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ECT Seizure Therapeutic Adequacy

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Summary: From the beginnings of convulsive therapy, the need for some way to assess the therapeutic adequacy of individual treatments has been apparent. Recent work suggests that seizure therapeutic adequacy and adverse effects are dependent on the extent to which the stimulus exceeds the seizure threshold (relative stimulus intensity). Applying this information in clinical practice is problematic because of the variable rise in the seizure threshold that takes place over the treatment course. Attributes of the ictal electroencephalogram (EEG) show promise for alleviating this problem by serving as a marker of relative stimulus intensity. Obstacles that need to be overcome in order to implement ictal EEG indices as a relative stimulus intensity marker in clinical practice are discussed and include artifacts, how to determine a threshold for deciding adequacy, variation in technique between sites, and inter-individual EEG variation; some strategies for overcoming these hurdles are described. It is anticipated that an ictal EEG algorithm that addresses these issues is likely to be of substantial clinical benefit in the practice of electroconvulsive therapy.

The need for some way to assess the therapeutic potency of individual treatments was evident from the beginnings of convulsive therapy. Meduna, commonly credited as the originator of convulsive therapy, realized as early as his first case that therapeutic change does not generally begin until several treatments have been administered (Meduna, 1985). Since this delay in response is typical of convulsive therapy, without some criteria for therapeutic adequacy, how could he and subsequent practitioners be confident that any given individual treatment is efficacious? Again, Meduna's own account of his work indicates that he utilized the criterion that an ''epileptic attack'' be induced. In this regard, he noted that on one treatment an epileptic attack was not observed and that the patient relapsed the next day. The absence of the desired response resulted in an increase in dosage at the next treatment, which was accompanied by an epileptic attack and a resulting decrease in symptom severity.

Despite the crudity of adequacy criterion used, this case illustrates that some conceptual basis for seizure adequacy is necessary in order to maximize therapeutic efficacy. Similarly, we shall demonstrate that criteria are also necessary to prevent unnecessary overstimulation that would accentuate amnesia related to electroconvulsive therapy (ECT). In short, there must be some way to discriminate between what is both necessary

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and sufficient and what is excessive. Without such tools it is impossible to achieve the ideal espoused by Androp in 1941, which has been similarly echoed many times since, that ''amperage and time (of the stimulus) should be kept down to the indisposable minimum'' (Androp, 1941). We have only to be able to identify the nature of what this ''indisposable minimum'' is.

THE HISTORY OF ECT SEIZURE ADEQUACY

A significant step toward being able to assess the treatment adequacy of convulsive therapy was the identification that the seizure is responsible for therapeutic effectiveness. The success of both pharmacologic and electrical (first introduced in 1938) seizure induction was one important piece of evidence in support of this view. Additional support came from a number of studies, the most widely cited being that of Ulett and co-workers (Ulett et al., 1956), which demonstrated a significant advantage of supraconvulsive stimuli over subconvulsive stimuli and sham ECT, thereby further bolstering the notion of the therapeutic importance of the seizure. These findings suggested that efforts to assure therapeutic adequacy with ECT should be focused on the presence of a seizure. This all-or-none view of induced seizures was shared by many early practitioners of convulsive therapy (Androp, 1941; Cerletti, 1956; Impastato and Almansi, 1942; Jessner and Ryan, 1941; Kalinowski and Barrera, 1940; Lowenbach, 1943).

Yet, these authors categorized all-or-none adequate treatments using a variety of different features. Kalinowsky and Barrera wrote that the presence of motor manifestations separated adequate ''grand mal'' from inadequate ''petit mal'' responses to the stimulus (Kalinowsky and Barrera, 1940). In addition to the presence of a tonic/clonic motor response, Androp felt that all adequate treatments were characterized by loss of consciousness, flushing, mydriasis, retrograde amnesia, and with a nonlocalized ictal electroencephalogram (EEG) pattern of polyspike activity giving way to spike-and-wave activity during the clonic phase, followed by postictal electrical silence (Androp, 1941). According to Impastato and Almansi (Impastato and Almansi, 1942), the presence of a clonic motor response, followed by a period of postictal confusion separated adequate from inadequate responses. Lowenbach also felt that clonic activity and postictal cognitive effects were central to an adequate ECT response but believed, like Androp, that postictal EEG suppression was also necessary (Lowenbach, 1943). In contrast to the above authors, Cerletti, one of the founders of ECT, believed that motor manifestations were not necessary for seizure adequacy (Cerletti, 1956).

This wide variation in definitions of the stereotyped ''adequate'' ECT seizure suggests that these ictal events may not be all-or-none phenomena. Indeed, many of the reports cited previously include descriptions suggesting that the seizures elicited by ECT are graded phenomena. For example, Kalinowsky and Barrera suggested that the length of the convulsion depended on the extent to which the stimulus exceeded the seizure threshold (Kalinowsky and Barrera, 1940). Similarly, Cerletti noted that the lengths of the tonic and clonic phases of the seizure could be varied by adjusting stimulus intensity and duration (Cerletti, 1956). A stimulus intensity dependence of both convulsion duration (Jessner and Ryan, 1941) and time to the onset of the tonic phase (Impastato and Almansi, 1942) were also reported.

Together, these observations suggest a significant heterogeneity in ECT seizures that is dependent on stimulus intensity. Hemphill and Walter considered the clinical importance of the relationship between the stimulus and the seizure threshold, now known as ''relative'' stimulus intensity (Hemphill and Walter, 1941). Specifically, these investigators speculated that a delay in the onset of the convulsion by more than 3 s indicated a rise in the patients seizure threshold (typically seen after each of the first few convulsions) and suggested the use of a slight increase in stimulus intensity at the next session to prevent administering inadequate treatments.

These early observations of ECT seizure heterogeneity gradually opened the door to a more detailed investigation of the relationship among stimulus parameters, seizure characteristics, and treatment response. A notable example is the methodologically rigorous work of Ottosson, who explored the effects of lidocaine on ECT in a controlled, prospective study (Cronholm and Ottosson, 1960; Kirstein and Ottosson, 1960; Ottosson, 1960, 1962b). This investigator reported that lidocaine shortened ECT seizure duration in a dose-dependent fashion (Ottosson, 1960). In terms of therapeutic response, the lidocaine-treated subjects had a less-pronounced, antidepressant effect than did those randomly assigned to receive ECT without lidocaine (Cronholm and Ottosson, 1960). In addition, the response rate per second of seizure did not differ between these two groups, leading to the speculation that the diminished efficacy seen with lidocaine might be due to a shortening of the seizure duration. However, a distinct relationship between seizure duration and therapeutic response was found only for the group receiving lidocaine. Still, even though Ottosson was careful to warn against assuming a relationship between seizure duration and therapeutic efficacy for non–lidocaine-modified ECT, many ignored this warning (Cronholm and Ottosson, 1960).

The viewpoint that there was a relationship between seizure duration and ECT therapeutic outcome persisted, despite Ottosson confirming the absence of any such relationship in the absence of lidocaine in a subsequent study (Ottosson, 1962b). In spite of this, later work by Maletzky with multiple monitored ECT had a powerful effect of perpetuating this belief among many ECT practitioners (Maletzky, 1978). In fact, a window of effective cumulative seizure time was suggested (210–1,000 s). However, most subsequent studies failed to support this conclusion (Miller et al., 1985; Sackeim et al., 1987, 1991, 1993; Weiner et al., 1986).

Liberson also studied alternative forms of ECT, in this case by exploring variations in the electrical stimulus, in order to further disprove the all-or-none model of ECT seizures (Liberson, 1953). Comparing ultrabrief-pulse ECT and conventional sine-wave ECT, he found that ultrabrief-pulse ECT was associated with less interictal EEG changes, less memory impairment, and less ictal autonomic alterations and required a greater number of treatments to obtain the same clinical antidepressant effect (Liberson, 1953). Two subsequent studies, including one by Ottosson, confirmed that ultrabrief-pulse ECT had weak antidepressant effects (Cronholm and Ottosson, 1963; Robin and deTissera, 1982). Since this type of ECT is now believed to involve a marginally suprathreshold form of stimulus, this work lends support to the observations described earlier, that stimulus intensity and the relationship of the stimulus to the seizure threshold have a large effect on ECT seizures (Impastato and Almansi, 1942; Cerletti, 1956; Jessner and Ryan, 1941; Kalinowsky and Barrera, 1940), including their therapeutic effectiveness (Hemphill and Walter, 1941).

Further evidence supporting this point of view is provided by additional studies carried out by Ottosson (Cronholm and Ottosson, 1960; Kirstein and Ottosson, 1960; Ottosson, 1960, 1962a,b), in which the effects of routine versus very high stimulus intensity bilateral (BL) ECT were compared. A faster response rate was reported for the latter, although no net therapeutic advantage existed in terms of degree of response.

The next series of studies that had a bearing on the issue of stimulus intensity and therapeutic outcome were those focusing on the effects of stimulus electrode placement (ELPL), in particular, the role of unilateral nondominant (UL) ECT, in which case both stimulus electrodes are applied contralateral to the cerebral hemisphere believed to be involved with speech function (Lancaster et al., 1958). Many studies comparing the antidepressant efficacy of UL with BL ECT have generated conflicting results as to whether there is a therapeutic advantage for BL ECT (for reviews, see Abrams, 1986; Ottosson, 1991; Overall and Rhoades, 1986; Sackeim, 1991). A critical analysis of these studies has suggested that much of the reported efficacy differences between UL and BL ECT may be due to a greater dependence on stimulus intensity with the UL technique, which is a particular problem with certain types of UL electrode placement (Pettinati et al., 1986; Weiner and Coffey, 1986). In particular, scalp shunting, produced by the use of short interelectrode distances, can be expected to result in a much lower intracerebral current density, and thereby lower ''effective'' stimulus intensity. In this regard, studies that have used a high stimulus intensity for both UL and BL groups have tended to show more of an equivalency between UL and BL treatments (e.g., Abrams et al., 1991). High efficacy rates for UL ECT have also been reported in Scandinavia, where ECT tends to be administered at a relatively high stimulus dosage (d'Elia et al., 1983).

In order to focus more precisely on the relevance of stimulus intensity to therapeutic outcome as a function of ELPL, Sackeim and colleagues embarked on a series of investigations in which seizure threshold (i.e., the amount of electricity necessary to induce a seizure) was controlled for, using a dose-titration procedure (Malitz et al., 1982). This technique allowed them to study ''relative'' stimulus intensity, which is the intensity of the stimulus with respect to the seizure threshold. Because of the extremely wide range of seizure threshold across individuals (40-fold; Sackeim et al., 1991), this measure is of considerably greater physiologic relevance than absolute stimulus intensity. Using this methodology, Sackeim and colleagues were able to show a pronounced efficacy advantage for BL ECT over UL ECT when stimuli were kept barely suprathreshold (Sackeim et al., 1987).

More recently, this situation was clarified even further by another study by Sackeim and colleagues in which subjects were randomly assigned to receive either barely suprathreshold UL ECT (TUL), moderately suprathreshold (250% of estimated seizure threshold) UL ECT (MUL), barely suprathreshold BL ECT (TBL), or moderately suprathreshold BL ECT (MBL) (Sackeim et al., 1993). This study more firmly established that it was the relationship of the stimulus intensity to the seizure threshold and not the absolute stimulus intensity that differentially affected ECT efficacy. The differences in therapeutic response rate among the four groups suggested that TUL ECT had minimal antidepressant properties (17% response rate) compared with MUL (43%), TBL (65%), and MBL (63%) ECT. However, amnestic effects were also found to be greater for BL than for either of the UL ECT groups and also to be greater with MUL than TUL ECT.

Overall, Sackeim and co-worker's studies make it clear that ECT seizure therapeutic adequacy depends on both stimulus ELPL and the extent to which stimulus intensity exceeds the seizure threshold. Furthermore, their findings suggest that the choice of relative stimulus level will reflect a trade-off between expected therapeutic response and side effects. Being able to make this choice, however, represents a significant step forward in the development of a criterion for ECT therapeutic adequacy. For UL ECT, it appears to be necessary to utilize a stimulus intensity that is at least moderately suprathreshold, to ensure that the treatment administered has an adequate antidepressant effect. In the case of BL ECT, all suprathreshold stimuli appear to be associated with roughly equivalent therapeutic adequacy, although both the rate of response and the extent of adverse cognitive effects will be greater with a higher stimulus intensity. Thus, a knowledge of relative stimulus intensity can theoretically be used to predict the likelihood of both therapeutic response and adverse effects associated with ECT, thereby offering the potential for the optimization of ECT administration. The issues involved in putting this information into practice in the clinical setting will be the subject of much of the remainder of this article.

PROBLEMS WITH MAINTAINING AN ADEQUATE RELATIVE STIMULUS INTENSITY: THE NEED FOR A MARKER

Despite growing evidence that it may be possible to determine the expected response rate and side-effect risk associated with an individual ECT treatment on the basis of relative stimulus intensity, it has not been possible to apply this information in clinical practice. Whereas the use of a seizure threshold titration procedure can allow a determination of the relative stimulus intensity at the beginning of the treatment course, the variable rise in seizure threshold that typically takes place over the treatment course results in an inability to maintain knowledge of relative stimulus intensity over time (Krystal et al., 1993b; Sackeim et al., 1983, 1991). Alternatively, the invariant use of BL ECT and maximal stimulus intensity to ensure therapeutic efficacy is suboptimal because of the greater cognitive deficits that are elicited. Performing multiple seizure threshold determinations over the treatment course is also impractical. Therefore, some marker of relative stimulus intensity is needed to allow the clinician to be able to administer treatments at a desired level of expected therapeutic response and side-effect risk over the entire treatment course. Although a number of indices have been explored as potential markers [such as seizure duration and prolactin release (Swartz, 1993a,b; Weiner et al., 1991, 1993)], the most promising at present are characteristics of the ictal EEG.

THE ICTAL EEG AS A MARKER OF ECT SEIZURE ADEQUACY

A number of the studies comparing forms of ECT that differ in efficacy have reported ictal EEG differences among the conditions studied and suggest the potential of the ictal EEG as a marker of ECT relative stimulus intensity. As a part of their seminal studies, Ottosson and colleagues (Kirstein and Ottosson, 1960; Ottosson, 1960) reported that, in addition to shortening seizure duration, lidocaine also diminished the spike activity in the ictal EEG, caused ''escapes'' of the ictal EEG spike/wave complexes, decreased the amplitude of the ictal slow-wave component in frontal and parietal areas, and diminished the extent of postictal EEG amplitude suppression [thought to reflect the intensity of the preceding seizure (Kaibara and Blume, 1988)]. Furthermore, since lidocaine is now known to raise the seizure threshold (Devanand and Sackeim, 1988), these findings also suggest a possible relationship between ictal EEG indices and relative stimulus intensity.

Robin and colleagues, in a within-subject comparison of ultrabrief-pulse versus wide-pulse and sine-wave BL ECT, found that the brief-pulse treatments were associated with lower ictal EEG amplitudes and less postictal EEG suppression (Robin et al., 1985). Although there was no formal determination of the relative intensity of these stimuli, as noted earlier, it is likely that the ultrabrief-pulse stimuli were closer to seizure threshold, thereby, further reinforcing a connection between relative stimulus intensity and ictal EEG indices. Additional evidence was provided by Small and colleagues, who reported greater postictal suppression early in the course of treatments (Small et al., 1970). Since seizure threshold tends to rise over the course of treatments, earlier treatments are more likely to have been delivered at a higher relative stimulus intensity.

Ictal EEG differences between UL and BL ECT are important given the different therapeutic response profile of these two forms of treatment (Sackeim et al., 1993). Therefore, greater ictal EEG amplitude, symmetry, coherence, regularity, and postictal suppression reported with BL ECT further suggest the promise of ictal EEG measures (Abrams et al., 1973; Brumback and Staton, 1982; d'Elia and Perris, 1970; Enderle et al., 1986; Gerst et al., 1982; Kriss et al., 1978; Krystal et al., 1992; Small et al., 1970; Staton et al., 1981, 1986; Swartz and Larson, 1986).

Two recent studies are particularly well suited to assessing the ability of ictal EEG measures to serve as markers of seizure therapeutic adequacy, since they are the first to simultaneously study both stimulus ELPL and relative stimulus intensity effects (Krystal et al., 1993b; Nobler et al., 1993). One of these studies employed a within-subjects design comparing TUL, MUL (225% of estimated seizure threshold), TBL, and MBL ECT, utilizing both computer and manual EEG measures (Krystal et al., 1993b); whereas the other employed a between-subjects design, randomly assigning subjects [a subset of those in a study described above (Sackeim et al., 1993)] to TUL, MUL, TBL, or MBL ECT using manual EEG measures (Nobler et al., 1993). Similar results were seen in both cases. Krystal and co-workers reported significantly greater immediate poststimulus (5.5–13 Hz) and mid-ictal (2–5 Hz) EEG amplitude, and mid-ictal symmetry (2–5 Hz) with BL as compared with UL ECT. Significant effects of relative stimulus intensity were present, with the moderately suprathreshold condition associated with greater immediate poststimulus and mid-ictal EEG amplitude and postictal suppression compared with barely suprathreshold stimuli.

The findings of Nobler and colleagues are in agreement with these results, with significantly greater postictal suppression reported in MUL, TBL, and MBL groups compared with TUL ECT (Nobler et al., 1993). In addition, compared with barely threshold stimuli, moderately suprathreshold ECT was associated with a greater mid-ictal (slow-wave) amplitude (also reported by Krystal and colleagues), a shorter polyspike phase, and a longer ictal slow-wave phase, all of which were independent of absolute stimulus intensity. The latter two findings agree with the greater immediate poststimulus amplitude and coherence reported by Krystal and co-workers, which are suggestive of an earlier onset of ictal slowing with higher relative intensity stimuli. The study by Nobler and colleagues also reported that increased postictal suppression was seen in therapeutic responders compared with nonresponders, although no other ictal EEG variable differences as a function of therapeutic outcome were present. It was not demonstrated whether this effect was independent of ELPL and stimulus intensity effects. It is important to emphasize, in this regard, that no evidence presently exists suggesting that ictal EEG indices are capable of predicting when an individual will respond independent of the treatment type, nor have they identified the physiologic changes that are responsible for the antidepressant effect of ECT. Rather, these two studies suggest that ictal EEG measures of the time to onset of slowing, the amount of ictal slowing present, and the degree of postictal suppression show promise as markers of ECT relative stimulus intensity and therefore of ECT therapeutic adequacy. In addition to elucidating the potential clinical utility of ictal EEG measures, these studies have implications regarding the neurophysiology of ECT.

NEUROPHYSIOLOGIC IMPLICATIONS OF ICTAL EEG FINDINGS

Since ictal slowing is believed to reflect the activation of subcortical structures, including synchronizing thalamo-cortical feedback loops (Gloor, 1984), an earlier onset and greater amplitude of ictal EEG slowing in more efficacious forms of ECT is consistent with an earlier and more intense thalamic activation with these treatments. Greater mid-ictal slowing in the forms of ECT with greater antidepressant properties is also consistent with a greater ability of these types of ECT to elicit endogenous inhibitory processes involved in seizure termination (Sackeim et al., 1991). Further support for this notion is the observation of a greater increase in seizure threshold over the treatment course with the more potent antidepressant types of ECT (Sackeim et al., 1993). In addition, the greater postictal suppression seen in these types of ECT has been found to be correlated with the amplitude of mid-ictal slowing (Krystal et al., 1993b) and therefore is also consistent with a more robust activation of inhibitory processes (Sackeim et al., 1991). Thus, there is evidence to support the hypothesis that more efficacious forms of ECT have an earlier and more potent ability to involve subcortical structures in seizure activity and may also be more effective in eliciting the endogenous seizure inhibitory mechanisms that have been speculated to play a role in the efficacy of ECT (Sackeim et al., 1991).

A possible role of subcortical structures in mediating the differential efficacy of variations in ECT technique is of interest, given the high incidence of depression in subcortical dementias and in individuals with basal ganglia strokes and lesions and reports of decreased basal ganglia size and metabolism in depression (Krishnan, 1992; Krishnan, 1993). Such findings have led to the hypothesis that a limbic-thalamo-cortical circuit is involved in the physiology of depression and is a target of antidepressant treatment (Drevets and Raichle, 1992).

THE CLINICAL APPLICATION OF ICTAL EEG SEIZURE ADEQUACY MARKERS

As described previously, present data support the clinical implementation of ictal EEG indices as markers of relative stimulus intensity, in order to optimize ECT technique (Krystal et al., 1993b; Nobler et al., 1993). In this regard, some considerations differ between UL and BL ECT.

For UL ECT ictal EEG markers could be used to ensure that the stimulus intensity remains at least moderately suprathreshold throughout the treatment course, a criterion that Sackeim and colleagues have reported to be necessary for an adequate therapeutic antidepressant effect (Sackeim et al., 1993). When ictal EEG indices suggest that the relative stimulus intensity is significantly below 2.5 times seizure threshold, because of a rise in seizure threshold, an increase in stimulus intensity would be indicated. Further, if an individual is having a poor therapeutic response and all treatments have been maintained at least moderately suprathreshold on the basis of ictal EEG indices then a switch to BL ECT could be made with more confidence that an adequate trial of UL ECT had been carried out.

For BL ECT the expected speed of response and the expected degree of cognitive impairment are important clinical factors that depend on the relationship of the stimulus to seizure threshold and therefore motivate the use of ictal EEG markers (Sackeim et al., 1993). In this case the clinician will need to determine a desired trade-off between cognitive effects and rate of response (both greater at increased stimulus intensity) that is optimal for each patient. Ictal EEG indices could then be used for maintaining the stimulus intensity at this level despite the changes in threshold that take place over the treatment course. Further, ictal EEG parameters could be used to maintain a stimulus intensity that is at least moderately suprathreshold before determining that an individual has been an ECT treatment nonresponder.

PROBLEMS IN THE IMPLEMENTATION OF ICTAL EEG MARKERS OF THERAPEUTIC ADEQUACY AND SOME STRATEGIES FOR DEALING WITH THEM

There are a number of problems that must be worked out before a successful clinical implementation (as described in the previous section) is possible. First, in order to utilize these ictal EEG measures, multivariate analytic techniques are necessary to determine whether and how ictal EEG indices showing promise as seizure adequacy markers can be combined into a single composite index for prediction of the relative stimulus intensity of a given treatment. It is important that such a determination be based on a large amount of data that are widely representative of the range of patients seen in clinical practice. Given such data, it will be necessary to explore the sensitivity and specificity of potential markers for identifying treatment relative stimulus intensity. The use of receiver–operator–characteristic (ROC) analysis is one approach that offers promise in determining the threshold for identifying an appreciable drop in relative stimulus intensity for individual seizures (McNeil et al., 1975). This type of analysis would entail choosing a threshold that maximizes the sensitivity and specificity for categorizing relative stimulus intensity, while taking into account an estimate of the cost associated with mis-classifying a moderately suprathreshold treatment as barely suprathreshold versus classifying a barely suprathreshold seizure as moderately suprathreshold.

Another substantial problem in implementing ictal EEG seizure adequacy measures is the presence of EEG artifacts. Present studies suggesting clinical utility for ictal EEG measures involved careful selection of data to avoid including segments contaminated with artifacts in analysis (Krystal et al., 1993b; Nobler et al., 1993). Therefore, resulting ictal EEG algorithms can be expected to function only as predicted on the basis of artifact-free data, which is not easily available on-line in the clinical setting. Much effort will need to be exerted in making future algorithms as insensitive as possible to artifact due to movement, myogenic activity, a bad EEG electrode, or electrocardiography. Intersite variation in the care taken in the placement of recording electrodes, as well as the dosing of muscle-relaxant agents, magnifies these problems.

One approach to dealing with artifacts is to develop algorithms that identify and eliminate artifacts on the basis of their unique EEG features such as frequency content, morphology, amplitude, and others. A different approach would be to develop measures that are relatively insensitive to artifacts without having to actively detect them. This latter technique has the advantage of simplicity. As an example, one might utilize only the low-frequency band of the EEG, which is likely to be free of myogenic artifact to determine seizure adequacy. This choice would minimize the problems of both site variation in muscle-relaxant dosage and the identification of muscle artifact. Whereas this procedure would minimize problems with myogenic activity, one would still need to address problems such as movement artifact, e.g., when the grip on the patient's chin is relaxed following the end of the stimulus and positive-pressure respiration is resumed. This situation can be improved by focusing on portions of the seizure that are less likely to be affected by movements, such as the mid-ictal period.

A further complicating factor in the clinical implementation of ictal EEG indices is intersite variation in EEG recording lead placement. This could be a problem if an algorithm is based on features of the EEG that are dependent on a particular recording electrode montage. In this regard, the most recent studies described above utilized two channels of EEG that reflected left and right prefrontal to ipsilateral ear (Nobler et al., 1993) or mastoid (Krystal et al., 1993b) leads. However, many practitioners utilize a single bifrontal EEG channel, which tends to cancel out the high-amplitude, widely synchronous slowing that dominates the mid-ictal portion of ECT seizures and which appears to be a promising index of relative stimulus intensity (Krystal et al., 1993b; Krystal and Weiner, 1993; Nobler et al., 1993). For this reason it appears to be advantageous to utilize intrahemispheric EEG recording derivations. At the same time, the optimal recording electrode configuration for seizure adequacy remains to be established.

One of the most imposing obstacles to the clinical implementation of ictal EEG adequacy markers is interindividual variation in the ictal EEG. As mentioned earlier, recent studies of the potential of the ictal EEG for identifying when ECT treatments are likely to be of therapeutic benefit (Krystal et al., 1993b; Nobler et al., 1993) are based on population statistics (mean differences between treatment groups or responders vs. nonresponders). To be useful in clinical practice, an ictal EEG algorithm will need to demonstrate high sensitivity and specificity for determining the adequacy of individual seizures. In order to improve the ability of an ictal EEG algorithm to accomplish this task, much work is needed to identify and control for factors that account for interindividual variation in the ictal EEG. For example, it has already been established that subject age has a profound effect on a number of characteristics of the ictal EEG and that taking these effects into account significantly decreases the interindividual variance in these ictal EEG indices, thereby making them more powerful tools for determining seizure adequacy (Krystal et al., 1993a; Nobler et al., 1993). Whether other factors, such as gender, race, or head circumference, affect ictal EEG measures remains to be determined.

In addition to identifying the factors responsible for interindividual ictal EEG variance, it is possible to diminish the effects of interindividual variation in the ictal EEG by basing the implementation of an ictal EEG seizure adequacy algorithm on an intraindividual comparison of ictal EEG data. For example, one can make a determination of the ictal EEG characteristics obtained at the first treatment administered at the desired stimulus intensity with respect to threshold [for many practitioners this follows estimation of seizure threshold at the first treatment, with use of a dose-titration procedure (American Psychiatric Association, 1990)]. The ictal EEG values so obtained can then serve as the standard to which ictal EEG indices from subsequent treatments in the same individual are compared for determining when a rise in the seizure threshold results in a change in ictal EEG parameters, suggesting a need for an increase in stimulus intensity. Even here, however, it will be important to consider the potential effects of treatment number, a form of intraindividual variability, on these measures.

Several automated EEG measures purporting to assess seizure quality have recently been implemented commercially (Swartz and Abrams, 1994). These measures include integrated amplitude of EEG activity over the entire seizure, the degree of drop in integrated EEG amplitude from maximal ictal to postictal levels, and an index of the concordance in time between EEG and motor seizure end points. Suggested seizure adequacy cutoffs for these indices appear to have been based on the distribution of values obtained in routine clinical practice, without regard to relative stimulus intensity or therapeutic outcome. The extent to which such measures reflect treatment adequacy and the validity of the suggested cutoffs remain to be established.

FUTURE WORK

The previous section illustrates that much work is needed before an ictal EEG algorithm for seizure adequacy is likely to be a clinically useful tool. At present the ictal EEG can be expected to serve only as a crude aid to the clinician in determining whether an ECT seizure is therapeutically adequate. Further work is needed to identify whether there is a relationship of ictal EEG measures to therapeutic response that is independent of treatment type. In addition to improving the utility of ictal EEG indices, such work may help to elucidate the neurophysiologic mechanisms associated with ECT's antidepressant response. For these purposes, better studies, with larger numbers of patients, performed in the clinical setting are needed to allow an optimal ictal EEG algorithm with wide clinical applicability to be developed. An algorithm derived from such studies, which adequately addresses the problems discussed above, will allow the prediction of the expected therapeutic efficacy and adverse effects associated with an ECT treatment and is likely to be of substantial clinical benefit in the practice of ECT.

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