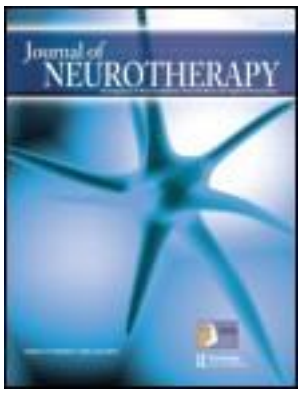

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Clinical Corner

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CLINICAL CORNER

D. Corydon Hammond, PhD, Editor

The purpose of the Clinical Corner is to provide responses to clinically oriented questions that may not, in many cases, have been evaluated yet by research. Therefore, the personal opinions expressed in the column are exactly that, the opinions of the individual authors, often based on their clinical experience. The opinions shared belong to the authors and are not necessarily those of the Society for Neuronal Regulation (SNR), or the Journal of Neurotherapy. Nonetheless, it is hoped that the diversity of opinion expressed in this column will stimulate thought and the further exchange of ideas.

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EFFECTS OF ANTIDEPRESSANT MEDICATIONS ON THE EEG

QUESTION: What effects do antidepressant drugs have on the EEG?

RESPONSE: Jack Johnstone, PhD, President and CEO, Q-Metrx, Inc., Burbank, CA. E-mail: jack@q-metrx.com

Effects of psychoactive medication on the human EEG have been studied nearly as long as the study of the EEG itself. Hans Berger, the discoverer of the human EEG, described the effects of cocaine on the

electroencephalogram in 1931, showing increased high frequency activity (see Herning, Jones, Hooker, Mendelson, & Blackwell, 1985, for a review). Today the study of quantitative EEG in predicting and monitoring effects of medications remains one of the most exciting fields in neuroscience research. Medication response prediction represents one of the most practical applications of quantitative EEG analysis.

Most applications of QEEG in clinical settings include comparison of an individual patient to a reference or normative database. It is important to note that the subjects that make up these databases are medication free. Significant deviations from the normal pattern can be found simply because the patient is medicated. Knowing the effects of commonly used medications is important in assessing the significance of these deviations. Those doing neurofeedback work must appreciate the effect of medication on the EEG signal.

The sensitivity of the EEG to medication effects is well known to the electroencephalographer. Indeed, psychotropic medications can be classified by effects on the EEG. For example, benzodiazepines can induce beta activity in the 14-25 Hz range. Barbiturates produce both increased delta activity and somewhat faster beta spindles in the 18-30 Hz range. The older tricyclic antidepressants such as amitryptiline (Elavil), imipramine (Tofanil), desipramine (Norpramin), doxepin (Sinequan), and nortryptyline (Pamelor) tend to produce both slow and fast activity, decrease alpha, and have sedative effects. The newer SSRI antidepressants such as fluoxetine (Prozac), venlafaxine (Effexor) and paroxetine (Zoloft) produce less delta and theta activity, decrease alpha, and increase beta. Antidepressant agents such as bupropion (Wellbutrin) have dopaminergic effects that tend to reverse vigilance impairment and drowsiness. Bupropion also decreases seizure threshold and may produce epileptiform discharges in the EEG. Neuroleptics can decrease fast and increase slow activity. Stimulants can decrease EEG slowing and increase fast activity. Topographically, most medication effects are seen maximally over midline frontal or parietal cortex.

Pioneering work on modern quantitative analysis of effects of psychoactive medication on the EEG was carried out in the 1960s by Itil, Shapiro, Fink, Hermann, and others (see Anderer, Saletu, Kinsperger, & Semlitsch, 1987). Dr. Itil (1982) noted that, “no pathognomonic findings have been established for various behavioral phenomena.” In contrast, the changes in the EEG due to medication effects have been confirmed and replicated in numerous pharmaco-EEG studies, most using a dose/response model.

Saletu et al. (1992) used QEEG analysis with 16 healthy volunteers in a double blind, placebo controlled study of the SSRI venlafaxine (Effexor). They found that venlafaxine exerted a significant action on brain function as compared to placebo, evidenced largely by decreased relative alpha activity over frontotemporal regions bilaterally as well as right temporal and temporo-occipital regions.

Quantitative EEG with reference to normative data has been used to predict the effects of medication in psychiatric disorders (predictive model). The study reported by Suffin and Emory (1995) showed that specific EEG markers of medication response were present in two distinctly different clinical populations, patients with either attentional or affective disorders. These investigators subsequently showed that similar markers were found across a wide range of neurobehavioral disorders. Clinical global outcome measures could be predicted based on the presence of a marker and the administration of specific agents. For example, individuals with elevated frontal alpha activity responded favorably to the administration of antidepressant class medications where those with low frontal alpha respond less favorably, and this was true independent of clinical diagnosis.

Tucker (1981) found relatively less alpha over the right frontal region in depression. A series of studies by Davidson's lab correlated frontal alpha activity, and particularly alpha asymmetry, with different aspects of depression, concluding that left frontal hypoactivation (increased alpha) was related to negative affect and right frontal hypoactivation was related to positive affect. Henriques and Davidson (1990) showed that hypoactivation of the left frontal regions was present in currently depressed versus never depressed persons. Baehr, Baehr, and Rosenfeld (reviewed in Rosenfeld, 2000) used EEG biofeedback of frontal alpha asymmetry measures in treating individuals with significant depression and noted clinical improvement as evidenced by changes in standard assessment instruments, clinical observations, and decreases in antidepressant medication use. The sample sizes reported were small and several technical factors limit interpretation but the trend toward clinical improvement was encouraging.

More recently, Cook et al. (1999) used a derived index of EEG features, termed "cordance," to predict differential response to fluoxetine (Prozac). Cordance relates the level of absolute power in a given frequency band to the amount of relative power for the band and has been shown to correlate with measures of cerebral profusion. "Concordance" indicates high absolute and high relative power in a band and correlates with adequate cerebral perfusion. "Discordance" indicates low absolute

but high relative power for the band and correlates with cerebral hypoperfusion. In a double-blind study, 24 adult subjects with current major depression of the unipolar type were studied over eight weeks while receiving fluoxetine or placebo. Clinical outcome was determined with rating scales and clinical interview. These researchers concluded that QEEG measures could be used to distinguish depressed adults who will respond to treatment with fluoxetine from those who will not. QEEG changes were not systematically related to placebo response. In a subsequent study, Cook and Leuchter (2001) studied a series of depressed subjects treated with antidepressants of different classes. The cordance measure showed decreases in prefrontal activity as early as 48 hours into treatment in responders and were absent in non-responders.

Recent advances in three-dimensional QEEG imaging have been used to demonstrate activity of specific neuroanatomical structures in relation to medication response in depression. Pizzagalli et al. (2001) used low-resolution electrical tomography analysis (LORETA) to study treatment response in 18 unmedicated patients with major depression and 18 matched comparison subjects. Baseline theta activity (6.5-8 Hz), localized to a rostral region of the anterior cingulate cortex, predicted better response to treatment with nortryptiline with the effect lasting four to six months later. The region identified by LORETA is close to that previously reported in similar studies using PET and SPECT. Based on these and previous findings it was suggested that increased theta from the anterior cingulate represents hyperactivity. No significant effects were reported for the alpha frequencies.

Other techniques, including the P300 cognitive evoked response, have been shown to be sensitive indicators of cortical activity with respect to medication response, particularly concerning memory function. EEG recordings during sleep also have provided important information on the neurophysiology of medication effects, including prediction of medication response. Studies using slow potentials, such as the contingent negative variation (CNV), are also likely candidates for the study of medications and brain function. Advanced spectral analysis techniques, such as the bispectrum, offer promise in further investigation of the mechanism of medication in treating psychiatric disorders. Neurophysiological studies are becoming increasingly useful to the clinician but are clearly still in the early stages of development. Enhanced sensitivity and specificity of these methods along with improved clinical behavioral and neuropsychological characterization are needed. Further advances in these and related technologies will eventually allow us to

predict the effects of many types of treatment interventions. We may soon be able to significantly improve the current standards of neurobehavioral treatment by using objective methods to both minimize negative side effects and maximize overall clinical outcome.

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