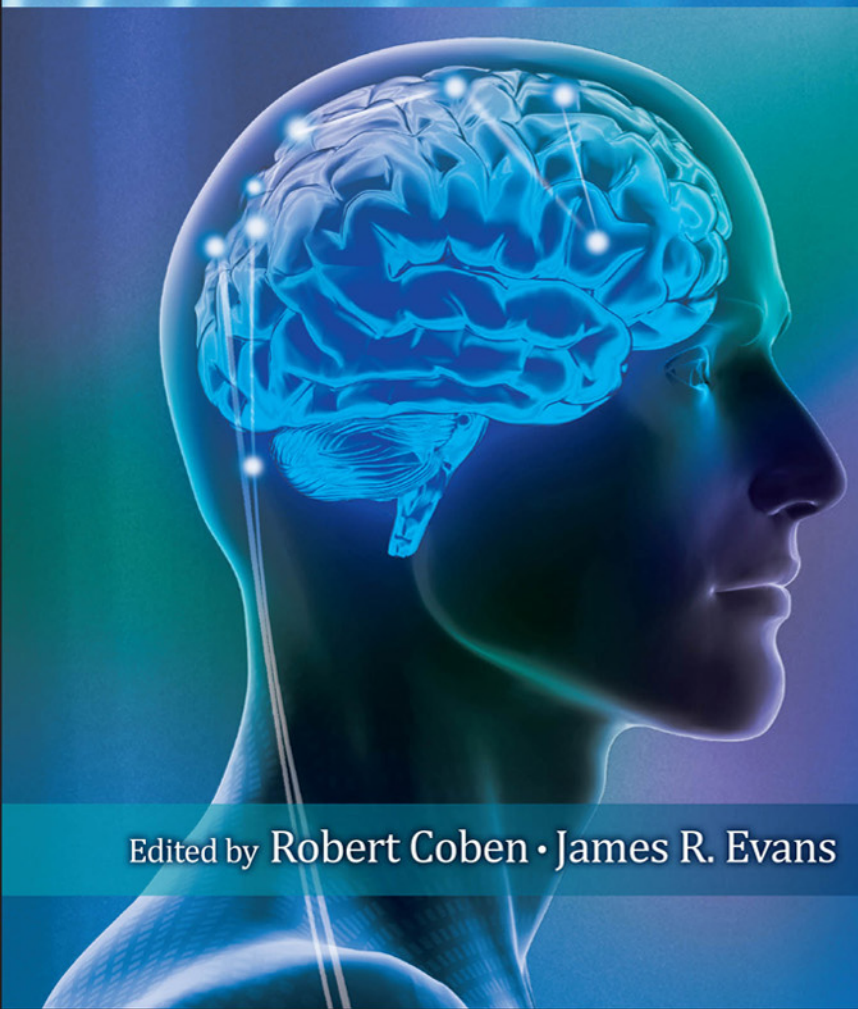
Neurofeedback and Neuromodulation Techniques and Applications



Edited by Robert Coben • James R. Evans

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Edited by

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PREFACE

It was not many years ago that the term "neuromodulation" would have been considered a contradictory term by many – at least in regard to modification of a damaged or dysfunctional central nervous system. Although it generally had been assumed that learning and memory somehow resulted in relatively permanent modifications of brain structure and/or function, the notion persisted that neural function and structure basically were set by genetics and were relatively immune to change. However, within the past couple of decades developments in neuroimaging have enabled scientific research providing evidence of neural plasticity far greater than previously had been imagined. Research on neural plasticity is burgeoning, along with a plethora of scientifically unsubstantiated claims by practitioners from many different professions for "brain-based" methods for remediation of various medical, psychological, and educational problems.

Despite the fact that, until recently, brain plasticity was not a generally accepted concept, for many years there have been remedial approaches where advocates make either explicit or implied claims that their use results in modulation of brain function. Some involve intensive, graduated practice of functions that had been impaired by brain damage, e.g., cognitive rehabilitation. Some involve exposure of clients to various types of stimuli, which usually are rhythmic or of specified frequency (e.g., auditory/visual stimulation with light/sound machines, music therapy). Often this is done with the assumption that rhythms of the brain are entrained or otherwise modified by such exogenous stimuli. Some consider electroshock therapy and transcranial magnetic stimulation to fall into this category. Still others emphasize self-directed activity, such as making precise movements in synchrony with a metronome, or learning self-control of one's brain rhythms (EEG) with the aid of electronic equipment that provides feedback concerning specific aspects of those endogenous rhythms, i.e., EEG biofeedback or neurofeedback. Practitioners of such remedial approaches generally have been marginalized by mainstream medicine, psychology, and education, partially due to the aforementioned belief in immutability of brain structure/function, but also due to perceived, or real, lack of scientific support for efficacy of the methods involved.

It is the editors' opinion that two procedures for neuromodulation hold special promise due to emerging scientific evidence of their enduring

effectiveness with a variety of conditions that are known, or believed, to be due to brain damage and/or dysfunction. These are neurofeedback (NF) and transcranial magnetic stimulation (TMS) in their various forms. Research and clinical practice in NF began in earnest in the 1960s and 1970s, decreased considerably for a while thereafter, but, since the early 1990s, have grown rapidly. There are NF practitioners in many countries around the world, professional NF associations have been formed on three continents, at least ten books have been published dealing primarily with NF, and a professional journal devoted almost exclusively to NF (*Journal of Neurotherapy*) has been published regularly since 1995. Unlike many other groups with claims of facilitation of neuromodulation, the field of NF actively promotes scientific research; and in Australia, Belgium, Canada, England, Germany, the Netherlands, Russia and the United States (as well as some other countries) rigorous scientific research on the mechanisms and efficacy of NF is being actively pursued. The field has evolved far from its beginnings when research participants or patients could be provided feedback concerning only degree of power or percentage of power in a specific EEG frequency band at a single scalp electrode site. Today, feedback can be adjusted to reflect not only EEG power at all frequency/site combinations (now including even ultra low frequencies such as 0.001 Hertz), but also degree of connectivity (e.g., coherence) between all site combinations. Using low resolution electromagnetic tomography (LORETA) procedures, feedback concerning EEG activity in various subcortical areas and cortical networks or "hubs" presently is possible. And, feedback of information concerning activity in cortical and subcortical regions using functional MRI (fMRI) is receiving considerable research attention as an alternative or supplement to EEG biofeedback.

TMS, as usually defined today, is a relative newcomer to the field of neuromodulation. In this approach weak electrical currents are produced in brain tissues by applying rapidly changing magnetic fields to specific scalp locations. In some contrast to NF, which historically has been associated mainly with the field of psychology, TMS primarily is associated with medical research and practice. Also in some contrast to NF, where laboratory discoveries quickly were applied to clinical practice, the field of TMS appears to be moving more cautiously, building upon solid research findings prior to making claims for clinical efficacy. As with NF, scientific research on TMS and its potential clinical uses is occurring in many parts of the world.

Despite growing clinical use of TMS, and especially of NF, and despite emerging research results supporting their efficacy, both remain on the

fringes of medical, psychological, and education practice. Charges of "show me the data" often are made by critics who claim there is no solid scientific support for these approaches. Such evidence exists, but heretofore has been scattered among many different professional journals and other sources. The editors perceived a need for the latest and best theorizing and research findings concerning these neuromodulation techniques to be brought together in a single source to which professionals and other interested persons would have ready access. We believe that this book accomplishes that goal. Although there certainly are others, it could be argued that the chapter authors of this text constitute the majority of the leading NF and TMS theoreticians and scientists of today's world. Several books have been published on the general topic of neuromodulation or specifically on neurofeedback. While a few have chapters detailing supportive research, most were oriented primarily toward theories of efficacy, descriptions of various approaches to NF, and/or details of clinical practice. This book is unique in its emphasis on solid scientific support as it brings together for the first time the neuromodulation fields of NF and TMS.

Rob Coben
Jim Evans

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PART *One*

Neuromodulation: Analysis Techniques

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CHAPTER 1

Use of Quantitative EEG to Predict Therapeutic Outcome in Neuropsychiatric Disorders

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Contents

INTRODUCTION

The thesis of this chapter is that recording and analysis of EEG signals can be used in more productive ways than to identify and categorize behavioral disorders. More recent applications of EEG have been directed toward prediction of outcome of therapeutic intervention. Here we review use of EEG to guide interventions using medication, neurofeedback, and transcranial magnetic stimulation.

Clinical electroencephalography (EEG) typically involves visual examination of multichannel waveform displays by an experienced clinician, usually a neurologist, to detect and characterize seizure disorders and encephalopathies. EEG is the technique of choice for this purpose because it is noninvasive and cost-effective. Further, EEG provides sub-millisecond time resolution so that changes in neurophysiological activity can be studied in detail over time, far exceeding the time resolution available with

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other functional neuroimaging measures such as functional magnetic resonance imaging (fMRI), single positron emission tomography (SPECT), and positron emission tomography (PET). A large body of work documents the general acceptance of EEG in the medical literature (for a comprehensive review see Niedermeyer & Lopes da Silva, 2004).

FOUNDATIONS OF CLINICAL EEG: RELIABILITY

When EEG is read visually by experienced experts there is often considerable lack of agreement on the presence and significance of EEG "abnormalities" and many patterns are considered "normal variants" or "maturational". There have been numerous studies of the inter- and intra-rater reliability in evaluation of EEG signals. An early study by Williams et al. (1985) investigated inter-observer reliability in a random sample of 100 electroencephalographers. Ten-second samples of EEG records were evaluated from 12 EEGs. They concluded that there is considerable variability in EEG interpretation and that characteristics of the individual performing the interpretation were an important factor. Spencer et al. (1985) included review of 144 scalp ictal EEGs from 54 patients by three electroencephalographers. They found approximately 60% agreement in determination of the lobe of the brain involved in seizure onset and approximately 70% agreement for side of onset. They concluded that reliable determination of localization in scalp ictal records requires additional formal criteria.

A more recent study by Williams et al. (1990) showed that prior clinical diagnosis was an influential factor in EEG interpretation. Piccinelli et al. (2005) studied inter-rater reliability in patients with childhood idiopathic epilepsy. They report that experienced electroencephalographers have an "at least moderate agreement" on the majority of features of a wake and sleep EEG. Importantly, they also conclude that agreement was "unsatisfactory" when assessing background EEG activity. Gerber et al. (2008) studied inter-observer agreement in EEG interpretation in critically ill adults. They found moderate agreement "beyond chance" for the presence of rhythmic and periodic patterns. Agreement for other features was "slight to fair".

Boutros et al. (2005) reviewed the basis for determining EEG as "normal", and, specifically, how normal adults are selected for studies using EEG in neuropsychiatric research. They noted that EEG abnormalities have been reported in as many as 57.5% of normal adults (Struve, 1985). The authors defined seven criteria for normalcy, including (1) absence of

systemic disorders with CNS involvement (metabolic, endocrine), (2) absence of traumatic brain injury, childhood neurologic disorders, and dementia, (3) absence of Axis I psychiatric disorders, excluding alcohol and drug abuse, (4) absence of alcohol abuse or dependence, (5) absence of psychotropic medications, (6) absence of first-degree relatives with psychiatric disorders, and (7) Axis II personality disorder or mental subnormality. These criteria were reviewed in 38 studies reported in the literature using visual EEG interpretation. They showed that the majority of studies met no criteria, or only one or two criteria. The overall conclusion is that boundaries for normal, unquantified EEG are poorly defined.

It is clear that because of the ambiguity about the definition of "normal", and lack of agreement among clinicians regarding the presence or absence of significant EEG abnormalities, either epileptic or abnormal rhythmicity, use of qualitative EEG alone does not have sufficient predictive power to effectively guide intervention in patients with neuropsychiatric disorders. The addition of quantitative EEG analysis increases both reliability and predictive power.

QUANTITATIVE EEG

The term "quantitative EEG" (qEEG) refers to quantitative signal analysis of the digitized electroencephalogram. The use of Fourier or Wavelet analysis is most often used to estimate the frequency spectrum. Many studies using qEEG compare an individual pattern of features such as absolute and relative EEG power, coherence, peak alpha frequency, asymmetry, and related measures to a reference database. Statistical deviations from the database can then be examined for clinical significance. A number of such databases are commercially available (see reviews by Johnstone & Gunkelman, 2003; Thatcher & Lubar, 2009). These databases each have strengths and weaknesses but overall were developed taking into account the criteria for normalcy suggested by Boutros et al. (2005), described above.

A number of studies indicate robust test–retest reliability for quantified EEG, and are reviewed below. The excellent reproducibility of findings in qEEG studies argues that the poor reliability seen for qualitative EEG is due to differences in interpretation rather than error of measurement or other technical factors.

An early qEEG reliability study by Fein et al. (1983) investigated the test–retest reliability of EEG spectral analysis in groups of dyslexic and

control children. They measured the coefficient of variation within subjects over two repetitions of 3-minute recordings with eyes closed and with eyes open. This technique showed significant second-to-second variability of EEG without a consistent pattern of effects of group, reference used, task or repetition. EEG spectra were averaged over the 3-minute segment and compared to a similar segment recorded following a battery of behavioral tasks, approximately 4 hours later. Intra-class correlations (ICC) were computed to assess stability comparing the two 3-minute segments. The ICCs were typically above 0.9 for control subjects. Similar analyses with dyslexics showed somewhat lower reliability in specific leads and reference configurations, but EEG spectral profiles also were stable over a 4–5 hour period. These results were consistent for measures of absolute power as well as relative power. The authors conclude that, overall, these data demonstrate a high degree of reliability in EEG spectra in children under well-controlled recording conditions.

A follow-up study (Fein, Galin, Yingling, Johnstone, & Nelson, 1984) with the same subjects indicated that despite differences in recording equipment and procedures, the EEG spectra were found to be highly stable over a period of 1–3 years. Subsequent studies confirm the generally robust test–retest reliability of qEEG analyses (Burgess & Gruzelier, 1993; Fernandez et al., 1993; Gasser, Bacher, & Steinberg, 1985; Harmony et al., 1993; Lund, Sponheim, Iacono, & Clementz, 1995; Salinsky et al., 1991; see also Thatcher, Biver, & North, 2003). It is clear that qEEG evaluation when based on standardized and well-controlled recording and analysis procedures can produce replicable and, therefore, potentially useful clinical results.

The utility of a method for producing valid and useful clinical findings is based on a foundation of accurate and reliable measurement. It is also relevant to address the clinical applications and "intended use" of the method, for example, EEG considered as a valid diagnostic procedure, aiding in placing individuals into distinct diagnostic categories with well-defined behavioral boundaries. Indeed, quantitative EEG has been criticized for not being diagnostic of complex neurobehavioral syndromes and was considered by the American Academy of Neurology to be "investigational for clinical use in post-concussion syndrome, mild or moderate head injury, learning disability, attention disorders, schizophrenia, depression, alcoholism, and drug abuse" (Nuwer, 1997). Many other authors disagree, however, providing evidence that application of qEEG to diagnose psychiatric disorders does have clinical utility (for reviews see Coburn et al., 2006; Hughes & John, 1999).

Clinical applications of qEEG now are also being explored in medication management, development of neurofeedback protocols, and guiding transcranial magnetic stimulation therapy. Visual interpretation of EEG waveforms alone has not been found to be useful in these important applications, likely because of the poor reliability of interpretation, as discussed above. In a recent comprehensive review of the topic, Thatcher (2010) reaches similar conclusions and also suggests that increased reliability allows for better predictive validity. Combining visual examination of the EEG waveforms by an experienced expert with quantitative EEG analyses, however, will likely improve overall predictive accuracy compared to each of these procedures used separately.

An alternate approach to using brain electrical activity to diagnose psychiatric disorders is consideration of individual EEG patterns as "intermediate phenotypes." Johnstone, Gunkelman, & Lunt (2005) suggested that since qEEG patterns are highly reliable and stable and often show a genetic basis, yet are not isomorphic with behavioral categories, these patterns may be useful as predictors of clinical response. Candidate phenotypes have been offered, and will be described in this chapter along with possible intervention strategies for medication and EEG biofeedback (neurofeedback) based on these phenotypes. Such use of qEEG to predict and guide therapeutic outcome is recent, and appears to the authors to be more promising than the often-used clinical diagnostic approach.

Different diagnostic categories are differentially represented in phenotype categories. Further, it should be recognized that individuals may manifest features of several phenotypes, and that features distinguishing phenotypes are on a continuum without distinct boundaries. For example, many children with attention deficit disorder show an excess of frontocentral activity in the theta frequency range, 4–7 Hz. However, not all individuals show this pattern and certain individuals show a pattern of excessive fast activity anteriorly. Therefore, although it is possible to accurately measure the amount of anterior theta or beta activity, these measures are not specifically "diagnostic" of the disorder. It is believed to be more effective to use the neurophysiological markers to guide neurophysiological intervention than to diagnose a behavioral category and use it as a guide.

QUANTITATIVE EEG/ERP AND MEDICATION MANAGEMENT

A large body of literature often referred to as "Pharmaco-EEG" has shown effects of most of the commonly used psychopharmacologic agents

Table 1.1 Effects of common psychiatric medications on EEG

Class	Medications (examples)	Effects on EEG
Psychostimulants	Ritalin, Dexedrine, Adderall	Decreases slow activity (delta and theta frequencies); increases fast activity (beta frequencies)
Benzodiazepines	Xanax, Valium, Ativan	Increased 14–25 Hz Anticonvulsant properties
Barbiturates	Phenobarbitol	Increases delta activity and increases 18–35 Hz beta spindles. High dosage produces "burst-suppression"
Tricyclic antidepressants	Elavil, Tofanil, Norpramin, Sinequan, Pamelor	Increases both slow and fast activity and decreases alpha frequency activity (sedating)
SSRIs	Prozac, Effexor, Zoloft, Luvox, Paxil, Lexipro, Celexa	Produces less delta, decreases alpha, and increases beta (less sedating)
Other antidepressants	Wellbutrin (Zyban)	Reduces seizure threshold, non-sedating
Mood stabilizers (anticyclics)	Lithium, Tegretol	Increases theta frequency activity. Overdose produces marked slowing and triphasic discharges

on most measures of brain electrical activity. The most commonly used psychopharmacologic agents have been shown to have specific effects on EEG. Table 1.1 shows a summary of known medication effects on EEG (for review see Saletu, Anderer, & Saletu-Zyhlarz, 2006).

More recently, quantitative EEG features have been used to predict therapeutic response to medication, and more effectively manage psychiatric medication clinically ("predictive model"). Suffin and Emory (1995) recorded baseline EEG after patients were washed out of all psychoactive medication. Two groups of patients were selected: One group of patients was diagnosed with attentional disorders without affective symptoms and another group with affective disorders without attentional symptoms. These patients were medicated according to standard clinical practice and the Clinical Global Improvement scale (CGI) was used to assess outcome.

There were clear associations between specific EEG features at baseline and effects of medications: Individuals with slow EEG patterns tended to respond better to stimulant medication. Individuals with excessive frontal alpha activity responded better to antidepressant medications and those

with deviations in EEG coherence responded better to anticonvulsants or anticyclics, *independent of clinical diagnosis.* The authors concluded that the pattern of deviations from the reference database was a better predictor of clinical response than was clinical diagnosis. A prospective follow-up study compared clinical outcome with medication selection based on patterns of deviations from a reference database compared to standard clinical practice (Suffin et al., 2007). Clinical outcome was significantly improved using qEEG guidance in medication selection. Based on these findings physicians were encouraged to select psychopharmacologic agents based on similarity with qEEG profiles of known responders to specific agents. The phenotype model, described above, was used by Arns, Gunkelman, Breteler, and Spronk (2008) in a study demonstrating the utility of the intermediate EEG phenotype model in selecting stimulant medications for treatment of children with ADHD.

Use of qEEG methods to guide selection and management of psychiatric medication has been studied extensively, and recently was reviewed by Leuchter, Cook, Hunter, and Korb (2009). These authors consider several EEG features as potential biomarkers of medication response in major depression, including some results from low resolution electromagnetic tomography, LORETA (see also Mulert et al., 2007). LORETA results are consistent with other imaging modalities such as PET, in suggesting that elevated theta activity in anterior cingulate cortex is measurable from prefrontal scalp recording electrodes and can be used as a biomarker for response to antidepressant medication.

Evoked and event-related potentials are related measures based on averaging EEG in response to sensory stimuli or other specific internal or external events. An evoked potential method that shows promise as a biomarker for antidepressant response is the loudness-dependent auditory evoked response (LDAEP). This evoked response originates in primary auditory cortex and appears to be sensitive to central serotonergic activity (Juckel, Molnar, Hegert, Csepe, & Karmos, 1997). When stimuli are presented with increasing intensity, individuals with diminished serotonergic activity show an increased or more sensitive response to increasing auditory stimulus intensity than individuals formerly diagnosed with depression and taking SSRI (selective serotonin reuptake inhibitor) medication. The presence of a strong LDAEP has been shown to predict treatment outcome with antidepressant medication in major depression (Juckel et al., 2007). Juckel et al. (2010) also provide evidence that the mechanism of the LDAEP has a genetic basis.

Auditory evoked potentials have also been used extensively in pharmacologic treatment in schizophrenia. The method most often used in evoked potential studies of schizophrenia is the auditory paired click paradigm, pioneered in the work of Freedman and Adler (see Adler et al., 1982; Freedman et al., 1983). This technique is the subject of a recent review (Patterson et al., 2008). Many studies have found a difference in the amplitude of the response to the first compared to the second click in closely timed paired stimuli, and that this decrement is smaller in schizophrenics. This has been widely interpreted as reflecting defective sensory gating in schizophrenics. There is considerable variability across studies, and the technique is sensitive to a number of technical factors, including electrode location, band pass filtering, number of trials averaged, age, and rules regarding inclusion of the P30 component (the preceding positive peak in the auditory evoked potential waveform).

Olincy et al. (2006) administered a low and a high dose of an α-7 nicotinic agonist to a group of 12 non-smoking schizophrenics and studied changes in the P50 component and neurocognitive performance. The drug produced inhibition of the response to the second click in paired stimuli. Improvements in neurocognitive measures of attention were documented for the low drug dose. This study showed not only the utility of the P50 biomarker in assessing change in the central nervous system associated with a specific agent, but also that the magnitude of changes in response could assist in determining the most effective dose.

Large clinical trials have now been carried out and published on the use of frontal EEG measures to manage antidepressant medications (Leuchter et al., 2009a; Leuchter et al., 2009b). The Biomarkers for Rapid Identification of Treatment Response in Major Depression ("BRITE-MD") was a large multisite trial (N = 220 participants completing the study) that used a neurophysiological biomarker to predict treatment response. Changes in the Hamilton-D scale were used to measure clinical outcome. An antidepressant treatment response index ("ATR") was derived from the power spectrum at baseline compared to the end of one week of the antidepressant escitalopram. The index is "a weighted combination of the relative theta and alpha power at week 1, and the difference between alpha 1 power (8.5−12 Hz) at baseline and alpha 2 power (9−11.5 Hz) at week 1".

Patients received quantitative EEG assessments at baseline and following one week of treatment with escitalopram. Patients were then randomized into treatment groups with (1) continued administration of escitalopram, (2) addition of bupropion to escitalopram, or (3) switch to bupropion. The

ATR predicted both response and remission at 8 weeks with 74% accuracy. Prediction of outcome based on genotyping, physician assessment, and serum drug levels were not significant (see Leuchter et al., 2009a). These authors reported that the ATR was also able to predict differential response to antidepressant medication. Patients with ATR values below a specific threshold were likely to respond to escitalopram and above the threshold were more likely to respond to bupropion.

Another large-scale study (N = 89) compared selection of medication for major depression based on algorithms developed in the "Sequenced Treatment Alternatives to Relieve Depression" (STARD) study that did not use EEG as a predictor (Rush et al., 2006), with medication guided by use of quantitative EEG features (DeBattista et al., 2009). There was a clear improvement on a number of measures of clinical outcome, including the Quick Inventory of Depressive Symptomatology and the Montgomery–Asberg Depression Rating Scale, with qEEG-guided intervention compared to STARD algorithms.

Overall, a number of qEEG and evoked potential procedures have been described that have significant potential for guiding therapeutic intervention with medication. The main use for quantitative EEG and evoked potential technology in this regard has been in studies of major depression and schizophrenia. In addition, however, quantitative EEG methods are being actively used in other neurophysiological interventions. A particularly productive line of inquiry involves consideration of changes in evoked potentials due to phase reset mechanisms (as opposed to the averaged activity of fixed generators of evoked potential components). Since it is our opinion that this could have major implications for guiding intervention strategies, we describe here some details of the procedure.

Evoked potentials are usually recorded by means of averaging segments or trials of EEG following the presentation of sensory stimuli. These potentials are generally considered to be fixed latency, fixed polarity, responses that appear superimposed on the background EEG. This is the basis of the "evoked" model. Recent literature has emphasized the need to consider that ERPs are generated at least in part by a reset of on-going oscillations, i.e., phase reset (Klimesch, Sauseng, Hanslmayr, Gruber, & Freunberger, 2007), the so-called "phase reset" model. Reduction in amplitude from the first to the second stimulus in a pair may be due to alterations in phase-locking. The role of phase-locking has been studied using intracranial recording in epilepsy patients (Rosburg et al., 2009). Poor gators showed less phase-locked beta frequency oscillation (20–30 Hz) in the 200–315 msec region

following the first stimulus. This was found to be related to poorer memory encoding.

The relation between brain oscillations and auditory evoked potentials has been studied directly in schizophrenia (Brockhaus-Dumke, Mueller, Faigle, & Klosterkoetter, 2008). This work included 32 schizophrenic patients and 32 controls with EEG continuously recorded during an auditory paired click paradigm. The authors concluded that analyzing phase and amplitude in single trials provides more information on auditory information processing and reflects differences between schizophrenic patients and controls better than analyzing averaged ERP responses. Unfortunately this study found group differences in the N100 component which was predicted by phase-locking in the theta and alpha frequency ranges, but not the commonly reported findings with the P50 component which was predicted by phase-locking in the beta and gamma frequencies.

PREDICTION OF NEUROFEEDBACK PROTOCOL EFFICACY

Neurofeedback involves recording, analyzing, and presenting results of quantitative EEG analyses in near real-time to individuals in order to promote changes in brain electrical activity. There is no requirement for conscious awareness in neurofeedback training. In fact, a need for conscious awareness would limit the applicability of training in real-world situations. Following neurofeedback training, individuals do not need to willfully and consciously modify specific EEG patterns in order to effect behavioral change.

In the past, most training criteria have been set for individuals based on evaluation of behavior using a concept of arousal or symptom presentation. Now, increasingly, training incorporates characterization of neurophysiologic status using EEG and quantitative EEG, and evoked potentials to help predict outcome.

There are different ways to examine "arousal". Physiologically, our arousal level is usually considered in terms of the sleep/wake cycle. It is not unusual to see individuals who have problems regulating this activity. People who fall asleep as soon as they sit still, or people who cannot fall asleep as they lay in bed are examples of what happens when there are difficulties managing arousal. Prominent EEG changes seen with decreased arousal are easy to detect with recordings from the sensorimotor strip. These changes are used to assess depth of sleep: For example, differential appearances of discharges at the vertex (Cz) signal progression to Stage II

sleep. Historically, neurofeedback practitioners began using protocols that remained on or near the sensorimotor strip (Lubar, 1985; Sterman & Friar, 1972; Tansey, 1984) with the goal of regulating arousal. Protocols often included Cz, C3 or C4, each with an ear reference.

The mechanism of arousal of the cortex by subcortical activity can be measured by sensors placed on the sensorimotor strip. When this mechanism is dysfunctional, we may observe particular aberrant behaviors. However, this remains a very subjective process and clinicians are not always able to make an accurate prediction of treatment efficacy based on this information alone. As clinicians employ more complicated protocols to help individuals modulate their arousal level, it is important to include objective information that can provide more guidance about the physiology of an individual's brain and how this might impact their level of arousal, and, hence, their response to treatment.

Early neurofeedback work with autism is a good example of the importance of modulation of general arousal. It was often thought that autistic children were highly over-aroused. This was based on their behaviors (e.g., "stimming"), and protocols were used to "calm" these children (Jarusiewicz, 2002). However, as more of these children had qEEG analyses done, it was noted that the pattern of brain electrical activity included far more slow content as compared to normative databases. It seemed that there was a mismatch between the observed "over-aroused" behaviors and the slower EEG patterns.

It is useful to think of the dimensions of arousal on an x, y graph. If we track the physiological arousal level on the y axis and the behavioral arousal on the x axis, we will find that there are times that these two match and times when they clearly do not. When neurofeedback practitioners have both pieces of information, they often better predict successful protocols that address issues of arousal.

At this point in the development of neurofeedback methods, neurofeedback clinicians need not limit themselves to the work on the sensorimotor strip, and, therefore, more comprehensive models have been considered. Johnstone (2008) suggested a role for qEEG in assisting in neurofeedback protocol development. Three main concerns were addressed: (1) general regulatory or arousal-based symptoms, (2) identifying focal regions of interest for training, and (3) evaluating connectivity among brain regions, both between and within hemispheres.

Assessment of general arousal is not as relevant and offers little guidance when looking at problems in localized areas of the brain. It is under these

circumstances that evaluation of regional brain function is needed. Identification of focal or regional abnormality using qEEG, when considered in the context of behavioral symptoms and neurocognitive function, can more specifically guide protocol development. Examples of behaviors that are often correlated with regional abnormality in qEEG include language disability, difficulty with perception of emotional expression, avoidance behaviors in sensory integration disorders, specific memory difficulties, poor impulse control, lack of judgment, and numerous others. While changes in behavior can be helpful in tracking progress, more information can be very useful prior to neurofeedback training in finding neurophysiological causes or correlates of symptoms. qEEG analysis can be especially helpful in these circumstances. Specific information about frequency ranges, locations and connectivity issues can then be matched with behavioral symptoms in developing neurofeedback protocols to address regionally based issues.

qEEG analysis can be used not only to ascertain the need to modulate arousal and regional activation, but also neural connectivity. Certain clinical presentations are best characterized as "disconnection syndromes", and in such cases detection and remediation of abnormalities in EEG coherence are often clinically effective. The importance of disconnection syndromes in clinical neuropsychology is well known and coherence abnormalities have been documented in many studies of pathological conditions (Leocani & Comi, 1999). Neurofeedback training to increase and decrease connectivity has been recently shown to be useful in studies of autistic individuals (Coben, 2007; Coben & Padolsky, 2007).

The most direct method for using qEEG information to guide neurofeedback training involves feedback of information based on the extent of the z-score deviation for a specific feature, often called "live z-score training". One of the most intriguing aspects of this method is the apparent capacity of the brain to respond to multiple z-score training demands simultaneously. If this aspect of the method can be further validated, it suggests a more efficient way to carry out complex protocols within a brief period of time. It is important that the selection of z-scores to be trained are based on clinical criteria and take into account artifact, drowsiness, and transients, which are best identified in the raw EEG signal. In addition, selection of z-scores to be modified should not be based exclusively on the magnitude of z-score deviations because this can lead to ineffective or negative outcomes. The case history presented below is an

example of when *not* to train certain patterns of z-score deviations. We emphasize the importance of clinical correlation with symptoms, complaints, and results of other diagnostic testing, including psychometric evaluation, in protocol development.

Also important is the dynamic information that can be gathered from the raw EEG signal. Identification of transient events and paroxysmal bursts are examples of information that can be helpful in protocol development. Neurofeedback training, both on the sensorimotor strip and in regions identified by visual inspection of EEG have been shown to be efficacious in treatment of epileptic disorders (Sterman, 2000), using such techniques as threshold adjustment. The threshold adjustment routine allows the clinician to provide feedback about transient paroxysmal events that are best identified in the raw EEG and can be characterized within a specific frequency range for feedback. These transient events may be of considerable clinical significance but are generally poorly resolved in time-averaged qEEG analyses.

EEG patterns, or phenotypes, have been identified that often can be linked to behavioral patterns (Johnstone et al., 2005). For example, excess frontal theta frequency activity is one of the phenotypes seen in individuals who suffer from attentional difficulties. However, it is important for clinicians to understand that this pattern does not exist exclusively as a biomarker for attention, and cannot be considered diagnostic. It is seen in other presentations as well. It can be seen in cases of brain injury, depression, and other difficulties. So, it remains important to know the specific behaviors and symptom presentation of each client to best make use of the objective data that can be collected from the raw EEG signal and the qEEG analysis.

Other measurement and analysis tools are emerging that are likely to enhance successful prediction of favorable outcome by helping in selection of specific neurofeedback protocols. For example, magnetoencephalography (MEG) provides additional information about sources of brain activity. EEG databases can be developed to specifically address predicting outcome in neurofeedback. Integration of neurocognitive assessment will provide a better understanding of the psychological correlates of phenotype patterns, and should allow more accurate prediction of therapeutic outcome using neurofeedback methods.

A case study demonstrating the utility of using the information in the raw EEG signal, results of a qEEG report, and the information gathered in a clinical interview follows.

Case Study

A 14-year-old male presents with multiple complaints that have not been resolved in treatment by two separate psychiatrists and a clinical psychologist. Parents began to seek treatment for him when his generalized anxiety escalated in the 6th grade. He would often be so anxious that he would crawl under either his, or the teacher's desk. He also experienced severe separation anxiety if his mother left the room for more than 5 minutes, and would repeatedly ask where she was and insist that he had to go find her. He was unable to go to sleep unless his mother sat at his bedside, and, even so, it would often take more than 2 hours for him to fall asleep. He was difficult to wake in the morning regardless of how long he had been allowed to sleep. Several times a week, he would sleepwalk to other areas of the house and often get into a bed, not his own, to sleep for the rest of the night. He was very hyperactive and was unable to sit at a table for a meal or sit still in a classroom. He constantly "drummed" on anything, including his own arms and legs. Recording his first EEG was a challenge. He displayed an extremely low frustration tolerance and poor impulse control. He often lashed out physically at his sister and also had physically aggressive episodes at school. Due to the unpredictably of his behaviors, his family rarely knew what to expect from him and he was unable to establish friendships.

Responses to medications were poor and/or adverse. Administration of Ativan for anxiety was followed by the patient putting his fist through a plate of glass and needing physical restraint to transport him to the hospital for care. Use of Ambien and Lunesta for sleep was followed by significant agitation. Following a small dose of Remeron, parents noted a slight improvement as it "took the edge off" and "subdued him slightly". But, there was no improvement in initiation of sleep or parasomnias. The patient used a low dose of Remeron for about 6 months. Because of negative or minimal response to medication the parents decided to begin neurofeedback training. Prior to training, a full clinical evaluation and an EEG/qEEG study was performed.

Visual inspection of his clinical EEG showed that there were bursts of spindling beta activity in the left frontal and right frontal regions, that were seen both bisynchronously and with shifting laterality. Results of qEEG analyses showed excessive beta activity in frontal regions bilaterally and an associated marked lack of interhemispheric beta coherence, particularly in prefrontal leads. These findings suggested the need to suppress beta activity in both hemispheres, and specifically *not* increase the significantly decreased z-scores for interhemispheric beta coherence. This approach has been described previously (Johnstone & Lunt, 2007). Neurofeedback protocols were developed emphasizing two-channel

sum training to suppress frequently occurring beta bursts over frontal regions of both hemispheres.

Following approximately 60 sessions of training using frontal beta suppression and additional protocols to modulate centroparietal activity, a repeat qEEG was performed. The EEG was now read as within normal limits and difference topographs comparing the two recordings show a marked decrease in anterior beta. Database comparisons indicated that there was no longer significantly elevated anterior beta or significantly decreased anterior beta coherence. This was accompanied by marked clinical improvement documented by parents and teachers.

The outcome following qEEG guided neurofeedback is summarized below:

Before	After
Chronic generalized anxiety	Occasional moments of anxiety that are appropriate to the situation
Separation anxiety	Gone – now able to be away from home for several days with friends or family
Chronic insomnia	Able to fall asleep easily without anyone staying with him
Sleep disturbances (sleep walking)	No longer does this
Hyperactivity "drumming"	Physical activity is now purposeful and within normal limits, no more drumming
Frustration tolerance	Now able to tolerate more frustrating circumstances without over reacting
Lack of impulse control	Now able to stop and consider consequences
Unable to establish friendships	Now has several good friends

It cannot be concluded that neurofeedback was the sole reason for clinical improvement but given prior repeated trials with medication and behavioral counseling, it is clear that neurofeedback had an important influence on favorable clinical outcome.

USING EEG TO GUIDE TRANSCRANIAL MAGNETIC STIMULATION

Puri and Lewis (1996) suggested that transcranial magnetic stimulation (TMS) is a viable and important tool for diagnosis and therapy in

psychiatric disorders. Subsequently, transcranial magnetic stimulation has been the subject of many hundreds of research studies over the past decade. Two main types of stimulation typically are used: low frequency stimulation (<1 Hz, "TMS") and high frequency stimulation (>5 Hz, "repetitive TMS", or "rTMS"). Low frequency high field stimulation generally produces inhibitory effects and higher frequency stimulation produces excitatory effects. TMS is currently being studied as a potential treatment for many disorders including epilepsy, depression, bipolar disorder, schizophrenia, posttraumatic stress disorder, obsessive–compulsive disorder, anxiety, stroke, and chronic pain. Numerous reviews of the technology and applications are now available (see George & Belmaker, 2006; Wassermann, Epstein, & Ziemann, 2008).

Most clinical work has been directed toward the treatment of depression, using rTMS over the left dorsolateral prefrontal cortex. In a recent review Brunelin et al. (2007) stated "the antidepressive properties of rTMS now appear obvious". Rosenberg et al. (2002) studied rTMS to left frontal cortex in patients with major depression. Stimulation was focused 5 cm anterior to the site of optimal motor stimulation. Seventy-five percent of the patients had a significant antidepressant response to rTMS, and 50% had sustained response at 2-month follow-up.

Overall, research shows the technique to be safe (Janicak et al., 2008). Lisanby et al. (2009) demonstrated efficacy using daily rTMS in a population of 164 individuals with major depression, showing a 22% reduction in symptoms compared to 9% with a sham control. It is clear that although rTMS may be clinically useful, it is not yet an optimal treatment, and techniques are needed to improve efficacy, particularly with treatment-resistant depression. One method used to improve efficacy was individualized placement of the stimulating coil by means of structural MRI (Fitzgerald et al., 2009). These researchers report significantly improved depression scales following 4 weeks of rTMS by using coil placement based on individual MRI compared to standard placement based on the motor response.

Jin et al. (2006) used measurement of individual alpha frequency to set stimulation rates in an rTMS study of schizophrenics. A series of 27 subjects with predominantly negative symptoms of schizophrenia received daily rTMS to midfrontal cortex for a period of 2 weeks. The authors documented that rTMS based on individualized alpha frequency ("αTMS"), significantly improved the therapeutic effect compared to lower frequency, higher frequency, and sham stimulation. In addition,

therapeutic improvement was highly correlated with increased frontal alpha activity.

Magno-EEG resonant therapy (MERT) is an innovative form of TMS developed by Jin (personal communication, 2010). The MERT technique uses EEG to identify stimulus intensity, frequency, location, and duration needed to normalize EEG activity, particularly the dominant alpha frequency. Most rTMS protocols use the same frequency, location, and duration of stimulation on all patients, and do not consider intrinsic EEG frequency. With MERT, a customized treatment is developed for each individual based on analysis of the resting EEG.

MERT has been used primarily to target the dominant background EEG activity. The amount and frequency of EEG alpha activity, typically in the 8–13 Hz range, has been shown to be associated with overall brain metabolism, as well as cognitive functions generally, and a variety of types of mental disorders. Research is now being directed towards study of depression, anxiety, schizophrenia, and addiction. Further work obviously will be needed to specify optimal frequencies and stimulation techniques for different disorders.

CONCLUSION

A growing body of literature suggests there is significant value in using EEG information for guiding clinical intervention with medication, neurofeedback, and TMS. Studies of medication have largely focused on applications in depression and schizophrenia. Further work should extend this approach to additional clinical populations. Further development of predictive algorithms should emphasize newer pharmaceutical and neutraceuticals, used separately and in combination with other agents of the same or different classes. In addition, more detailed outcome measures beyond clinical global improvement scales should be employed in studies that use a combination of agents.

Research on neurofeedback would also benefit from development of predictive algorithms that combine behavioral analysis, neurocognitive assessment, and neurophysiological methods. It is expected that specific constellations of these features could be identified to more objectively guide development of successful neurofeedback protocols.

Much research is under way to apply transcranial magnetic stimulation to problems in neurology and psychiatry. Basic research to facilitate our understanding of intracranial current flow is likely to be helpful in optimizing

rTMS procedures. Further individualization of stimulation rates and stimulation site(s) based on EEG and ERP features will also likely increase clinical efficacy of these techniques.

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