EEG as a Predictor of Medication Response

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This report will examine the evidence that the human electroencephalogram (EEG) can be used to help predict medication response in clients with mental health concerns. The focus of this review will be depression, which is typically treated with antidepressants, and ADD/ADHD which is commonly treated with stimulants. The ultimate question to be asked is, "can EEG be used clinically to help to select the most appropriate medications for a client?" These questions are addressed by examining the published literature in this area, specifically controlled studies that look at specific EEG parameters and how they relate to medication response in mental health patients. The report will describe some of the basic brain mechanisms that are accessible to the EEG, and how they relate to mental disorders. I will then review research articles that evaluate EEG parameters in particular patient populations, and determine how these parameters relate to how patients respond to medications for their disorders. In certain patient populations, recognizable EEG parameters or patterns could be used as useful guides in determining how a given individual will respond to a particular medication. This is the element of prediction. As a second question, the possible value of EEG in selecting medications in a clinical setting will be addressed. This question focuses on the issue of whether clinical decisions can be positively impacted by considering EEG data, and is this data of demonstrable value in designing a medication plan for a given patient. Prediction should have particular value in determining nonresponders, or those prone to abreaction. Thus, by screening them at the outset, and simply not administering adverse substances to these patients, efficacy and safety statistics would rise, and the likelihood of success with any given medication would increase.

I have chosen this topic because I have a long-standing interest in EEG, and have been active in research and publication in this area for several decades. However, my work has been

primarily in epilepsy and in neurofeedback. Very little of my background relates to psychoactive medications. This study is intended to help provide directly applicable information that can be used clinically in the practice of mental health counseling and consulting. The ability to more objectively manage medications is significant because a considerable amount of modern pharmacology consists of selecting drugs based upon diagnosis or symptoms, and then using a medication on a trial basis. This can lead to the need for successive or combined pharmacology, in the face of treatment failures, abreactions, or noncompliance. It is hoped that this approach can lead to a useful contribution to clinical psychopharmacology in the context of a mental health counseling practice.

This report is intended to help clinicians predict how clients will respond to proposed medications, and help to avoid some of the trial-and-error method now used. This will allow clients to achieve benefits sooner and with less risk of abreactions or side-effects, by using the most appropriate medications in the shortest time frame. One of the author's first such experiences with a neurofeedback client was an individual who had abreacted to an SSRI, becoming agitated and unable to continue in school. A subsequent EEG analysis revealed a pattern known to indicate an SSRI non-responder. Specifically, this finding included the commentary, "some central Beta spindling, although it does not appear to be excessive in the averaged spectra due to the intermittent nature," "associated with the COMT gene expression (COMT=0) which predicted a poor SSRI response (even some side-effects of over-arousal)." "Associated with anxiety (agitated depression) and OCD" (Gunkelman, 2009) REF. If this individual had been given this EEG-based analysis initially, the abreaction to the SSRI could potentially have been avoided.

Goals/Objectives

The goals of this report are to:

Review the literature describing EEG in relation to medication response.

Review the literature regarding the value of EEG in psychiatric medication management.

Review the underlying principles of the EEG and which brain mechanisms it can indicate, and how EEG can relate to the major mental health disorders of depression and ADD/ADHD.

Evaluate the current status and prospects for the use of EEG in this manner, in the clinical environment, and evaluate the possible impact or value for mental health counseling.

Literature Review

Sufficient literature exists demonstrating that EEG is sufficiently relevant to mental health concerns to provide a useful indicator of medication response. There are also studies relating to use of EEG to select medications, and its possible value.

Studies have been published describing EEG patterns in mental health, and how they relate to mental disorders (Arns, Gunkelman, Olbrich, Sander, & Hegerl, 2011; Hegerl, Stein, Mulert, Mergl, Olbrich, Dichgans, et al., 2008; Suffin & Emory, 1995). Studies have been published on how different EEG parameters and patterns can be used to predict drug response Bares, Brunovsky, Kopecek, Novak, Stopkova, Kozeny, et al., 2007, 2008; Bruder, Sedoruk, Stewart, McGrath, Quitkin, & Tenke, 2008; Bruder, Steward, Tenke, McGrath, Leite, Bhattachary, et al. 2001; Bschor, Muller-Oerlinghausen, & Ulrich, 2001; Iosifescu, Greenwald, Devlin, Mischoulon, Denninger, Alpert, et al., 2009; Johnstone & Lunt, 2011). Further studies

have specifically examined the value of using EEG in a clinical practice, as a resource for information relevant to medication selection (Arns, Gunkelman, Olbrich, Sander, & Hegerl, 2011; DeBattista, Kinrys, Hoffman, Goldstein, Zajecka, Kocsis, et al., 2010; Hermens, Rowe, Gordon, & Williams, 2006).

Underlying Principles

The underlying brain mechanisms that are shown in the EEG have potential relevance to psychiatry and to psychopharmacology (Johnstone & Lunt, 2011). For example, the frontal areas are known to mediate high-order mental processes such as planning, judgment, emotion, and decision-making. The cingulate gyrus, which is lies in the middle of the cortex and connects widely to other areas, is involved in attentional control, setting priorities, and shifting of focus from one task or topic to another. The temporal and posterior areas, involved in visual and auditory sensation and processing, are involved in sense of self, audiovisual and spatial integration, and memory processes.

Sterman, Mann, Kaiser, and Suyenobu (1994) used EEG studies to identify and articulate a model based upon the concept of the "concentration/relaxation" cycle that appeals to the notion that brain functional areas must alternate between periods of activity and periods of rest. Sterman (1996) further described how this relates to self-regulation as revealed by the modulation of EEG rhythms. This is not the same as the entire organism's diurnal cycles of activity and rest, and occurs on much shorter time frames, of 10 or 20 seconds. For example, when pilots are performing a controlled task, Sterman found that effective performance is predicated on a natural alternation between a low-amplitude, high-frequency Beta state, and a high-amplitude, low-frequency Alpha state. Effective performers exhibited a natural, fluid, and flexible alternation between states. These individual were able to regulate attention, perform,

recover, and repeat tasks with significantly less difficulty or fatigue than others. These "high-performing" individuals also had shorter reaction times, and higher scores, than the others who did not have this innate sense of self-regulation.

When the concentration/relaxation model is applied to specific brain locations, it becomes a way to understand diagnostic categories as sets of functional dysregulations, not simply constellations of symptoms. For example, if "little Johnny's" posterior cingulate is stuck in a Beta state, it is functionally "offline" and will not perform its function in co-ordination with the rest of the brain. Therefore, the rest of the brain is not being told when to let go of something of attention, so that attention has a chance to switch to something else. This will lead to his being "stuck" on particular objects of attention, be inflexible, and consequently, quite possibly angry and defiant. An intervention that begins by focusing on this type of functional block will presumably be able to identify interventions that are relevant to the fact that little "Johnny's" posterior cingulate is offline in a Beta state, rather than the fact that he is angry, defiant, and has an attention problem. Another child with quite comparable behavior may, for example, have primarily an excess of frontal Theta, causing attention difficulties of a different type, and different reasons to become, again, angry and defiant. Recognizing the difference between a child with a locked-in posterior cingulate gyrus, and one with frontal lobes in Theta ("la la land") can make a potentially vital contribution to the planning, administration, and assessment of his treatment.

Arns, Gunkelman, Olbrich, Sander, and Hegerl (2010) developed and applied a model based upon a time-series of vigilance states that could be associated with particular EEG patterns. Based on their analysis, there is a specific sequence of states that the individual, and his or her EEG, undergo in moving from a highly alert state into a less alert, or even a sleep, state.

This transition is characterized by shifts from a state of high occipital Alpha power to one of more frontal Alpha, then a desynchronized (low amplitude) state, and finally, Theta, Delta, and "spindling" sleep. By appealing to this sequence, they were able to identify dysregulations of two types. One, "rigid" regulation, is characterized by a lack of modulation, and continual wakefulness, which corresponds to activation in the previous analysis. The other form of dysregulation is "labile" regulation, and is characterized by a proclivity to slow-waves and a de-activated state. Their analysis places a specific set of markers on the concept of graded activation. They were able to put this model into use as a way to personalize drug choices, based upon observed abnormalities.

Hegerl et al (2008) further refined this into a model that sees ADD/ADHD as a disorder with the two subtypes, hyperactive and inattentive, arising from a vigilance autostabilization syndrome, or from impaired sustained attention, respectively. That is, when a child is hyperactive, it is because he or she is in a continual state of vigilance. When inattentive, the child has an impaired ability to sustain attention, which is in some ways the opposite of vigilance. The ability to distinguish children along this axis, rather than purely by behavioral indicators, has the potential to enable an individualized approach to diagnosing and treating each child.

There is a philosophical basis to this approach, in that the physiological substrate of a mental or emotional disorder may have a discernable deviation from normal, and that this deviation may be observable in the EEG. By using physiological factors instead of, or in addition to, the diagnosis or symptoms, a more functional view of the patient can be obtained. Based upon this functional understanding, the mechanisms of medication use, and the likelihood of particular medications being effective, can be determined. This becomes a form of

individualized therapy, in which patients are assigned to medications based upon functional knowledge of their brain physiology, not just their diagnosis or symptoms. Since a given symptom such as depression or anxiety can arise from a variety of different causes, determining the underlying causation can be a possible means of specifying medications to use with more accuracy and likelihood of success.

From a historic viewpoint, this approach becomes a modern integrative approach that incorporates known psychopharmacological approaches, and supplements them with newer technology (DeBattista, Kinrys, Hoffman, Goldstein, Zajecka, Kocsis, et al., 2010; Hermens, Rowe, Gordon, & Williams, 2006). The methods used include quantitative EEG (QEEG) and referenced EEG (rEEG), which have been developed over the past few decades. QEEG has not become an accepted form of clinical EEG, in the current medical community. EEG is still used primarily for epilepsy, head injury, and brain disease, to find and localize gross abnormalities. QEEG in psychiatry is an emerging field. The application of QEEG or rEEG to psychopharmacology is a unique combination of existing and emerging technology, which has the potential to change the ways that clinicians view clients and their responses to medications.

The effect of a psychoactive substance on the EEG is also significant, as it pertains to expected pharmacokinetic mechanisms, and changes in brain regulatory dynamics. Hermens et al. (2007) reported on a randomized, placebo-controlled trial with 32 adult males treated with methylphenidate. They participated in 18 sessions, each with subjective, objective behavioral and biological assessments. The employed computerized testing for cognitive performance assessment while EEG, event-related potentials (ERPs), and autonomic arousal measures were also taken. It was found that methylphenidate had significant effects on increasing sustained attention and vigilance in cognitive performance tasks, higher heart rate and blood pressure, and

also lower EEG Theta power. This combination of markers was proposed as an objective measure of MPH response. This finding is consistent with the reported studies that indicate that high initial levels of Theta, primarily frontal Theta, is associated with a positive response to stimulants. An important consideration possibly missing from this study is a distinction between what is simply the amplitude level of the Theta rhythm, in contrast to the lowering of the frontal Alpha rhythm. It is possible that this group included both subtypes of the EEG. In that case, in participants who had high initial Theta, the MPH lowered it; in those who had initially a low-frequency frontal Alpha, the MPH speeded it up. In both cases, the QEEG findings would be essentially the same, indicating what is shown as a reduction in Theta amplitude.

In a study similarly designed to identify the effects of psychotropic drugs and how they relate to EEG, Herrmann and Kubicki (1981) administered a variety of agents to 75 volunteers, and assessed EEG changes using a Latin square design. They were able to determine that certain general changes were common. These were that benzodiazepines used as anxiolytics cause an increased Beta, while when used for sedation, they produce an increase in Delta and a reduction in Alpha power. Psychostimulants (amphetamines) increased total EEG power and increased Alpha, as well as decreased Delta if Delta was initially high. Neuroleptics produced increased Theta and Delta, and a decrease in Beta. TCA's caused a shift between Delta, Theta, Alpha, and Beta, indicating a dissociative shift in vigilance.

In the field of psychiatry, Gordon (2007) used the term "neuro-marker," which corresponds roughly to what Johnstone, Gunkelman, and Lunt (2005) described as a "phenotype." The basic concept is that a specific profile or set of indicators can be found which is useful to differentiate patients. If such a marker has an objective relationship to a salient underlying mechanism or variable, it will have potential value in determine the nature of the

disorder, hence the likely response to an intervention such as a drug. Whereas a given symptom may arise from a wide range of causes, and manifest itself in various ways, an underlying variable would have a more consistent and foundational role. This would allow psychopharmacology to move beyond a strictly disorder-based method, or even a symptom-based approach.

Key questions that will remain are, how (or if) this approach will affect or fit into the role of the mental health counselor. Currently, thousands of mental health counselors practice biofeedback or EEG biofeedback (neurofeedback) as part of their licensure and certifications. It is not unusual for an experienced practitioner, be they a social worker, psychologist, or counselor, to take a full-head QEEG, and have it evaluated. Currently, the use of this information for drug selection is limited to the scope of the M.D. However, even a 1, 2, or 4-channel EEG can provide information relevant to this issue, such as the amount of global frontal Theta, or the Theta/Beta ratio, for example. These measures can also be used to monitor drug effectiveness and progress, much quicker and cheaper than running hospital EEG's. Therefore, the role of the ancillary mental health community could incorporate EEG, QEEG, and biofeedback in concert with, rather than as opposed to, medication.

ADD/ADHD

In the pharmaceutical treatment of ADD/ADHD, the fundamental questions to be answered are, does a particular child have ADD/ADHD, and will he or she respond favorably to a proposed medication. The first question addresses the concern about overdiagnosis of ADD/ADHD, and the second question addresses the advisability of using medications on those who are deemed in need of it. A consideration of contributory factors including environment, upbringing, family dynamics, diet, exercise, and school environment should also contribute to

the evaluation (REF re. ADD overall). If medication is to be used, it is important to determine early whether the individual will respond to proposed medication, and what is the likelihood of abreactions or side-effects, particularly in the case of depression (Schatzberg, Cole, & DeBattista, 2010).

With regard to ADD/ADHD, in the NIMH-MTA trial, a large, multicenter study of different treatments for ADD/ADHD, there was no long-term benefit seen for the use of stimulant medication, beyond 2 years. It was not possible to separate those who took stimulants from those who did not, using behavioral and observational measures as the children matured. (Swanson et al., 2007). In addition, the overall rate of nonresponse was estimated at 30%, indicating that 1 in 3 children given stimulants did not benefit, but was still exposed to risks (Hermens, Rowe, Gordon & Williams, 2006). In view of the current shortage of stimulant medications, reducing the demand by 30% would have the additional benefit of ensuring that those who respond to it will have sufficient quantities available and affordable (LA Times, 2012).

The current limitations in efficacy and response rates are all predicated on the use of group data in determining protocols and predicting response. Therefore, all individuals with a particular profile of symptoms will be included in a particular diagnosis, and that diagnosis is used to select appropriate medications. However, as the cited studies show, the effectiveness of this approach is approximately two-thirds. Moreover, this leads to a trial-and-error approach which is taxing to the patient as well as to the system. Because of the possible variations in individual origins and types of ADD/ADHD, an individualized approach is indicated. Therefore, rather than relying on combinations of symptoms to select medications, it may be beneficial to focus on underlying mechanisms and dysregulations, and to address these directly. If biomarkers

can be identified and used to select medications, a potential improvement in overall outcomes can be expected. These can include genetic and other information, and can also incorporate the EEG. EEG can be used to differentiate subtypes of ADD/ADHD, which can be helpful in predicting medication response, therefore in selecting and evaluating medications.

This question addresses not only individual differences, but also the complexity inherent in psychological disorders, their origins, and response to treatments. A system that has multiple adaptive and compensatory mechanisms may not have a simple, or even a predictable response to a perturbation. Therefore, individual differences are paramount in understanding individual pathology, as well as the reaction to therapeutic interventions or agents. This concept also underlies the reasoning behind administering a stimulant to a person who superficially appears to be overstimulated. This approach moves beyond the concept of average effectiveness, and introduces the concept of individual effectiveness in prescribing treatment, the importance of which was emphasized by Simon and Perlis (2010).

Specific EEG correlates of ADD/ADHD are well established. One of the most prominent early observations was that overall Theta activity (4-7 Hz) appears increased in the ADHD population (Chabot & Serfontein, 1996; Mann, Lubar, Zimmerman, Miller & Muenchen, 1992). Increased Delta (1-3 Hz) activity has also been observed (Bresnahan et al., 1999; Matsuura et al., 1993). Williams et al., (2010) analyzed the EEG's of 275 ADHD patients, and found increased Theta ($p < .0001$) and decreased relative Beta power ($p < 0001$) when compared to a matched control group. Lubar (1991) developed the use of the EEG ratio of Theta/Beta power, and established it as a discriminant that could be used to separate normal children from children with ADD/ADHD or learning disorders.

The relationship between EEG and stimulant response has been recognized for decades. Satterfield used this approach as early as 1971, and found that excess slow wave activity and large evoked potentials could identify likely responders to stimulant medication (Satterfield, Lesser, & Podosin, 1971; Satterfield et al., 1973). Chabot, di Michele, Prichep, and John (2001) were also able to demonstrate that abnormal EEG could be used to identify those who would have a positive reaction to treatment. Suffin and Emory (1995), for example showed that 95% of children who exhibited excess Theta responded to stimulants. In a more recent study, Arns, Gunkelman, Breteler, and Spronk (2008) demonstrated that particular patterns in EEG expression, referred to as "phenotypes," were predictive of stimulant outcome. They further pointed out that the 20-40% of children with ADHD who do not respond to stimulants could be related to the EEG subtypes. The EEG parameters that they examined were: excess frontal slow, slow anterior peak frequency, excess frontal Alpha, and frontal Beta spindles. These were recognized by visual interpretation, not by an automated QEEG process. The inter-rater reliability was 0.90 or better, indicating consistency in this visual approach. When EEG phenotypes were compared with treatment effects, several findings appeared. One was that the frontal slow type showed improvement in a CPT task, in the area of false negative errors. Also, the frontal slow group and the slow Alpha peak frequency group showed a similar amount of initial errors, but only the frontal slow group responded to stimulants. It was also found that the EEG subtypes did not correspond well to the ADHD subtypes based upon behavior.

Therefore, the EEG phenotyping method is sensitive to factors other than those that are accessible to behavioral observations or CPT test results. This implies that the EEG approach provides a different type of information, and that it is not redundant with existing cognitive or behavioral assessments. In applying this to drug prediction, the authors recommended that

quantitative EEG analysis should avoid using fixed frequency bands, but should clearly distinguish between slowing of the anterior peak frequency, and the presence of frontal slow waves, which look the same to a QEEG, but are visually and functionally different. They also pointed out that this type of classification should not be a simple yes/no decision, but should assess the degree of severity of each phenotype, in each individual.

As a further refinement on an EEG-based classification method, Sander, Arns, Olbrich, and Hegerl (2010) described a model that can be used to assess the state of vigilance in pediatric patients. They used this model to determine the amount of instability in children, and the consequent likelihood that they would respond to simulants. Lansbergen et al. (2011) studied forty-nine boys with ADHD, and analyzed their EEG's in multiple frequencies. They reported that the pattern of increased Theta, and increased Theta/Beta ratio, was largely dependent on the presence of a slow Alpha peak frequency, rather than increased Theta. This subgroup responded differently to medication, demonstrating that simply measuring the Theta/Beta ratio was not a sufficient method for predicting drug response. That is, rather than simply looking at the levels of standard EEG bands, it was necessary to take into account the overall EEG energy, over the entire spectrum.

In addition to the excess Theta and slow peak frequency groups, there is a group of approximately 15-20% of children, who have excess "spindling" Beta visible in the frontal areas (Chabot & Serfontein, 1996; Clarke et al., 2001b). Interestingly, this pattern is commonly seen in response to benzodiazepines (Blume, 2006). In the case of children with ADHD, this subgroup is more prone to moody behavior and tantrums (Clarke et al., 2001a). This subgroup does respond to stimulant medication (Clarke et al., 2003). Family studies show that this is a

familial pattern, and that it is associated with GABA-A receptors. This association may be related to the fact that benzodiazepines themselves produce a "Beta buzz" (Porjesz et al., 2002).

Depression

The pharmaceutical treatment of depression is often characterized by trial and error, response failures, and combining drugs (Schatzberg, Cole, & DeBattista, 2010). Patients with depression are often given antidepressants or lithium, to which they may or may not respond. Indeed, at least one antidepressant is marketed specifically for patients whose first antidepressant is not sufficiently effective (Abilify, 2012). However, results are mixed, and choosing and maintaining an antidepressant can be an extended and difficult process (Schatzberg, Cole, & DeBattista, 2010). Negative side-effects and metabolic and physical damage are also an issue, and steps must be taken to avoid and manage these. The significance of individual differences is clinically relevant to the diagnosis and treatment of depression. The inability to predict treatment response appears to be a considerable cost factor and source of failure. The STAR*D trial studied 3,671 patients receiving antidepressants as well as CBT. In this study, remission rates of 36.8% per treatment phase were seen, and 33% of patients were entirely treatment resistant, after 4 successful series of treatment (Rush et al., 2006). This was not a placebo controlled study, and involved primarily patients without health insurance. However, if it were simply possible to identify that 33% of the depressed population before administering medication, those patients could be spared the process of taking medication that will not be effective. Studies by Keller et al. (2000) and Kirsch et al. (2008) have also pointed out the need for improved efficacy in the treatment of depression.

With regard to EEG correlates of depression, one prominent finding is that the Alpha wave power in the left and right dorsolateral frontal lobes is associated with overall mood. In

order to sustain a positive mood, the Alpha power on the left is typically 10% to 20% lower than on the right. This reflects a differential activation of the hemispheres, which results in the individual emphasizing positive responses and approach behavior, which is mediated by the left hemisphere, in contrast to negative responses and withdrawal or avoidance behavior, which are mediated by the right hemisphere. (Schaffer, Davidson & Saron, 1983; Henriques & Davidson, 1990). Cook et al. (2002) used EEG absolute and relative power, and found a metric called cordance, that was able to identify medication responders, by only after 48 hours of using a trial medication. It did show that the frontal brain areas are likely involved in how a patient is responding to an antidepressant. Bruder et al. (2008) reported an explicit relationship between the amount of asymmetry in the Alpha wave, and how patients responded to SSRI's. In this study, 52 major-depressive disorder (MDD) patients were treated with fluoxetine for 12 weeks. Alpha asymmetry measurements differentiated responders from nonresponders ($p < 0.005$).

Spronk Arns, Barnett, Cooper, and Gordon (2011) investigated a combination of markers from EEG, genetic, and cognitive sources, and examined their relationship to treatment response to antidepressant medication. They evaluated twenty-five patients with Major Depressive Disorder drawn from an initial group of 128, and compared a pre-treatment assessment with one taken at 8 weeks follow-up. These patients remained under the care of their own treating physician, who was responsible for any medication choices, changes, or dosages. Of the 25 patients studied, 14 took an SSRI, 8 took an SNRI, and 2 were treated with a TCA. The best predictor of treatment outcome was a genetic marker, the "Met/Met" variety of the COMT gene. The best cognitive predictor was Impaired Verbal Memory performance on the HAM-D test. In the EEG, higher absolute Theta power in the pre-assessment was the best predictor of a decrease in depressive symptoms following antidepressant treatment. IT was possible to determine the

sensitivity of this prediction as that for every 0.4 microvolts squared of Theta power, the HAM-D scores decreased by 1 point ($p < 0.039$). The authors interpreted the Theta increase at baseline as reflecting higher activation in the cingulate gyrus.

The relationship between Theta activity and response to antidepressants was also described by Pizzagalli et al. (2001). This work went beyond using surface EEG measurements, and used a technique that was capable of resolving the activity of particular brain locations. This method, Low-Resolution Electromagnetic Tomography, or LORETA, was developed by Robert Pascual-Marqui (Pascual-Marqui, Michel, & Lehmann, 1994), and has been validated as a method of estimating, and even visualizing, brain electrical activity from surface recordings alone. The region that Pizzagalli's group identified was the rostral anterior cingulate cortex (rACC). The rACC is a central control site, known to have extensive connections to outlying cortex, and responsible for regulating attention and judgment, among other roles. When patients had high levels of Theta in these regions, they were found to have superior treatment response in the Beck Depression Inventory, when given nortriptyline.

Korb and colleagues (Korb et al., 2009) also used LORETA, and did a retrospective study of patients who had participated in a prior cordance-related study. They found that high pretreatment levels of resting Theta in the rACC and in the orbitofrontal cortex differentiated patients who had responded well to fluoxetine and venlafaxine in the previous studies. Interestingly, this metric did not differentiate placebo responders from nonresponders, indicating that the differential mechanism of response to the antidepressants is different from that with the placebo.

While LORETA results are encouraging, this method has some limitations. These include the fact that accurate localization is not possible in the presence of artifact. Another is

that the LORETA algorithm makes some strong assumptions that the client's anatomy is normal and that the solution uses a "maximum likelihood" method. It is thus not a "true" imaging method in the sense of a CT or MRI, but is a form of highly processed scalp data, rendered in a way that shows a likely, but not guaranteed, profile of brain activity. However, in the case of robust structures such as the dorsolateral cortex and the cingulate areas, and with normal brain anatomy, these sensitivities and limitations are of minimal concern (Pascual-Marqui, Michel, & Lehmann, 1994).

Ulrich et al. (1984) found different response to antidepressant medication, when patients had a slower posterior Alpha frequency, being near 8 Hz rather than the typical 9.5 Hz. They also found that responders showed an increase in this frequency, but only if they started with a normal frequency. The low-frequency group seemed "stuck" with regard to the possible benefits of antidepressants. Another important indicator is spindling Beta, noted previously in connection with ADD/ADHD. In genetic studies, the COMT "Met/Met" group has been found to be strongly related to outcome with SSRI's (Benedetti et al., 2009); similarly, the "Met" COMT variant has been associated with negative response to TCA's and SSRI's (Arias et al., 2006).

Leuchter and Iosifescu developed an antidepressant treatment response (ATR) prediction measure, which is now commercialized by Aspect Medical Systems. It incorporates a set of EEG measures from the frontal area, and combines measured including relative Alpha and Theta power, and Alpha changes after 1 week of treatment (Iosifescu, 2008; Leuchter et al., 2009). Patients with a low ATR could be expected to respond to an SSRI (74% overall accuracy) or to Bupropion, which is dopaminergic. They concluded that this measure identifies two subgroups, and that two different modes of action seem to lead to this particular finding. One disadvantage is that the medication must be prescribed and tried, before the prediction can be made.

In a recent review, Iosifescu (2011) identified biomarkers that had shown value in predicting antidepressant response. He examined EEG-based methods such as Alpha and Theta band levels, the ATR cordance described by Cook et al. (2002), rEEG predictions, EEG source localization, and evoked potentials. He emphasized that a useful predictor should be easy to measure, consistent, and potentially widely available at a low cost. It should also be minimally confounded by comorbid disorders such as anxiety, substance abuse, or medical illnesses.

DeBattista et al. (2011) conducted a multicenter, randomized controlled study that compared two matched groups of depressed patients. One group received antidepressant medications based upon the STAR*D protocols (Rush et al., 2006), while the other group received medications based upon a "referenced" EEG (rEEG) analysis. The rEEG procedure involved first converting the EEG into frequency-band data, and then comparing each participant's results with a database of over 10,000 EEG's to predict optimal drug response. rEEG consists of a QEEG procedure that include not only a referenced normative EEG database, but also to a symptomatic database. Subjects were derived from 12 clinics across the United States, and consisted of 114 patients culled from 465 initial records. All participants had previously experienced some sort of treatment failure using SSRI's or other antidepressants. Exclusion criteria included washout failure, EEG or physical abnormalities, alcoholism, and other diseases and disorders.

Of these 114 patients, half were referred for antidepressant medication using the standard STAR*D protocol. This resulted in the use of 7 different antidepressants, consisting primarily of Bupropion, Citalopram, Lithium, and Venlafaxine. The other group was referred for medication based upon the rEEG findings. One primary finding was that the recommended medications were more often stimulants or anticonvulsants than antidepressants. The primary medications

indicated by the rEEG were Methylphenidate, Dexedrine, Gabapentin, Divalproex sodium (Valproate), Carbamazepine, and Selegiline. Of the antidepressants selected by STAR*D, only two were recommended more than once by the rEEG. These were Venlafaxine (2 patients) and Bupropion (8 patients). Therefore, the rEEG recommendations were essentially at "right angles" to the traditional yet contemporary best practices.

DeBattista's group used a battery of efficacy variables, with multiple points of measurement across the trial. These included the QIDS-SR16, the Q-LES-Q-SF, and the CGI-I. Using a mixed-model repeated-measures analysis, they were able to show that the rEEG was significantly more effective at identifying candidate drugs than the STAR*D method. For example, the QIDS-SR16 response rate for rEEG was 65% for rEEG, compared with 38.8% for the control group. The mean change from baseline scores for the two groups were significantly different in the QIDS-SR16 (-6.8 versus -4.5, $p < 0.0002$) as well as in the Q-LES-Q-SF (18.0 versus 8.9, $p < 0.0002$). Significant differences were also found showing superior improvement in the rEEG group, for the CGI-I assessments. The clear conclusion that can be drawn from this study is that, if it reflects real-life situations, then using rEEG in the selection of medications for treatment-resistant depression is an evidence-based, effective, and low-cost approach.

Limitations of the DeBattista study include the fact that the STAR*D may not exactly capture current clinical practice, because it depends on a strict serial design. Another consideration is that the rEEG recommendation process essentially requires that the patient be washed out of all medications. This may not be practical in all situations. It is possible to acquire a rEEG analysis while the patients are still on medications, but this is considered by the provider, CNS Response Inc. (2012), to have lower accuracy and predictive value.

Conclusion

The results described here make a case for considering the inclusion of EEG as an important consideration in assessing patients with ADD/ADHD or depression. The parameters available from EEG as well as QEEG analysis provide a strong foundation for improving psychopharmacological management, avoiding treatment failures, and assessing treatment progress. It is found that certain underlying factors visible in the EEG can predict drug response and indicate potentially useful medications, beyond what is possible with behavioral or cognitive assessments. For example, in a group of non-responders to antidepressants, studies have shown that the subgroup with excess Theta power may respond well to stimulant medication, despite there being no diagnosis of ADHD. As another example, EEG-based analyses, as well as emerging practice standards, may indicate anticonvulsants for the treatment of mood disorders, even though these are normally used for the treatment of epilepsy (Suffin & Emory, 1995).

Iosifescu (2011) put some of the clinically relevant realities into perspective. According to his analysis, the application of EEG-based markers in clinical practice may not be primarily for the selection of treatments, but for the evaluation of treatments already under consideration. However, the findings of DeBattista et al. (2011) would challenge this view, at least in the case of depression. The latter study showed explicitly that a rEEG-based method can indicate medications that would not otherwise be considered, such as stimulants or anticonvulsants. Moreover, the profound success of the rEEG analysis in producing a positive response rate of 65%, would seem to recommend it highly. A primary concern with the use of rEEG is the necessity for complete drug washout in order to achieve a reliable result. This consideration may place the value of rEEG more in line with a rehabilitation facility or acute psychiatric setting, in which withdrawal from all drugs is part of an existing protocol.

Another reality with the use of rEEG is that there is a cost associated with recording the EEG (typically $100 or more), plus the cost assessed by CNS Response, Inc. to perform the analysis (over $500). Without a specific insurance code that will cover this expense, practitioners are forced to subsidize this outright, apply a partial or total out-of-pocket charge on the client, or seek partial reimbursement under an existing EEG code. This latter option will be limited to practitioners who have an accepted EEG credential, and for whom the insurance carrier agrees to cover this expense.

Overall, the potential of EEG as a means to determine optimal medications is a promising one, and warrants further research and application. If the limitations with regard to economy, access, and possible "turf" issues can be surmounted, this can become a valuable addition to pharmacological planning and evaluation.

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