseline. The fact that these differences did not reach statistical significance, suggests that the study might have been underpowered concerning this aspect. However, findings suggest that EEG vigilance level is related to initial performance on the CPT, and tends to also predict treatment outcome numerically on most measures.

One important limitation of this study was the brevity of the available EEG data. In usual practice, EEG-vigilance classification is based on recordings of 10 minutes or longer, since differences in vigilance regulation manifest themselves only after sufficient time. By analyzing vigilance during 2 minutes of resting EEG 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 may have been easier to distinguish patients with more or less severe vigilance instability if longer EEG recordings had been available.

EEG PHENOTYPE MODEL

Classifying disorders as being “subtypes” of specific disorders where the subtypes match the various EEG patterns seen in the disorder is a seductive exercise. Though the clustering of EEG patterns together as subtypes may expand our understanding of client response to therapy, it still remains attached to diagnosis based on the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), which is based not on physiology, but on behavior. Unfortunately, DSM classification frequently does not predict therapeutic response by individuals within the DSM grouping (as was explained above in the Personalized Medicine section).

Endophenotypes are an intermediate step between genetics and behavior, which represent the expression or lack of expression of the genetics. In 2005 the second author (J.G.) and associates submitted a paper proposing a set of EEG patterns as “phenotypes” where the genetic links were known, and as “candidate phenotypes” where the linkage to genetics remained unknown (Johnstone et al., 2005). These proposed EEG-based phenotypes are semi-stable states of neurophysiological function, and can be identified from the raw EEG waveforms.

The authors proposed a framework that 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 groupings, and they are observed to cut across

the DSM categories. Unlike the DSM, these phenotypes were observed to predict an individual's response to both neurofeedback and medication approaches to therapy.

Past research involving statistical analysis of electroencephalography (EEG) has documented groupings of EEG/qEEG features within psychiatric populations (John, Prichep, & Almas, 1992). And, extensive experience with clinical EEGs and QEEG across the last four decades has shown that a limited set of EEG patterns characterize the majority of the variance seen in the EEG. The proposed phenotype approach to EEG/qEEG groupings considers phenotypes as an intermediate step between genetics and behaviors, involving expression of both genetic and environmental factors. They are seen as reliable indices of brain function which can help predict response to therapy, whether with medications or with neuro-modulation techniques such as neurofeedback.

Any single phenotype may be seen in a wide variety of DSM groupings, from post-traumatic encephalopathy, to affective- and attentional-related DSM groupings, like depression or ADHD. The very concept of an EEG pattern's being a "subtype" of a specific disorder seems fatally flawed due to the lack of specificity of any of these patterns for any single DSM classification (as was demonstrated above in the examples of excess theta, theta/beta ratio, and frontal alpha asymmetry). It is our opinion that transcending the limited perspective of the DSM through the use of the EEG phenotypes will result in improved outcomes. Of course, this will need to be validated by results of research and clinical practice.

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), showing attentional and affective disorders to respond better to medication related to their EEG pattern than to behavior. 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.

EEG patterns known to be genetically linked provide a databased start for a proposed initial list of EEG phenotypic patterns. The low-voltage fast pattern was shown to have genetic correlates in a recently published study of the EEG in alcoholism (Enoch, White, Harris, Rohrbaugh, & Goldman, 2002), and by others who have identified the genetic link to gene 4's regulation over gamma amino butyric acid (GABA-A) receptors (Bierut et al., 2002) and the serotonergic HTR3B gene (Ducci et al., 2009). Furthermore,

a clear relationship was recently reported between the COMT gene and alpha peak frequency, where the Val/Val genotype showed a 1.4 Hz slower APF as compared to the Met/Met group (Bodenmann et al., 2009).

Another genetically linked EEG pattern was identified in idiopathic epilepsy (Haug et al., 2003). The paroxysmal epileptiform bursts seen in the EEG in these clinical cases may occasionally exceed 400–600 microvolts, with spikes and slow components emerging from a relatively normal background EEG. In a paper surveying genetic factors in epilepsy, Kaneko, Iwasa, Okada, and Hirose (2002) showed that the most common human genetic epilepsies display a complex pattern of inheritance and that the identities of the specific genes are largely unknown, despite recent advances in genetics. They showed the genetic markers associated with certain types of epilepsy, including those with neurodegenerative characteristics and some familial idiopathic epilepsies (Haug et al., 2003). A similar pattern is seen in a group of subjects with benign childhood epilepsy with centro-temporal spikes, found in a small number of cases with *de novo* terminal deletions of a portion of chromosome 1q. This suggests that this chromosomal location could be a potential site for a candidate gene (Vaughn, Greenwood, Aylsworth, & Tennison, 1996).

The listing in Table 4.1 of the candidate phenotype patterns is presented for the reader's convenience, though a reading of the original 2005 article (Johnstone et al., 2005) is advised for more detail regarding implications for neurofeedback or medication response prediction.

One critical point must be remembered when viewing the listing: *the various phenotypes may coexist*. The various combinations and permutations 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.

Inter-rater Reliability

In Arns et al. (2008) the inter-rater reliability for rating the EEG phenotypes between two raters (MA & JG) were investigated in children with ADHD and a matched control group. The inter-rater reliabilities were found to be generally high, as can be seen in Table 4.2. This suggests that these EEG phenotypes can be reliably identified by two well-trained raters, with most Kappa values around 0.90 or better. However, persistent

Table 4.1 A summary of the EEG phenotypes

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

Table 4.2 Number of subjects in the different EEG phenotype groups and the inter-rater reliabilities for the different EEG phenotypes

	ADHD (N)	Controls (N)	Inter-rater reliability
“Normal EEG”	5	11	Kappa: 0.90; p <0.000
Frontal slow	13	9	Kappa: 0.94; p <0.000
Low APF	13	5	Kappa: 0.90; p <0.000
Frontal beta spindles	8	10	Kappa: 0.97; p <0.000
Low voltage	6	1	Kappa: 0.93; p <0.000
Frontal alpha	8	4	Kappa: 0.47; p <0.000
Persistent alpha EO	7	5	Kappa: 0.64; p <0.000
Temporal alpha	5	6	Kappa: 0.89; p <0.000
High APF	3	5	Kappa: 0.94; p <0.000

eyes-open alpha and frontal alpha phenotypes had lower inter-rater reliability. Table 4.2 shows the number of subjects per EEG phenotype subgroup, together with the exact Kappa values. For ADHD 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. For the depression EEG phenotype data the rating was performed blinded to diagnosis and similar effects are found, suggesting that blinding probably did not affect the ratings.

Prevalence of EEG Phenotypes in ADHD and Depression

Figure 4.12 shows the prevalence of the different EEG phenotypes in ADHD (top) and depression (bottom) and in matched normal controls. The depression data are unpublished and are from a group of 113 unmedicated Depressed patients and 121 matched controls and the ADHD data are from Arns et al. (2008). Note that these EEG phenotypes deviate slightly from the originally published phenotypes and that the presence of mu rhythm was also included, whereas this was not part of the original EEG phenotypes and this is in principal considered a normal variant type EEG.

The ADHD group tended to show a higher occurrence of frontal slow, slow APF, and low voltage EEG as compared to the control group. However, the Mann–Whitney test found a significant difference only between the ADHD and control group for the low APF ($p = 0.038$; $Z = -2.076$) and a near significant difference for the low voltage EEG ($p = 0.051$; $Z = -1.951$). The difference for frontal slow was not significant ($p = 0.335$). This lack of effect is probably due to the low subject numbers per sub-group.

For depression, the Mann–Whitney test results showed that only the prevalence for frontal alpha ($p = 0.017$; $Z = -2.385$) and mu at C4 ($p = 0.020$; $Z = -1.707$) were significant between groups. Furthermore, One-Way ANOVA revealed no difference for age. There also was a significant difference in frontal alpha peak frequency ($p = 0.025$; $F = 5.089$; $DF = 1, 214$) between the depressed (9.62 Hz) and non-depressed groups (9.27 Hz), which was not different for Pz ($p = 0.632$; $F = 0.231$; $DF = 1, 225$), indicating the depressed clients had a faster APF at frontal sites.

It is an interesting finding that the prevalence of the different EEG phenotypes is comparable for the ADHD, depression, and control groups, demonstrating that, in principle there are no large fundamental and qualitative differences in the brain activity of these disorders. However, as was already shown in Figure 4.2, the expression of a given EEG phenotype is more deviant for the ADHD group as compared to the control group, indicating the differences have to be sought in the quantitative deviation *within* a respective phenotype, i.e. it is not the “eye color” but the intensity

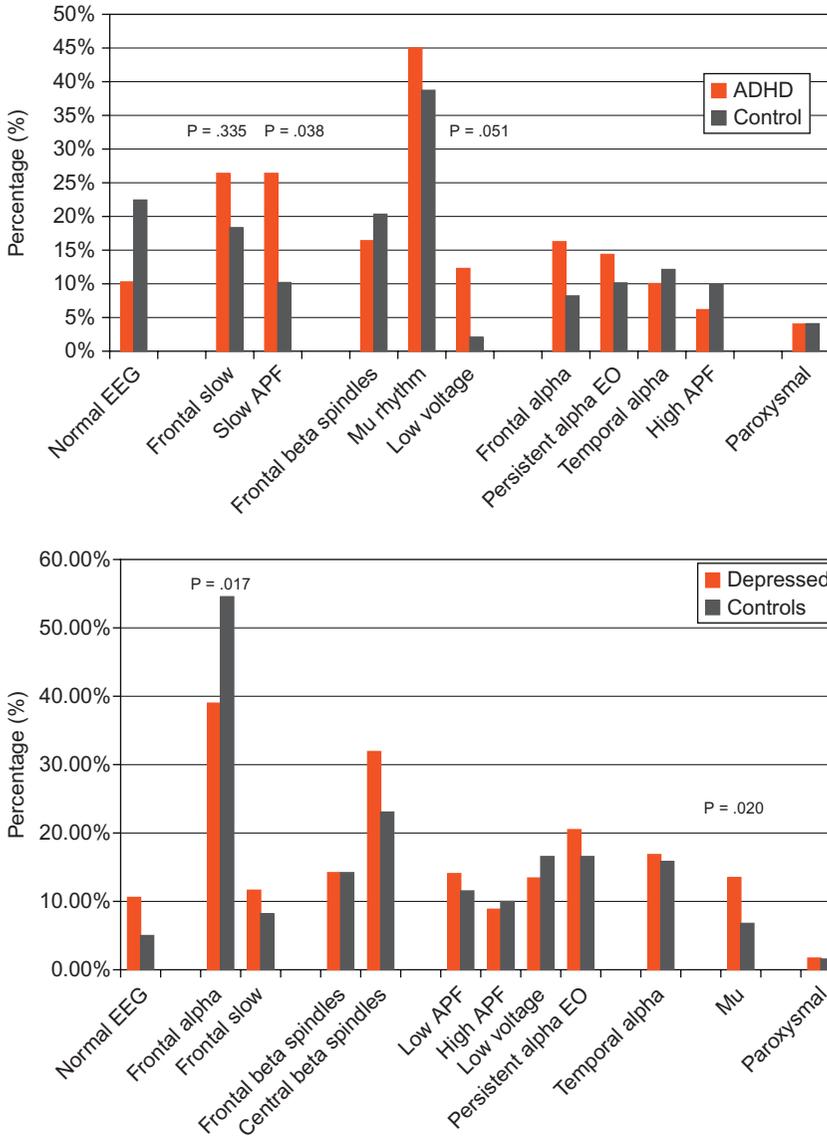


Figure 4.12 The occurrence of the different EEG phenotypes for ADHD (top), depression (bottom) and matched control groups (black). Note the higher occurrence of frontal slow, slow alpha peak frequency, and low voltage EEG in the ADHD group. For depression note the lower prevalence of frontal alpha and the higher prevalence of mu rhythm. Also note that the control group has similar prevalences of most of the EEG phenotypes and for all groups between 2 and 4% display a paroxysmal EEG.

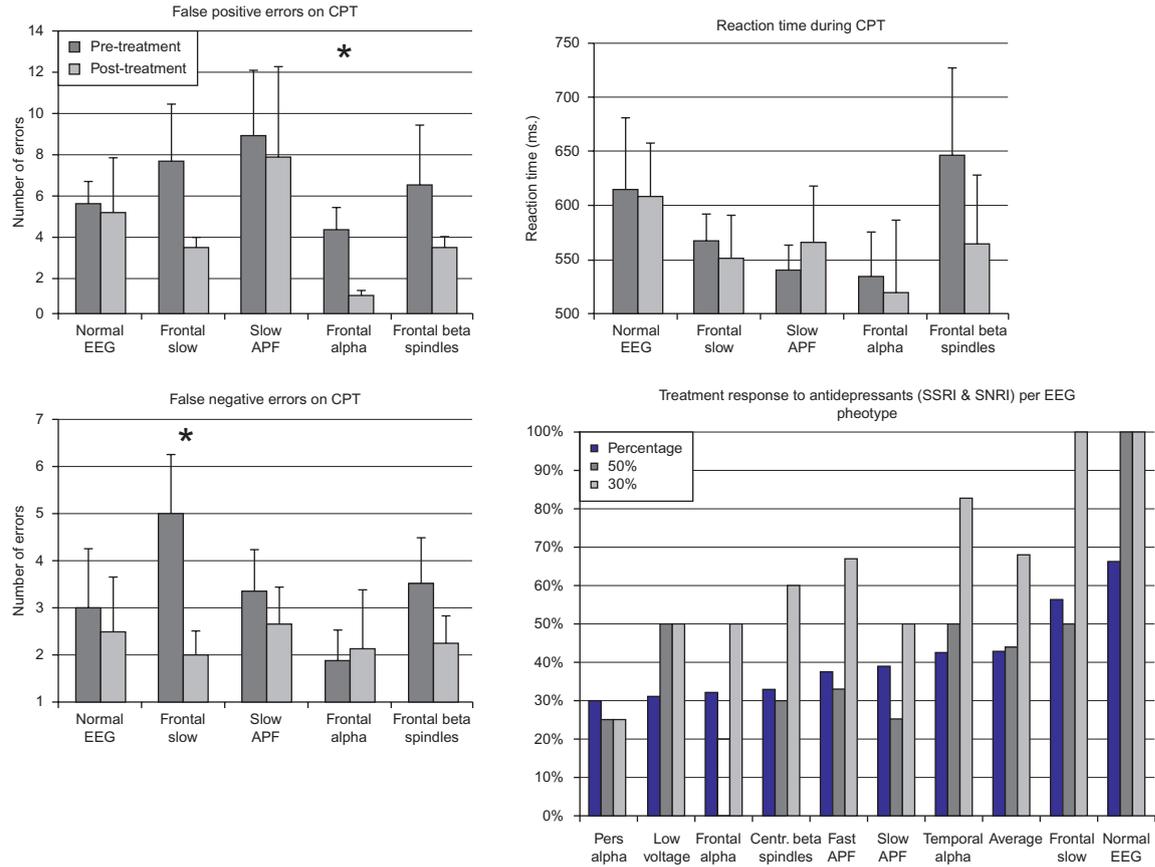


Figure 4.13 Pre-treatment and post-treatment performance for the ADHD (CPT measures: left) and depression (HAM-D measures: right) for EEG phenotypes (ADHD: N = 45; depression N = 27). (* p < 0.05). (ADHD figures from Arns et al., 2008.)

of the eye color that makes the distinction between normal and pathological. Furthermore, as was also demonstrated in Arns et al. (2008), and shown in Figure 4.13, these phenotypes do predict treatment outcome to stimulant medication in ADHD. The group with frontal slow EEG and the group with frontal alpha both responded to stimulant medication, whereas the other groups did not. The frontal slow group also performed worst initially suggesting a relation between their frontal slow EEG and inattention during intake. Importantly, these data also clearly demonstrate that the slowed APF group does not respond to stimulant medication, thereby further emphasizing the need to separate the slow APF from the frontal slow group (as noted above in the theta/beta ratio discussion).

In regard to depression, only a limited sub-sample of 27 subjects' post-treatment HAM-D scores were available. These data are currently published in the *Journal of Affective Disorders* (Spronk et al., 2010) and data suggest for this group an integrative approach employing neuropsychological data, genetic data, and ERP data predicted treatment outcome best. In Figure 4.13 the EEG phenotypes showing the largest decrease in HAM-D scores due to antidepressant medication are shown. Although results have to be treated with caution due to very low subject numbers, these data suggest that the frontal alpha phenotype (a reasonably large sub-group of $N = 10$) does not predict treatment outcome well (in contrast to what would be expected based on work of Suffin & Emory [1995] and others).

EEG PHENOTYPE VS. EEG VIGILANCE: TOWARDS A COHERENT MODEL?

In this chapter we have reviewed the history of EEG findings in ADHD and depression and presented some new data employing the EEG Vigilance model and the EEG Phenotype model. We have pointed out that some of the older concepts such as excess theta, theta/beta ratio, and frontal alpha asymmetry have many limitations such as low specificity and low predictive validity and hence their use in predicting treatment outcome or guiding treatment is limited. Both the EEG Vigilance approach and EEG Phenotype approach have shown some promise in predicting treatment outcome, but have also shown some limitations. Below we discuss the presented data in a somewhat more detailed way and strive to incorporate these results in a more coherent framework with Personalized Medicine as the goal in mind.

Similarities Between EEG Phenotypes and EEG Vigilance

From the previous two sections it should be clear that there are similarities among the qualitatively different EEG phenotypes on one hand and the EEG vigilance stages on the other hand. In the EEG Vigilance model, several “phenotypes” are seen as involving state changes related to vigilance, such as the frontal alpha being similar to vigilance stage A3, or the frontal slow similar to vigilance stage B3. At first sight, this appears to be contradictory; phenotypes are by definition regarded as stable — trait like — biomarkers, which should not be susceptible to state changes. However, the EEG Vigilance model has shown that several of these EEG phenotypes can occur within the same subject as time progresses with corresponding probabilities of switching from stage A1 to stage A2 vigilance. On the other hand Hegerl also proposed EEG-vigilance regulation as a *state-dependent trait* (Hegerl et al., 2008), suggesting the EEG Vigilance approach is not just state-related. Given these similarities in these models we propose that the “EEG phenotype” in this respect can be interpreted as the “predominant vigilance” state of a given person. Below we will demonstrate this further based on the data presented in the previous sections.

In the EEG Phenotype studies, what was classified as a “normal EEG” was in reality an EEG that could not be classified in any of the EEG phenotypes, often consisting of regular and well-developed parieto-occipital alpha, or stage A1 in EEG Vigilance terms.

ADHD

ADHD was characterized by an increased incidence of frontal slow (not significant) and low voltage EEG. Furthermore, there was a tendency for increased frontal alpha and decreased “normal EEG” in ADHD. These results are all in line with the EEG Vigilance results, suggesting a labile vigilance regulation (frontal slow = B3; low voltage = B1; frontal alpha = A3) and normal controls demonstrated higher EEG vigilance (more “normal” EEG = A1). Furthermore, the EEG phenotypes characterized by this “lower vigilance” level (frontal slow = B3 and frontal alpha = A3) also were the only groups responding to stimulant medication.

Depression

Depression was characterized by a lower occurrence of the frontal alpha EEG phenotype and a higher occurrence of a “normal” EEG (not significant) suggesting less A3 and more A1 EEG-vigilance stages. These results

hence support a rigid vigilance regulation in depression (Ulrich, 1994). 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. In line with the EEG vigilance and the auto-stabilization concept it is understandable that depressive symptomatology with sensation avoidance and withdrawal may have the autoregulatory function to counteract the hyperstable vigilance regulation.

Unique Contributions of Both Methods

The unique contribution from the EEG Phenotype model is the identification of a slow APF group, which was shown to be a group that does not respond to stimulant medication. In the EEG Vigilance model APF does not play a role. As a matter of fact the algorithm “personalizes” EEG frequency bands based on the individual APF, thereby ensuring the individual APF does not contaminate the data. Therefore, in ADHD there is a large sub-group of children with a slow APF, who do not respond well to treatment with stimulant medication. Their symptomatology cannot be explained by a labile vigilance regulation and autostabilization behavior. Therefore, it is important that future studies investigate what treatments are best suited for treating this sub-group of ADHD. Neurofeedback in the treatment of ADHD has shown great promise (Arns et al., 2009) but at this moment it is not known if children with a slow APF are also among the children who respond well to neurofeedback. Several studies have employed rTMS at or above the APF with good results in schizophrenia (Jin et al., 2006), in healthy people to improve cognitive function (Klimesch, Sauseng, & Gerloff, 2003) but without an improved effect in depression (Arns, Spronk, & Fitzgerald, 2010). It is obvious that more research is required to find appropriate treatment for patients with a slowed APF.

Some specific EEG phenotypes have not been covered extensively in this chapter, but do deserve further study. For example the beta-spindle or beta excess sub-group – which has been observed in ADHD (Arns et al., 2008; Chabot et al., 1996; Clarke et al., 1998; Clarke et al., 2001b) – rarely has been investigated. And, in depression research cited earlier, it was shown that a very large proportion of the depressive patients (>30%) exhibited beta spindles at Cz and these also tended to respond unfavorably to antidepressant medication (see Figure 4.13). Finally, from many studies

it has become clear that a small sub-group with paroxysmal EEG is found in both patient populations as well as control groups. Although these cannot be considered as status epilepticus, there is some evidence suggesting this brain pattern has behavioral implications (Lennox-Buchthal et al., 1960) and may require a different treatment approach such as anticonvulsants or SMR/SCP neurofeedback.

Whereas the EEG phenotype approach is based on visual inspection of the EEG and hence subject to interpretation, the biggest advantage of the EEG Vigilance approach is that it is a quantified approach using a computer algorithm, and hence may be considered more objective. However, there are no reliable norms or cut-off scores available yet to classify EEG vigilance stages into “normal” or “deviating” values. Furthermore, with the EEG Vigilance approach it is very hard to distinguish the true B1 (alpha drop-out, low-voltage beta stage) stage from a desynchronized EEG due to cognitive processing.

At this time there is no single framework, theory or approach that can be used to interpret all EEG and qEEG findings. In this chapter we attempted to explain a small part of the large spectrum of related findings, and provide a theoretical framework based on the Vigilance model, and its relationship to EEG and behaviors. Obviously, much more research is required to understand the role of psychophysiology (EEG, ERPs) in the future of Personalized Medicine.

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