

The Promise of the Quantitative Electroencephalogram as a Predictor of Antidepressant Treatment Outcomes in Major Depressive Disorder

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WHY DO WE NEED PREDICTORS OF ANTIDEPRESSANT TREATMENT OUTCOME?

A large percentage of patients (30%–53%) fail to respond to an initial course of antidepressant medication [1–3], and for those who do respond clinical improvement often takes a long time. Results of the recently completed multisite study of Sequenced Treatment Alternatives to Relieve Depression, reviewed extensively by Nierenberg and Fava in this issue, highlight this point. With 2876 analyzable participants, this landmark study is the single largest trial of treatment outcomes for depression to date; in contrast to many clinical trials, minimal exclusionary criteria ensured that participants were representative of real-world, treatment-seeking outpatients who had nonpsychotic major depressive disorder. At study outset, all subjects were treated with the maximum tolerated dose of citalopram (up to 60 mg) for up to 14 weeks. Even with aggressive dosing, this representative selective serotonin reuptake

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inhibitor (SSRI) showed only modest effectiveness. Examining a response criterion of a reduction of 50% or more on the 16-item Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR) and a remission criterion of five or lower on the QIDS-SR, only 47% of subjects responded and 29% remitted. Moreover, even for subjects who responded and/or remitted after 14 weeks of treatment, symptomatic improvement was slow. After 6 weeks, only about two thirds (65.2%) of ultimate responders had responded, and just over half (52.9%) of ultimate remitters had remitted [3]. These data mirror the typical experience in clinical practice; that is, response or remission to a given medication is uncertain, and it takes a long time to determine outcome.

The inability to predict a patient's response to a particular treatment can lead to a delay in effective treatment, which in turn can have a number of deleterious consequences. Without any reliable means of predicting outcome, patients and physicians are left to use a trial-and-error strategy in which the trial often lasts 6 to 12 weeks. Patients who do not respond to an initial treatment must endure subsequent trials to determine the effectiveness of different regimens, and many abandon treatment while still symptomatic [4]. The most apparent consequence of delayed effective treatment is that patients continue to suffer from the symptoms of depression including increased risk for suicide [5]. There also is evidence that prolonged depression is associated with deleterious effects on the central nervous system. Major depression has been associated with reduced hippocampal volume [6], and longer durations of untreated depressive episodes have been associated with lower hippocampal volume [7]. Patients who do not respond to their first antidepressant trial are at increased risk for never receiving adequate treatment [4], and delays in effective treatment are associated with a poorer prognosis for the course of illness over subsequent episodes. A longer index episode (>12 weeks) has been associated with a 37% lower rate of recovery in subsequent episodes [8]. One study examining the impact of 16 sociodemographic and clinical factors identified rapid remission as the most important predictor of favorable long-term outcome [9]. In addition to health concerns, medical expenditures also increase with increasing numbers of ineffective treatment trials. A study of 7737 depressed subjects found higher inpatient, outpatient, and pharmaceutical health care costs with increasing numbers of changes in antidepressant treatment regimen [10]. The introduction of reliable predictors of response to treatment thus could potentially shorten the course of treatment and improve long-term treatment outcomes in depression.

CLINICAL AND PHYSIOLOGIC PREDICTORS OF ANTIDEPRESSANT RESPONSE

The clinical relevance of predicting response has driven a great deal of exploration of possible sociodemographic, clinical, and pretreatment physiologic predictors [11–16]. Many inconsistencies exist across studies, however, and most factors that seem to have heuristic value in differentiating groups

of responders or nonresponders have not proven to be reliable pretreatment predictors of response for individual patients [17–21]. As yet, none has proven sufficiently useful to be adopted into clinical practice for predicting treatment response [14–22]. A few notable measurements have begun to demonstrate increased levels of reliability and accuracy as predictors of antidepressant response. For example, considerable data in the burgeoning literature on pharmacogenetics have linked response to SSRI treatment with genetic variants in the sequences coding for specific molecules including the serotonin (5-HT) transporter, 5-HT-2A-receptor, tryptophan hydroxylase, brain-derived neurotrophic factor, G protein beta3 subunit, interleukin-1beta, and angiotensin-converting enzyme, but with inconsistencies among results [23]. Further work with large patient samples stratified for intervening variables is needed before drawing more definite conclusions [24]. Although there is hope is that the identification of key genetic components eventually will facilitate individualized treatment planning (so-called “personalized medicine”), small variances of analyzed polymorphisms may diminish optimism for immediate application at the clinical level [25]. In a line of work examining functional brain asymmetry, perceptual asymmetry as assessed using dichotic listening tests has been demonstrated repeatedly as a predictor of response to fluoxetine with some evidence of clinically meaningful accuracy; however, gender-dependent relationships between predictor and outcome variables require further study [26–28]. Also, it is unknown whether this marker is medication specific.

Other investigations have examined changes in physiologic function during antidepressant treatment as biomarkers of therapeutic response. Several studies using positron emission tomography (PET) to assess cerebral metabolism during treatment have reported differences in prefrontal and/or cingulate activity between responders and nonresponders to antidepressant medications. Most studies report that metabolism increases in ventral paralimbic areas or in the caudate nucleus during effective antidepressant treatment [29]; cortical metabolism, however, has been reported either to increase or decrease, depending upon the study [30,31]. Most studies of cerebral blood flow, as well as most recent studies of cerebral metabolism, indicate that a decrease in cerebral perfusion in dorsolateral prefrontal cortex is associated with effective antidepressant treatment. In reports of a relatively large sample of subjects who had depression, investigators found decreases in perfusion in prefrontal cortex [32,33]. Previous findings also have reported decreases in prefrontal cerebral perfusion in subjects responding to various antidepressant medications [34]. Other investigators have reported decreases in prefrontal cortex metabolism in subjects responding to paroxetine treatment [35,36]. Despite these encouraging findings, the real-world clinical application of PET scans for predicting treatment outcomes may be limited. Dosimetry concerns impose limitations on the safe use of radioactive tracers for serial scanning. This technology also is costly and invasive, and access is limited outside a research setting.

ELECTROENCEPHALOGRAPHIC PREDICTORS OF ANTIDEPRESSANT OUTCOMES

Overview

Electroencephalography (EEG) has long held appeal as an easily accessible technique to measure central nervous system activity. Since Hans Berger's first recording of the human EEG in the mid-1920s and early demonstrations that drugs that influence human behavior also produce obvious effects on human EEG, numerous attempts have been made to apply the recording of electrical activity from scalp electrodes to a wide range of psychiatric concerns including diagnosis, treatment selection, and drug development. Historically, the field has covered a broad range of applications and methodologies. Researchers have examined various spontaneous and activation-induced EEG features measured at different time-points, recorded using a variety of electrode montages, and analyzed using different approaches. Moreover, few early studies controlled for potentially confounding variables. Although the lack of standardization makes comparisons among early findings difficult, and the absence of controls leaves open the interpretation of results, these early reports provide the first evidence of the potential capability of quantitative electroencephalography (QEEG) measurements to predict clinical outcome to antidepressant medications. More recently, studies have begun to refine methods to give EEG markers greater predictive capability and to standardize those methods to allow replication of results. In addition, some newer studies have used more rigorous experimental designs and controls, thus allowing greater certainty in interpretations of the observed relationships between EEG markers and clinical response during treatment with antidepressant medication.

Rationale Behind Electroencephalographic Markers of Response

A potential EEG predictor of antidepressant response can be measured (1) before treatment (ie, as a baseline or pretreatment measure), (2) shortly after start of drug, or (3) as a "change variable" or "change indicator" describing change in the EEG from a pretreatment baseline to a time-point after initiating treatment. In any case, to have clinical utility as a predictor, the EEG measure of course must precede the clinical response. The assumption underlying a baseline EEG indicator is that state and/or trait factors reflected in the EEG are related to how the subject will respond to antidepressant medication. The assumptions behind an EEG predictor measured sometime early after the onset of drug treatment are that (1) antidepressant medication produces changes in the EEG soon after beginning treatment, and (2) identifiable medication-related EEG changes are reliably linked to later clinical changes. A subject's brain state or change in brain state after a brief period of antidepressant treatment presumably reflects the interaction between patient factors and exposure to medication and would be a leading indicator of eventual clinical trajectory.

Early Work Suggesting Relationships Among Electroencephalographic Findings, Symptoms of Depression, and Antidepressant Medication Effects

A considerable body of research supports the assertion that antidepressant medication effects are physiologically detectable in the EEG. Prior work in the “pharmacology-EEG” tradition has shown that administration of antidepressant compounds to healthy subjects produces reliable EEG changes within hours of dosing [37–47]. Although there are reproducible EEG effects of antidepressant medications across subjects, variances in the EEG response also have been noted [48]. Differences in medication effects on the EEG have been linked to individual differences in the pre-exposure EEG [48], suggesting that the baseline EEG may indeed capture state or trait aspects of central nervous system function that moderate subsequent effects of medication on the central nervous system.

Use of the EEG to predict antidepressant outcome has roots in an early study that examined pretreatment EEG and the change from pre- to post-treatment EEG as potential predictors of outcome to amitriptyline and pirlindole [49]. Responder versus nonresponder groups assessed after 4 weeks of treatment were differentiated on the basis of both their pretreatment baseline EEGs and pre- to posttreatment EEG changes after 4 weeks. Responder groups were distinguished by a number of EEG parameters, especially in the alpha range. Among other features, responders were characterized by left lateralization of baseline alpha power, decreases in absolute alpha power, and increases in slower frequencies over 4 weeks. Although EEGs were recorded from occipital, central, and frontal regions, only occipital regions were evaluated in the primary report. Later reanalyses of these data examined the topographical distribution of alpha activity across recording regions and found lateralized differences in anterior as well as posterior regions between responders and nonresponders [50,51]. Some EEG correlates of response were medication specific [50,51], whereas others were observed with both medications [49].

A later study examining EEG predictors of 3-week response to the heterocyclic antidepressants clomipramine and maprotiline found that early changes in the EEG (ie, changes from baseline to 2 hours after the first daily drug infusion) distinguished between later responders and nonresponders to either medication [52]. In that study, the EEG measure used as a predictor measure was the frequency of non-A epochs (ie, 2-second epochs that do not represent alpha activity) as calculated using a novel procedure to quantify spatiotemporal changes in alpha activity [53].

Lateralized baseline alpha power was associated with response to fluoxetine in a study of 53 depressed adults [27]. Left dominant pretreatment values of alpha power (indicative of greater right hemisphere activation) were associated with 12-week response as measured using the Clinical Global Impression Improvement scale. This predictive relationship was evident for women but not for men.

Pretreatment baseline and postdrug change differences in theta-band log transformed relative power were found to distinguish responders from nonresponders to 4 weeks of open-label treatment with the tricyclic antidepressant imipramine [54]. At pretreatment, responders exhibited significantly less overall theta power; pretreatment differences in other frequencies were not significant. Acute (3 hours after initial dose) postdrug change in overall theta power distinguished responders from nonresponders. Considering EEG changes over the first 2 weeks of treatment, responders showed significantly greater increments in anterior theta power than did nonresponders.

In a study examining baseline EEG predictors of response to the SSRI agent paroxetine, lower baseline relative theta power again was associated with greater improvement [55]. Of note, all significant pretreatment indicators were localized to frontal brain regions. This finding is in contrast to the study of imipramine that reported a positive association between overall lower baseline theta power and response [54]. Differences in these findings could be related to different mechanisms of action between tricyclic and SSRI medications.

Taken together, these reports provide evidence suggesting that pre- and posttreatment EEG measurements (especially measurements in alpha and theta bands and potentially lateralized and frontal measurements) are related to later clinical outcome of antidepressant treatment. These reports show subtle but statistically significant EEG differences between groups of responders and nonresponders; however, the considerable overlap in the distribution of values for responders and nonresponders limits the predictive validity for individual patients. Another consideration regarding these studies is that none examined placebo-control conditions; therefore, a limit of these investigations is that it is not possible to discern whether the EEG findings were related generally to clinical improvement or more specifically to drug efficacy (specific versus nonspecific or placebo-like effects).

Quantitative Electroencephalographic Biomarkers: a New Wave of Accuracy in Predicting Antidepressant Response

Neurobiologic conceptual model underlying relationships between frontal theta measurements (relative power and cordance) and antidepressant response

Several lines of reasoning support the rationale for examining frontal EEG measurements in the theta band (4–8 Hz) in relation to antidepressant medication effects and changes in depressive symptoms. The underlying neurobiologic conceptual model draws on prior work indicating that (1) activity in anterior cingulate and dorsolateral prefrontal regions is related both to depression and changes in mood in response to treatment; (2) prefrontal theta activity is associated with other measurements of cortical activity in the anterior cingulate and seems to be related to network processing of affective information; and (3) the effects of antidepressant medication produce alterations in theta band activity.

A consistent finding in neuroimaging studies from independent research groups is that of abnormal metabolism or perfusion in the dorsolateral

prefrontal cortex and/or the anterior cingulate cortex in depressed subjects [29,30,36,56–62]. Prefrontal and cingulate regions also figure consistently and prominently in studies using EEG to examine brain function associated with depressed mood [27,63–69], and these regions also have been examined using functional MRI [70,71]. Networks of projecting white-matter fibers connect these regions, both neuroanatomically and functionally [72–76]. The importance of these anatomic tracts in this context is that rhythmic theta activity recorded at the scalp in prefrontal channels may reflect both the intrinsic activity originating in the dorsolateral prefrontal cortex and the projected rhythms that are generated in deep locations (eg, the anterior cingulate) and influence activity in the cortex nearer to the recording electrodes.

Theta band activity in particular has been examined with regard to coordinated activity between the midline prefrontal and cingulate regions. Studies that combined surface EEG recordings and magnetoencephalographic (MEG) data have indicated that surface theta rhythms recorded from prefrontal channels are correlated with deep theta MEG activity in the anterior cingulate [77,78]. Activity in the theta band seems to be important to the integration of activity across distributed neural networks [79,80]. Shifts in theta band activity also have been particularly linked with processing emotionally related stimuli and meditation-related changes in emotional state [81–84].

Antidepressant compounds [54,55,85–88] and treatment with electroconvulsive therapy [89] have been shown to alter theta activity. Pretreatment theta cordance measured from electrodes overlying the cingulate cortex has been related to the response to electroconvulsive therapy in major depressive disorder (MDD) [90]. Using EEG tomography, pretreatment theta activity associated with antidepressant response has been localized to the anterior cingulate [63].

Theta band relative power

Several naturalistic studies using open-label, flexible-dose SSRI treatment have demonstrated the predictive capability of theta band relative power measured from frontal electrodes. In a cohort of 36 adult outpatients meeting criteria for MDD, frontal theta band relative power 1 week after start of drug was significantly lower in responders than in nonresponders [91]. Response was defined as a reduction of 50% or more in scores on the 17-item Hamilton Depression Rating Scale (HamD₁₇) from baseline to week eight. Lower theta band relative power at 1 week also correlated with percent improvement in the HamD₁₇ score over 8 weeks. Importantly, this measure predicted response with 83% overall accuracy (76% sensitivity, 93% specificity) and .88 area under the receiver operating curve. This essential finding was replicated by the same group of investigators in a larger sample of 68 patients who had MDD treated with SSRIs [92]. Again, frontal theta band relative power 1 week after start of drug was significantly lower in responders than in nonresponders and was negatively correlated with the magnitude of clinical improvement. The predictor yielded an overall accuracy of 67% with 71% sensitivity and 61% specificity.

Another analysis of frontal theta band relative power, also from the same investigators, examined 52 subjects who had MDD grouped by depressive subtype (melancholic, atypical, or typical) [93] and treated naturalistically. Baseline frontal theta band relative power was significantly lower in SSRI responders than in nonresponders, and the difference in frontal theta band relative power between responders and nonresponders was similar across clinical subtypes. Baseline theta band relative power alone predicted response with 71% accuracy (72% sensitivity, 70% specificity) and in combination with measurements of theta band relative power at 1 week resulted in improved prediction (79% accuracy, 84% sensitivity, and 70% specificity.) Here, the addition of the week one measure added to the ability to correctly identify responders.

An independent study of 22 outpatients who had MDD examined frontal theta band relative power measurements as predictors of 8-week response to citalopram [94]. Mean decreases in frontal theta band relative power were observed in responders but not in nonresponders at weeks one, two, and four. The decrease in theta band relative power 2 weeks after start of medication was significantly greater in treatment responders than in nonresponders, and decreases predicted response with 73% accuracy (73% sensitivity, 73% specificity).

These studies are comparable in many respects. Each used identical, automated EEG recording methods to measure frontal theta band relative power, examined outpatients who had MDD receiving open-label treatment with SSRIs, and assessed response/nonresponse outcome as an improvement of 50% or more on the HamD₁₇ scale after 8 weeks of treatment. Each of these studies demonstrated significant associations between clinical response to antidepressant medication and lower frontal theta band activity or decreases in frontal theta band activity within the first 2 weeks after start of medication. Strong predictive capability was demonstrated for frontal theta band relative power biomarkers, but there was some variability in the EEG time-points used as predictors in these studies of theta band relative power. Predictive capability was shown either for baseline, week one, or change at week two EEG measurements, depending on the study; therefore they cannot be viewed as direct replications of the same finding. Furthermore, because these studies did not examine control subjects treated with placebo, the capacity of these indicators to discriminate between specific response to medication and nonspecific effects is unknown.

Quantitative electroencephalographic cordance development

Cordance is a measure that combines absolute and relative power with the goal of extracting information with greater physiologic meaning from QEEG. Absolute power, the amount of power in a frequency band at a given electrode (measured in μV^2), and relative power, the percentage of power contained in a frequency band relative to the total power across the entire spectrum, are associated inconsistently with direct measurements of cerebral

energy use, making their physiologic significance unclear [95]. For example, relationships between EEG power measurements and perfusion or metabolism show considerable variability across frequency bands and sites [96,97], with some studies showing only weak associations [98]. Absolute power and relative power are, in fact, complementary measurements of brain activity [99] that have independent associations with perfusion [100]. Cordance combines traditional absolute power and relative power measurements to achieve a stronger association with cerebral perfusion than is seen with either measure alone. A detailed description of how cordance is calculated is provided elsewhere [101].

Several studies have demonstrated relationships between QEEG cordance and other physiologic measurements. In a series of outpatient case studies, cordance was reported to have strong associations with other measurements of brain structure and function including white-matter lesions detected on MRI, metabolism measured by PET using fluorodeoxyglucose, and perfusion measured by hexamethylpropyleneamine oxime single-photon emission computed tomography (SPECT) [95]. A larger study examining 27 outpatients who had degenerative or vascular dementia showed that cordance had a stronger association with perfusion (measured using SPECT) than either absolute or relative power measurements alone, and this relationship held across multiple brain regions as evidenced by data from frontal, temporal, and occipital electrode sites [102]. Finally, a study of normal healthy subjects compared associations between perfusion (measured using O¹⁵ PET) and QEEG measurements including absolute power, relative power, and cordance [101]. Of the three EEG measurements examined, cordance was found to have a moderately strong association with perfusion and was the strongest of the measurements examined, both during a resting state and motor task performance. In addition, cordance was as effective as PET in detecting lateralized activation associated with a motor task; EEG power measurements did not detect this activation.

Theta cordance as a predictor of antidepressant treatment outcomes. The first systematic report to indicate that theta cordance might be sensitive to pharmacotherapy interventions was made in the context of a study that used cordance to assess cerebral energy use in late-life depression [100]. QEEG theta cordance measurements were obtained for 27 depressed subjects and 27 matched controls with the hypothesis that depressed subjects would show overall alterations consistent with the decreases in perfusion and metabolism seen using PET [59] or SPECT [103]. Results supported the hypothesis and demonstrated differences in global and regional cordance between depressed and control subjects. It is important for response prediction that cordance patterns were found to differ significantly between depressed subjects who were being treated with antidepressant medication and those who were not. This observation, albeit cross-sectional, suggested that theta cordance might be sensitive to changes in brain function attributable to antidepressant treatment.

The relationship between theta cordance and treatment response was explored in a series of individual cases that illustrated frontal decreases in theta cordance as early as 48 hours after beginning medication preceding clinical improvement in depressed outpatients receiving open-label treatment with SSRI or serotonin-norepinephrine reuptake inhibitor (SNRI) medications [31]. Later, a larger case series prospectively examined decreases in prefrontal cordance as a predictor of 2-month outcome in seven subjects who had major depression receiving naturalistic open-label treatment with SSRI or SNRI antidepressants [104]. Subjects were free of psychotropic medications for 2 weeks before enrollment in the study. All four responders showed large decreases in cordance 48 hours and 1 week after initiating medication. None of the three nonresponders showed this pattern; one showed only a slight decrease, and the other two nonresponders showed frank increases in prefrontal theta band cordance. Using a simple dichotomous decrease/no decrease predictor (in which decrease predicted response), change in prefrontal theta band cordance yielded an overall accuracy of 86%, with 100% sensitivity and 67% specificity.

Data from individual cases prompted the first hypothesis-driven placebo-controlled study of theta band cordance as a potential biomarker of antidepressant response [105]. Decreases in prefrontal theta band cordance at 48 hours and at 1 week after start of medication were hypothesized to predict 8-week antidepressant response (final $\text{HamD}_{17} \leq 10$). Data were pooled from 51 depressed patients across two placebo-controlled studies that used fluoxetine or venlafaxine, respectively, as the active medication. There was a trend finding at 48 hours, and at 1 week change in prefrontal theta band cordance significantly distinguished medication responders from all other groups (medication nonresponders, placebo responders, and placebo nonresponders). In addition, the degree of change in prefrontal cordance was significantly associated with degree of response. Using prefrontal cordance decrease/no decrease as a dichotomous predictor of response accurately classified 9 of 13 medication responders (69%) and 9 of 12 medication nonresponders (75%) for an overall accuracy of 72%. Decreases in prefrontal theta band cordance did not predict response among subjects assigned randomly to placebo. In fact, a separate study of the same 51 subjects revealed a distinctly different pattern of change (4- and 8-week increases in prefrontal cordance) for placebo responders as compared with all other groups [106].

The finding of early decrease in prefrontal cordance as a predictor of response has been replicated by the same group of investigators and by an independent research team. In a study of patients who had treatment-resistant depression, prefrontal theta band cordance EEG measurements were obtained a cohort of 12 outpatients at baseline and approximately 1 week after beginning a new treatment [107]. These patients had not responded to monotherapy and were beginning a new treatment as prescribed by their treating psychiatrists. In contrast to earlier studies that had used a drug-free interval or drug washout period before obtaining the baseline EEG [104,105], these treatment-resistant

subjects were evaluated without a drug-free interval between trials. Response was evaluated after 8 to 10 weeks. Of six responders, five showed an early decrease in cordance; only two of the six nonresponders showed an early cordance decrease. The predictor yielded accurate classification for 75% of the subjects. Findings using cordance have been replicated independently in a study of 17 depressed inpatients receiving open-label treatment with antidepressants from a variety of classifications [108]. Prefrontal theta band cordance decreases after 1 week predicted response ($>50\%$ reduction of Montgomery-Asberg Depression Rating Scale scores after 4 weeks of treatment) with an overall accuracy of 88% (100% sensitivity, 83% specificity). In a pooled analysis of 54 subjects from three studies across investigative teams, decreases in prefrontal cordance yielded an overall accuracy of 78% [109].

Across studies of MDD subjects treated with various antidepressant medications, decreases in prefrontal theta band cordance 1 week after start of medication have predicted response consistently with overall accuracy ranging from 72% to 88%. Examination of this predictor in randomized, double-blind, placebo-controlled trials has demonstrated specificity for this marker as an indicator of medication efficacy.

Future Directions Using Spontaneous Electroencephalographic Measurements to Predict Other Antidepressant Outcomes

Recent evidence suggests that EEG measurements might be useful in predicting other positive outcomes as well as negative outcomes of antidepressant treatment (ie, treatment-emergent adverse events). Although most studies to date examining QEEG predictors of clinical outcome have focused on treatment response (typically $\geq 50\%$ improvement in symptoms or a final HamD₁₇ score ≤ 10), there is growing emphasis on remission (eg, final Ham-D score ≤ 7 or ≤ 5) as the endpoint goal of treatment. Although prefrontal channels seem to predict response with a high degree of accuracy, recent evidence suggests that electrodes overlying the midline and right frontal region may predict remission [110,111]. With regard to treatment-emergent adverse events, a promising new line of work suggests that EEG markers also may be able to predict worsening of somatic and mood symptoms. EEG markers have been linked to the overall occurrence of common side effects including headache, nausea, and sexual dysfunction [112] and to the emergence of increased thoughts of suicide [92] reported during antidepressant treatment.

OTHER ELECTROENCEPHALOGRAPHIC-RELATED PREDICTORS OF ANTIDEPRESSANT OUTCOMES

Loudness Dependence of Auditory Evoked Potentials

In addition to measurements of spontaneous EEG activity, such as relative power and cordance, measurements of brain response to a stimulus have been examined as predictors of treatment response. A variety of preclinical and clinical studies have suggested that the loudness dependence of auditory evoked potentials (LDAEP) may reflect activity in the brain's serotonergic

system. These auditory evoked potentials arise from activity in the primary auditory cortex and can be studied using dipole source analysis [113]; the ratio of N1/P2 amplitude values increases with increasing tone loudness during auditory stimulation, and LDAEP values are inversely related to central serotonergic activity. Patients who had a strong LDAEP (a marker of a low serotonergic state) before treatment responded significantly better to SSRI medications than did patients who had a lower LDAEP (and, presumably, high or normal serotonergic activity) [114–119]. One study has examined the predictive value of the LDAEP in relation to treatment with the SNRI reboxetine. In contrast to the direction of amplitude changes associated with SSRI response, lower pretreatment intensity-dependent N1 amplitude slopes were significantly associated with reboxetine response, suggesting that LDAEP differentially predicts clinical response to serotonergic versus noradrenergic antidepressant psychopharmacotherapy [120]. As with the approaches described previously in this article, the LDAEP method shows promise in differentiating between patients who may or may not respond to a particular medication; further independent replication under controlled conditions will help clarify how it might best be used for guiding treatment decisions in clinical care.

Nonlinear Measurements of Brain Physiology

EEG power and cordance are both linear measurements of the EEG power spectrum. A nonlinear measure of EEG activity, the bispectrum, also has been examined for use in detecting pretreatment differences between responders and nonresponders to antidepressant treatment. The bispectrum quantifies phase and power coupling between EEG components [121] and could offer a complementary measurement of regional brain activity. In an investigation of adult outpatients treated with fluoxetine, venlafaxine, or placebo [122], bispectrum values were calculated for frequency triples of the form $[f_1, f_2, f_1+f_2]$ at 1 Hz resolution using a single frontotemporal channel (T3-Fp1). Across all treatment groups, the bispectrum in the range $[12 \text{ Hz} < f_1 < 24 \text{ Hz}, f_2 < 6 \text{ Hz}]$ was higher in the more severely depressed patients, with a significant correlation between HamD₁₇ score and bispectrum value. Additionally, there were baseline differences between responders and nonresponders to medication. Further replications and extensions of that work are underway, and bispectrum-based measurements might be combined with cordance or other linear measurements to create a composite biomarker with improved predictive accuracy.

HOW MIGHT INFORMATION FROM ELECTROENCEPHALOGRAPHIC PREDICTORS BE USED IN CLINICAL PRACTICE?

Reliable prediction of antidepressant treatment outcomes would have benefit regardless of whether indicators for a given antidepressant regimen point toward response or failure for a patient. Pretreatment, as compared with

postdrug, indicators might be interpreted slightly differently. The value of a positive EEG change indicator would be to provide the patient and physician with some degree of assurance that continued treatment will be fruitful and to avoid unnecessary (and perhaps ineffective) switching and/or augmentation of medications. Increased confidence in a positive outcome also could encourage treatment adherence even as patients contend with side effects that can peak before therapeutic effects are realized. In the case of a negative change indicator, the probably ineffective treatment regimen could be changed far sooner than is current common practice, and the new regimen could be initiated shortly thereafter. Evidence from a study of subjects who had stage I treatment-resistant depression suggests that the predictive capability of QEEG concordance biomarkers does not require a drug-free interval between treatments [107]. Positive baseline indicators could suggest that a given individual is generally suitable for antidepressant medication whether because of state or trait factors; pretreatment EEG biomarkers (LDAEPs notwithstanding) have not been studied extensively with respect to their ability to predict differential response to different medications. The value of a negative baseline indicator for antidepressant response is unknown, although it is possible that other types of interventions would be more effective for individuals who have a poor prognostic indicator for pharmacotherapy. Another interpretation is that a negative baseline indicator suggests that the transient state of the individual is not conducive to antidepressant response at that time. In this view, medication-free measurements repeated over time might change from an unfavorable to a favorable indicator for pharmacotherapy, thus identifying a particular time during which initiation of antidepressant treatment would likely lead to clinical response or remission.

CAVEATS AND CAUTIONS

The comparatively low cost, high patient acceptability, and technological ease of performing QEEG data collection and analysis can be viewed as strengths of this approach. On the other hand, these same attributes mean that there is a low barrier to entry in the field, and individuals and groups with little training or experience can gather QEEG data on patients or research subjects. The reliability and interpretability of these data may be inconsistent or worse.

The conclusions that can be drawn from any innovative clinical research study need to be subjected to scientific scrutiny through peer review and independent replication of findings before they can be considered for use in advancing clinical care, whether the innovation is a new molecule designed for therapeutic use or a technology proposed for guiding treatment. Unfortunately, the low barriers to entry in the QEEG arena have meant that naively designed, poorly executed, or inappropriately analyzed data are not subjected consistently to the normal checks and balances of the scientific method, and systems purporting to diagnose and/or provide guidance for care are available without having been subjected to rigorous review expected of other advances in biomedical research. The research and clinical communities therefore must

be attuned to the reality that not all “QEEG” systems represent the same measure or technique. Only through thoughtful consideration of each method separately can the claims advanced for a particular technique be assessed. After this type of careful review, methods for which there is an adequate evidence base enter the mainstream of care.

SUMMARY

Recent studies have shown overall accuracy rates of 72% to 88% using baseline and/or 1-week change in QEEG biomarkers to predict clinical outcome to treatment with various antidepressant medications. In some cases, findings have been replicated across academic institutions and have been studied in the context of randomized, placebo-controlled trials. Recent EEG findings are corroborated by studies that use techniques with greater spatial resolution (eg, PET, MEG) in localizing brain regions pertinent to clinical response. As such, EEG measurements increasingly are validated by other physiologic measurements that have the ability to assess deeper brain structures. Continued progress along these lines may lead to the realized promise of QEEG biomarkers as predictors of antidepressant treatment outcome in routine clinical practice. In the larger context, use of QEEG technology to predict antidepressant response in major depression may mean that more patients will achieve response and remission with less of the trial-and-error approach that currently accompanies antidepressant treatment.

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