

# The Ictal EEG as a Marker of Adequate Stimulus Intensity With Unilateral ECT

Andrew D. Krystal, M.D., M.S.  
Richard D. Weiner, M.D., Ph.D.  
C. Edward Coffey, M.D.

*Relative stimulus intensity above seizure threshold has been shown to affect therapeutic outcome with unilateral ECT. The authors sought to explore whether a multivariate ictal EEG model would permit ongoing clinical assessment of this parameter. Twenty-five depressed subjects were randomized to either barely (T) or moderately (2.5T) suprathreshold ECT treatments. Seizures in 2.5T subjects had significantly greater ictal spectral amplitude and coherence, greater postictal suppression, and shorter latency until ictal slow-wave onset. A multivariate logistic regression ictal EEG model distinguished between stimulus intensity groups with 90% accuracy. Preliminary evidence suggests a relationship between several ictal EEG indices and therapeutic outcome. A multivariate ictal EEG algorithm holds promise as a tool for clinical determination of adequate stimulus intensity with unilateral ECT.*

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Recently, Sackeim and colleagues<sup>1,2</sup> have reported that the degree to which electroconvulsive therapy (ECT) stimulus dosage exceeds the seizure threshold (relative stimulus intensity) is a strong determinant of therapeutic outcome, particularly for unilateral nondominant (UL) ECT. Specifically, although UL ECT is associated with less cognitive impairment than bilateral (BL) ECT,<sup>3,4</sup> barely suprathreshold (T) UL stimuli have a reduced antidepressant effect compared with moderately suprathreshold stimuli (2.5T). This work is important because previously there had been no effective criteria for ensuring the therapeutic adequacy of individual ECT treatments.<sup>5</sup>

Applying these results in clinical practice to ensure the therapeutic potency of UL ECT is problematic. Although the use of a seizure threshold titration procedure<sup>6</sup> allows dosing with respect to relative stimulus intensity at the beginning of the treatment course, the rate of rise in seizure threshold over the ECT course is uncertain. In the absence of repeated seizure threshold titration, which is impractical, this uncertainty makes it impossible to estimate relative stimulus intensity at later treatments.<sup>1,5</sup> Alternatively, the use of a high absolute stimulus intensity would help to assure the attainment of high relative stimulus intensity in many cases; however, it would also

Received June 29, 1994; revised September 30, 1994; accepted November 2, 1994. From the Department of Psychiatry, Duke University Medical Center, and Department of Veterans Affairs Medical Center, Durham, North Carolina; and the Departments of Psychiatry (Neuropsychiatry) and Medicine (Neurology), Medical College of Pennsylvania, Allegheny Campus, Pittsburgh, Pennsylvania. Address correspondence to Dr. Krystal, Department of Psychiatry, Box 3309, Duke University Medical Center, Durham, NC, 27710.

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be associated with greater adverse effects.<sup>1,3,4,7</sup> Another practical solution, the development of a technique that would allow ongoing assessment of relative stimulus intensity, would permit maintenance of a therapeutically adequate stimulus intensity over the treatment course while at the same time minimizing adverse effects.

Some evidence suggests that certain attributes of the ictal EEG may be useful in this regard.<sup>5</sup> For example, a number of studies have reported ictal EEG differences between UL and BL ECT.<sup>8-18</sup> These observations are of interest, given the differences in therapeutic response reported by some investigators for these two forms of treatment.<sup>2</sup>

Even more pertinently, two recent studies provide direct evidence for a relationship between such measures and stimulus intensity.<sup>19,20</sup> Previously, only indirect evidence had suggested that ictal EEG variables might differ as a function of stimulus intensity.<sup>8,21-23</sup> The first of these two investigations was a within-subject comparison of T and 2.25 times threshold (2.25T) ECT for both UL and BL electrode placement, employing computer-derived ictal EEG measures.<sup>19</sup> Compared with T ECT, 2.25T ECT was associated with significantly greater immediate post-stimulus (5.5-13 Hz) and midictal (2-5 Hz) spectral amplitude, greater immediate poststimulus 2-5 Hz interhemispheric coherence (that is, interhemispheric correlation of low-frequency activity), and lower postictal (2-5 Hz) spectral amplitude (greater postictal suppression). These findings were independent of stimulus electrode placement.

Similar results were obtained in a study by Nobler et al.,<sup>20</sup> who performed an interindividual comparison of similar ECT types by using manual EEG ratings. In their investigation, 2.5T ECT, when compared with T ECT, was again associated with greater midictal slow-wave amplitude and postictal suppression. In addition, these investigators reported 1) that their 2.5T group had a shorter time to onset of high-amplitude ictal slowing and a longer duration of the ictal slow-wave activity, 2) that age was a significant covariate for many of their ictal EEG indices,<sup>20,24</sup> 3) that the ictal EEG findings were independent of seizure threshold, 4) that seizure threshold was inversely related to midictal slow-wave amplitude, and 5) that postictal suppression was greater in therapeutic responders. The results of both of these studies<sup>19,20</sup> suggest that ictal EEG indices have substantial promise for differentiating EEG seizures on the basis of relative stimulus intensity.

We now report the ictal EEG findings of a new interindividual study of subjects randomized to either T or 2.5T UL ECT for treatments 2-5. In addition to providing the first interindividual comparison of differences between T and 2.5T ECT in terms of computer-derived ictal EEG

measures, this study includes the first use of a multivariate ictal EEG model of relative stimulus intensity to predict whether individual seizures were elicited by a T or 2.5T stimulus. The development and testing of this model represent a step toward the implementation of a much-needed clinically applicable marker of the relative stimulus intensity, and thus the therapeutic adequacy, of individual ECT seizures.

## METHODS

### Subjects

Twenty-five patients clinically referred for unilateral nondominant ECT were included in the study after providing informed consent. All patients referred for UL ECT during the period of the study were screened for entry into the study. Subjects participating in the study all met DSM-III-R criteria for major depression<sup>25</sup> (ascertained by a single trained research rater using a structured interview<sup>26</sup>), were between 21 and 75 years old, were strongly right motor dominant on a motor performance test,<sup>27</sup> had not had ECT in the last 3 months, and were without evidence of active cerebral disease (on the basis of neurologic history and physical exam and chart review performed by C.E.C. or R.D.W.). In addition, subjects were free of antidepressant, antipsychotic, and benzodiazepine agents for at least 5 days prior to and during ECT (except for 1 subject who received three nighttime 15-mg doses of temazepam over the ECT course and 3 individuals who had shorter drug-free intervals: clomipramine 3 days, sertraline 2 days, and trifluoperazine 4 days). In terms of other medications known to affect seizures, one subject received a fixed dosage of theophylline throughout the study. Additional subject characteristics are listed in Table 1.

### ECT Administration

All subjects received bidirectional pulse ECT (Mecta SR1 ECT device, Mecta Corp.) with right UL electrode placement as described by d'Elia.<sup>27</sup> Routine pharmacologic agents used with ECT included methohexital 1 mg/kg, succinylcholine 1 mg/kg, and 100% oxygen by mask. Estimation of seizure threshold was accomplished at treatment 1, beginning with a dose of 32 millicoulombs (mC) for females and 48 mC for males. When necessary, restimulation at the same treatment was carried out, using 50% increments, until a seizure of at least 25 seconds' EEG duration had been achieved. This resulting final stimulus intensity represented the estimated seizure threshold (T) at the first treatment. Thereafter, subjects were randomized to receive subsequent treatments with either T or 2.5T intensity stimuli for the next 4 treatments

TABLE 1. Subject characteristics by treatment group

| Characteristic                   | T Group     | 2.5T Group  |
|----------------------------------|-------------|-------------|
| Gender (M/F)                     | 2/9         | 7/7         |
| Age                              | 48.8 ± 14.4 | 54.0 ± 10.6 |
| Methohexital dosage (mg)         | 85.4 ± 24.3 | 85.8 ± 22.7 |
| Succinylcholine dosage (mg)      | 79.2 ± 17.7 | 86.0 ± 19.7 |
| Estimated seizure threshold (mC) | 44.3 ± 19.6 | 41.1 ± 12.7 |
| Baseline MADRS score             | 38.7 ± 6.4  | 36.7 ± 7.4  |
| Seizure duration (s)             | 73.8 ± 18.7 | 66.7 ± 24.0 |

*Note:* All values except gender are means ± SD. T = barely suprathreshold stimuli; 2.5T = moderately superthreshold stimuli. MADRS = Montgomery-Asberg Depression Rating Scale.

(T:  $n = 11$ ; 2.5T:  $n = 14$ ). All subjects then underwent redetermination of seizure threshold at treatment 6. Finally, for ethical reasons, T group subjects who were nonresponders after treatment 5 (on the basis of the Clinical Global Impressions Scale; see below) were switched to the 2.5T dose condition beginning at treatment 7. As a result, ictal EEG data from treatments 2–5 were the focus of the analyses that follow. If a seizure was elicited that was less than 25 seconds in duration at treatments 2–5, restimulation was delivered at a 50% increment for 2.5T subjects and 25% for individuals assigned to the T condition. Subjects and their treatment teams were both blind to group assignment. Interestingly, neither seizure threshold nor seizure duration differed between the two groups (see Table 1).

#### EEG Recording

Two channels of EEG were recorded, using a MECTA SR1 ECT device, with left and right prefrontal-to-ipsilateral mastoid derivations and Ag/AgCl electrodes.<sup>19</sup> To ensure a low EEG electrode-scalp impedance, the electrode sites were cleaned with alcohol and an abrasive cleanser (Omniprep, D. O. Weaver and Co.), and conduction gel was applied. Simultaneous recordings were made onto magnetic tape by using a Vetter Corporation C-4 FM tape recorder for subsequent digitization (256 Hz) and analysis by a computer-based EEG acquisition and analysis system (EEGSYS, Friends of Medical Science, Inc.) and by additional custom software written by A.D.K.

#### Computer EEG Analysis

Manual artifact rejection of EEG data was performed by A.D.K. and was carried out blind to subject, stimulus intensity group, and therapeutic outcome. The manual artifacting focused on the detection of myogenic and motion artifacts. Although it is possible that the latter may be present even with the relatively high succinylcholine dosages used in this study (1 mg/kg), it is unlikely that such artifacts affected the results of the present study

because such movements would likely be accompanied by electromyographic activity that would have been picked up during the careful artifact rejection that was employed.

The digitized EEG was split into 3 frequency bands (2–5 Hz, 5.5–13 Hz, and 13.5–30 Hz) by using the fast Fourier transform as previously reported.<sup>18,19</sup> Spectral analysis was performed on 6-second (three 2-second epochs) segments of EEG data from the immediate post-stimulus (early), midictal, and immediate postictal portions of the seizure (Figure 1). A.D.K. chose the first 6 artifact-free seconds of data following the ECT stimulus for early segment analysis and the first 6 artifact-free seconds of data following seizure termination for postictal analysis. (High interrater reliability between A.D.K. and R.D.W. had already been established on manual determination of EEG seizure endpoint.<sup>18</sup>) The segment for midictal analysis was chosen by a computer program that automatically selected the 6-second portion with the maximum mean peak-to-peak amplitude by testing sequentially overlapping 6-second segments of artifact-free data (epochs 1–3, 2–4, 4–6, etc.). All selection of data segments to be analyzed was done blind to group assignment and treatment number.

For each of these 3 segments, *spectral amplitude* and *interhemispheric coherence* were computed for each of the three frequency bands.<sup>18,19</sup> Spectral amplitude was calculated to determine the amount of EEG activity in the three frequency bands. Coherence was used to reflect the degree of physiologic coupling between the two EEG channels. It is analogous to the interhemispheric correlation of the EEG data in each frequency band. Coherence values vary from 0.0 to 1.0, with a value of 1.0 suggesting a strong linear relationship between the data in the two hemispheres in the frequency band being studied.<sup>18,19</sup> An additional measure, *time to onset of ictal slowing* (TSLOW), defined as the first 6-second artifact-free period in which activity in the 2–5-Hz frequency band became greater in amplitude than activity in any other band, was determined by computer. A sample EEG tracing with the associated ictal EEG indices appears in Figure 1.

#### Therapeutic Outcome Measurement

The Clinical Global Impressions Scale<sup>28</sup> (CGI) was used to make a dichotomous therapeutic outcome assessment. The CGI consists of a 7-point severity subscale and a 9-point improvement component. A *responder* was defined as a subject who achieved at least moderate improvement on the CGI (improvement score < 4) and was no more than mildly ill (severity rating ≤ 3). The CGI was administered by a trained rater three times: at baseline, 1 day after treatment 5, and 2–3 days after the treatment course. Because T nonresponders after treatment 5 were

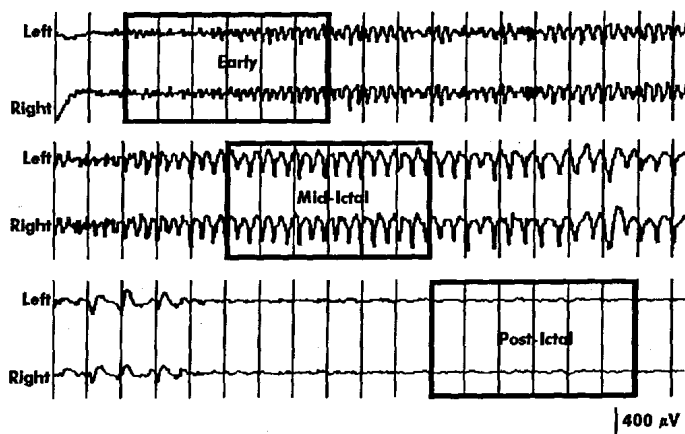
then switched to 2.5T stimuli, posttreatment course ratings were not used in analysis. Baseline Montgomery-Asberg Depression Rating Scale<sup>29</sup> (MADRS) ratings for the two groups appear in Table 1 and were not significantly different. Stimulus intensity-related differences in efficacy and cognitive effects will be presented in another report.

### Statistical Analyses

All data were checked for distribution normality and were transformed as indicated to an approximate normal distribution.<sup>30</sup> All measures except coherence data were normalized by a logarithmic transformation. Coherence data were normalized by the Fisher's *z* transform, as has been reported for data of this type.<sup>31</sup> The mean treatment number of seizures included in EEG analyses (treatments 2–5 only) did not significantly differ between the two treatment groups (3.38 for T subjects and 3.60 for 2.5T subjects). All analyses were carried out by using the SAS statistical analysis system (SAS Institute, Inc.) with two-tailed tests of significance.

Three separate analyses were carried out to 1) determine T versus 2.5T differences in ictal EEG parameters, 2) develop an ictal EEG model for prediction of treatment-relative stimulus intensity, and 3) preliminarily assess the relationship of ictal EEG measures and therapeutic outcome.

**FIGURE 1.** EEG tracing from a seizure elicited by a 2.5T stimulus. The vertical lines appear at 1-second intervals. The segments of the seizure used in ictal EEG analysis appear in the boxes. The ictal EEG parameters associated with this seizure are: left early 5.5–13-Hz amplitude = 39.3  $\mu$ V, right early 5.5–13-Hz amplitude = 39.4  $\mu$ V, early 2–5-Hz coherence = 0.94, left TSLOW = 4 s, right TSLOW = 4 s, left 2–5-Hz midictal amplitude = 120  $\mu$ V, right 2–5-Hz midictal amplitude = 127  $\mu$ V, left 2–5-Hz postictal amplitude = 8.9  $\mu$ V, right 2–5-Hz postictal amplitude = 8.6  $\mu$ V. TSLOW = time to onset of ictal slowing.



*Effects of Relative Stimulus Intensity on Ictal EEG Parameters:* This analysis compared the mean values of ictal EEG variables in the T and 2.5T groups. First, the mean value for each EEG measure for treatments 2–5 was calculated for each subject. These values were then used in a single multivariate analysis of covariance (MANCOVA) to test for the presence of significant effects while controlling for the use of multiple, possibly correlated measures. Relative stimulus intensity (T, 2.5T) served as the independent variable, and the EEG variables (left and right early 5.5–13-Hz amplitude, left and right 2–5-Hz midictal amplitude, left and right postictal 2–5-Hz amplitude, left and right TSLOW, and early 2–5-Hz coherence) were the dependent measures. Age and initial seizure threshold (mC) were included as covariates on the basis of previous work.<sup>20,24</sup> Heterogeneity of slopes in the two groups was ruled out (*P* not significant). The use of ictal EEG data from treatment 1 (where all subjects received T ECT) was considered as a potential covariate in this analysis to remove some of the interindividual variability in the ictal EEG data that was not due to differences in relative stimulus intensity. This could not be done, however, because only subjects with artifact-free treatment 1 data for all nine ictal EEG variables could be included in such an analysis, a requirement that would prohibitively diminish the number of available subjects.

The effect of hemisphere (asymmetry) could not be assessed in the previous analysis because coherence involved both left and right hemisphere data; therefore, a repeated-measures MANCOVA, involving cerebral hemisphere as the repeated measure, was performed, including all of the EEG variables except coherence as dependent measures.

*An Ictal EEG Model for Prediction of ECT Relative Stimulus Intensity:* The previous analysis served as a prelude to the more directly clinically relevant task of developing a multivariate ictal EEG model of the relative stimulus intensity of individual ECT treatments. A multivariate logistic regression model was developed and tested for its ability to correctly identify T and 2.5T seizures. The model was developed by using the average of ictal EEG data from treatments 2 and 3 for each subject and was then tested on data from treatments 4 and 5. Averaged data from treatments 2 and 3 were used to develop the model rather than data from one treatment because averaging diminished the effect of missing data (*n* = 21) while avoiding using more than one nonindependent observation per subject. As in the MANCOVA described above, available data are particularly an issue in this analysis because of the requirement that each seizure utilized have artifact-free data available for all nine EEG parameters.

To avoid the incorporation of intercorrelated measures, and also to reduce the number of variables in the model, principal components analysis was performed.<sup>32,33</sup> In this case, the principal components were linear combinations of the original nine EEG variables after z transformation.<sup>33</sup> Although nine potential principal components were generated by the analysis, only those principal components that individually accounted for 10% or more of the variance of the nine ictal EEG variables were utilized. As shown in Table 2, the resulting four principal components together accounted for 93% of the variance in the nine EEG variables.

Each of these four principal components was then entered into a logistic regression model for prediction of stimulus intensity group.<sup>34</sup> Age, but not initial seizure threshold, was included in the model because only the former was found to be a significant covariate (see Results). The ability of the model to predict the stimulus intensity group assignment for data from treatments 4 and 5 was then assessed.

Because many ECT practitioners record only one channel of EEG data, reserving the second data channel of most ECT machines for electrocardiographic or electromyographic data,<sup>35</sup> an EEG model of relative stimulus intensity based only on left hemispheric data was also developed and tested (left hemispheric intergroup differences tended to be more significant than for the right hemisphere; see Results). This single-channel model was developed by using identical methodology to that described above and included left early 5.5–13-Hz amplitude, left 2–5-Hz midictal amplitude, left 2–5-Hz postictal amplitude, and left TSLOW.

*Preliminary Assessment of the Relationship of Ictal EEG Variables and Therapeutic Outcome:* Because of the small

sample size and the inherent limitation of studying therapeutic outcome after treatment 5, we performed only a preliminary assessment of the relationship between ictal EEG variables and therapeutic outcome. Specifically, this analysis involved a multivariate ictal EEG logistic regression model of CGI response after treatment 5; this model allowed a preliminary determination of the potential for ictal EEG measures to directly predict therapeutic outcome while controlling for Type I error. The treatment 2–5 means of all of the ictal EEG variables were entered into this exploratory analysis, along with age. Variables that did not significantly contribute to predicting variance in therapeutic response were removed in a stepwise manner. The model was tested by using the “leave-one-out” procedure in which the data for each subject were sequentially removed, a separate logistic regression model was developed with the remaining data, and the resulting model was then tested on the data from the removed subject.<sup>36</sup> Correlation among the ictal EEG variables was expected, and model parameters are therefore not reported because they are likely to be unreliable. Instead, we present the overall performance of the model and the degree to which ictal EEG variables relate to therapeutic outcome.

**RESULTS**

**Effects of Relative Stimulus Intensity on Ictal EEG Parameters**

MANCOVA, performed to assess the effects of relative stimulus intensity (T vs. 2.5T) on ictal EEG indices, revealed a significant main effect for relative stimulus intensity (multivariate  $F = 6.9$ ,  $df = 9,9$ ,  $P = 0.004$ ). Age was a significant covariate (multivariate  $F = 4.2$ ,  $df = 9,9$ ,

**TABLE 2.** First four principal components of ictal EEG variables<sup>a</sup>

| Variable                                  | PRIN1     | PRIN2     | PRIN3    | PRIN4     |
|---|-----------|-----------|----------|-----------|
| Percentage of variance accounted for      | 45        | 25        | 13       | 10        |
| Left 5.5–13-Hz early amplitude constant   | 0.337023  | 0.145347  | 0.457368 | -0.330347 |
| Right 5.5–13-Hz early amplitude constant  | 0.372703  | 0.129997  | 0.387851 | -0.186116 |
| Left 2–5-Hz midictal amplitude constant   | 0.416869  | 0.184744  | 0.072316 | 0.387599  |
| Right 2–5-Hz midictal amplitude constant  | 0.403066  | 0.164246  | 0.126853 | 0.525657  |
| Left 2–5-Hz postictal amplitude constant  | -0.312297 | -0.275883 | 0.505134 | 0.214998  |
| Right 2–5-Hz postictal amplitude constant | -0.28841  | -0.292221 | 0.530298 | 0.259721  |
| Left TSLOW constant                       | -0.275992 | 0.515537  | 0.180023 | -0.247008 |
| Right TSLOW constant                      | -0.270843 | 0.525611  | 0.192756 | -0.084358 |
| Early 2–5-Hz coherence constant           | 0.284657  | -0.444206 | 0.114569 | -0.49787  |

Note: PRIN = principal component; TSLOW = time to onset of ictal slowing.

<sup>a</sup>Where, for example, PRIN1 would be calculated from the z-transformed data from a given seizure as follows (A = amplitude):  
 $PRIN1 = (0.337023 \times \text{left early A}) + (0.372703 \times \text{right early A}) + (0.416869 \times \text{left mid A}) + (0.403066 \times \text{right mid A}) - (0.312297 \times \text{left postictal A}) - (0.28841 \times \text{right postictal A}) - (0.275992 \times \text{left TSLOW}) - (0.270843 \times \text{right TSLOW}) + (0.284657 \times \text{early coherence})$ .

$P = 0.05$ ); however, initial seizure threshold was not.

The significant findings of this omnibus analysis were followed up by performing separate univariate analyses of covariance (ANCOVAs) for each of the EEG variables (Table 3). All of the ictal EEG measures significantly differed in the T and 2.5T dosing conditions ( $P < 0.05$ ). All effects were in the expected direction of 1) greater ictal amplitude and postictal suppression and 2) a more rapid and synchronous onset of slowing associated with higher relative intensity stimuli. Age was a significant covariate for all ictal magnitude measures, with older subjects having lower amplitude seizures.

A significant main effect or interaction involving hemisphere was not found on multivariate repeated-measures ANCOVA. Similarly, longer seizure duration was *not* observed in the 2.5T compared with T subjects (see Table 1).

#### An Ictal EEG Model for Prediction of Relative Stimulus Intensity with ECT

As a more direct test of the clinical utility of ictal EEG measures as markers of the relative stimulus intensity of individual ECT treatments, a multivariate ictal EEG logistic regression model was developed and tested for its ability to correctly identify T and 2.5T seizures. As outlined in the Methods section, the first four principal components of the treatment 2–3 means of all nine ictal EEG variables, along with age, were entered into a stepwise logistic regression analysis. Only age and principal components 1 and 4 (see Tables 2 and 4) contributed significantly to the prediction of stimulus intensity group, and therefore principal components 2 and 3 were dropped from the model. Based on the weightings of the two principal components used in the model (1 and 4; see Table 2), the ictal EEG variable that contributed most strongly to the model was midictal 2–5-Hz amplitude,

TABLE 3. 1.0 vs. 2.5 times threshold (T) analysis of covariance results (adjusting for age and seizure threshold)

| Measure                                 | Mean $\pm$ SD  |                | P         |        |
|---|----------------|----------------|-----------|--------|
|   | T              | 2.5T           | Intensity | Age    |
| Ictal spectral amplitude ( $\mu$ V)     |                |                |           |        |
| Left 5.5–13-Hz early                    | 26.1 $\pm$ 8   | 37.0 $\pm$ 11  | 0.0002    | 0.0002 |
| Right 5.5–13-Hz early                   | 32.1 $\pm$ 9   | 43.3 $\pm$ 20  | 0.009     | 0.01   |
| Left 2–5-Hz middle                      | 72.9 $\pm$ 55  | 115.6 $\pm$ 40 | 0.0045    | 0.001  |
| Right 2–5-Hz middle                     | 88.2 $\pm$ 61  | 120.3 $\pm$ 47 | 0.04      | 0.009  |
| Postictal spectral amplitude ( $\mu$ V) |                |                |           |        |
| Left 2–5-Hz                             | 11.0 $\pm$ 7   | 5.2 $\pm$ 4    | 0.005     | 0.22   |
| Right 2–5-Hz                            | 9.0 $\pm$ 4    | 4.5 $\pm$ 3    | 0.005     | 0.17   |
| Coherence                               |                |                |           |        |
| Early 2–5-Hz                            | 0.43 $\pm$ .18 | 0.69 $\pm$ .1  | 0.006     | 0.28   |
| Time to slow-wave onset (s)             |                |                |           |        |
| Left                                    | 12.2 $\pm$ 6   | 5.6 $\pm$ 8    | 0.05      | 0.54   |
| Right                                   | 10.9 $\pm$ 6   | 3.8 $\pm$ 6    | 0.01      | 0.64   |

followed by early 5.5–13-Hz amplitude, early 2–5-Hz coherence, postictal 2–5-Hz amplitude, and T<sub>SLOW</sub>.

This model correctly identified the relative stimulus intensity group in 95% (20/21) of the seizures from the set from which it was developed. This result included a 100% success rate for identifying T seizures (10/10) and a 91% success rate for identifying 2.5T seizures (10/11)—a sensitivity of 100% and specificity of 91% for identifying T seizures. To make a more realistic assessment of the performance of this model, we tested it on data from treatments 4 and 5.<sup>36</sup> The resulting overall accuracy of 90% (26/29 correct predictions) included 80% accuracy for identifying T seizures (8/10) and a 95% success rate for identifying 2.5T seizures (18/19)—a sensitivity of 80% and specificity of 95% for identifying T seizures. Testing the model on data for all treatments after treatment 5 yielded a similar predictive accuracy: 88% overall accuracy (35/40); T accuracy 82% (9/11); 2.5T accuracy 90% (26/29). The lowest predictive accuracy was associated with treatment 1 data (71%, 10/14).

As described in Methods, a separate model was developed using only data from the left hemisphere. This model was composed of the first and fourth principal components of the four left-sided EEG variables (none of the other principal components made a significant contribution) and age. This model correctly predicted the stimulus intensity group of all 22 seizures from which it was developed (100% accuracy) and was only slightly less successful in predicting relative stimulus intensity group than the two-hemisphere model described above when tested on treatment 4 and 5 data. An 88% overall success rate was found (37/42), with a T accuracy of 70% (7/10) and an accuracy of 95% (18/19) in identifying 2.5T seizures.

#### A Preliminary Assessment of the Relationship Between Ictal EEG Variables and Therapeutic Outcome After Treatment 5

The relationship between the means of treatment 2–5 data for ictal EEG variables and therapeutic outcome (after treatment 5) was explored through the development of a multivariate ictal EEG logistic regression model of therapeutic response. As reported by Sackeim and colleagues,<sup>1,2</sup> our results were compatible with a higher therapeutic response rate for 2.5T (70%, 7/10) compared with T (50%, 5/10) ECT, although, because of the small number of subjects included, this difference was not significant. Both right early 5.5–13-Hz ictal EEG amplitude ( $\chi^2 = 6.1, P = 0.01$ ) and right 2–5-Hz postictal amplitude ( $\chi^2 = 4.9, P = 0.03$ ) were significant predictors of therapeutic outcome. There was a trend toward significance for early 2–5-Hz interhemispheric coherence ( $\chi^2 = 4.9, P = 0.08$ ). A logistic regression model including these variables and age correctly predicted the therapeutic out-

**TABLE 4. Multivariate logistic regression model coefficients and significance level**

| Variable | Regression Coefficient ( $\beta$ ) <sup>a</sup> | $\chi^2$ | P     |
|----------|---|----------|-------|
| PRIN1    | 0.7709  | 7.7      | 0.005 |
| PRIN4    | -0.1880   | 3.9      | 0.05  |
| Age      | 4.7875  | 4.1      | 0.04  |
| Constant | -18.3229  | —        | —     |

Note: Group membership is predicted for seizure *i*, as follows (PRIN = principal component):

$G(i) = PRIN1 \times \beta_{PRIN1} + PRIN4 \times \beta_{PRIN4} + Age \times \beta_{Age} + \beta_{Constant}$   
 where for the present study  $G(i) < 0$  indicated a T ( $1.0 \times$  threshold) seizure and  $G(i) > 0$  indicated a 2.5T seizure.

The probability of group membership is  $P(i) = 1/(1 + e^{-G(i)})$ .  
 $P(i) < 0.5$  indicates a T seizure, and  $P(i) > 0.5$  indicates a 2.5T seizure.

come for 75% (15/20) of the subjects used to develop the model (resubstitution). When the "leave-one-out" technique was employed, the model had a successful prediction rate of 70% (14/20).

## DISCUSSION

The results of this study provide the strongest evidence to date that attributes of the ictal EEG are likely to be clinically useful as a marker of adequate stimulus intensity with UL ECT. This conclusion is supported in a number of ways. First, ictal EEG differences between T and 2.5T ECT confirm that more highly suprathreshold UL ECT stimuli are associated with ictal EEG evidence of more intense seizure activity; greater early and midictal amplitude and more extensive postictal suppression are seen in the 2.5T condition. The earlier onset of slow-wave activity and greater early coherence of ictal slowing suggest that moderately suprathreshold seizures may also be more rapidly generalized.

Findings in the present study are highly consistent with those reported in our earlier intraindividual protocol.<sup>19</sup> Similarly, these results agree with the findings of a previous interindividual study based on manually derived EEG ratings.<sup>20</sup> Good agreement would have been expected between manual and computer-derived ictal slow-wave amplitude because we previously found a high degree of correlation between these indices ( $R = 0.8$ ,  $P < 0.001$ ); however, manual and computer postictal suppression measures were not as well correlated ( $R = 0.58$ ,  $P < 0.08$ ).<sup>19</sup> Further, agreement between our computer-derived ratings and manual TSLOW ratings reported previously by others supports the validity of the automated TSLOW algorithm used in this study. The present results also agree with previous work<sup>20,24</sup> that age is a significant covariate for ictal EEG measures; older sub-

jects had lower amplitude seizures. However, in the present study initial seizure threshold was not found to be significantly related to ictal slow-wave amplitude. The fact that seizure duration was not longer in 2.5T compared with T subjects further supports the notion that seizure duration is not useful for the determination of adequate stimulus intensity with UL ECT.<sup>19</sup>

Still, the strongest evidence contained herein for the clinical utility of the ictal EEG as a marker of treatment adequacy is the development of an accurate multivariate ictal EEG model for prediction of relative stimulus intensity with UL ECT. This work represents a further step toward the development of a clinically useful model of UL ECT seizure adequacy. The performance of the model suggests an expected sensitivity and specificity of at least 80%. Nonetheless, it will be important for this model to be tested in other sets of subjects. Only principal components 1 and 4 contributed significantly to the model, suggesting that, among the ictal EEG variables, midictal 2–5-Hz amplitude was the strongest predictor of stimulus intensity group. Although to a lesser extent, the other three types of ictal EEG indices all also contributed to the model and had similar weightings on these two principal components. Further work will be needed to better delineate the relative utility of these ictal EEG measures. It is also of note that model performance was less accurate on treatment 1 data than on data from any other treatment. This may reflect a physiologic difference between treatment 1 and subsequent treatments and is consistent with our clinical impression that treatment 1 seizures tend to be more intense. Further studies are also needed to determine the consistency and size of this effect.

An additional model was developed by using ictal EEG data from only the left hemisphere. This model was only slightly less accurate in prediction of group membership than the model including data from both hemispheres. The performance of this model suggests that an ictal EEG algorithm implemented by using only one channel of EEG data may still have a high rate of success in the prediction of relative stimulus intensity.

Before an ictal EEG algorithm for the determination of adequate stimulus intensity, such as has been presented here, could be implemented in the clinical setting, it would need to be fully automated. Accomplishing this task presents several difficulties that still need to be addressed, such as variations in recording technique and how to handle artifacts that arise in the clinical setting.<sup>5</sup> Another step that might improve the clinical applicability of a model of seizure adequacy would be including a measure to compare the "cost" of misclassifying a barely suprathreshold seizure as moderately suprathreshold (risk of administering therapeutically inadequate treatment) versus the cost of identifying a moderately su-



prathreshold seizure as barely suprathreshold (likely to result in an increase in stimulus intensity and a consequently increased risk of adverse cognitive effects<sup>2</sup>).<sup>5</sup> Nonetheless, the above analysis demonstrates that the ictal EEG indices of this study show promise as a much-needed clinically applicable marker of UL ECT relative stimulus intensity, and hence of the therapeutic potency of the seizures induced by these stimuli.

A natural question to ask about a promising algorithm of seizure therapeutic adequacy is how well it predicts therapeutic response. In this regard, the present study must be considered preliminary because of the number of subjects and the restriction to assessing therapeutic response after treatment 5. Yet measures of early and postictal amplitude were found to be significantly related to therapeutic outcome (with a trend present for coherence) in a multivariate logistic regression model that had a 75% success rate in predicting therapeutic response. These preliminary findings complement those of Nobler et al.,<sup>20</sup> who reported a relationship between postictal suppression and therapeutic outcome in a study using manual ratings (coherence and 5.5–13-Hz early amplitude could not be measured), and also support a relationship between ictal EEG variables and therapeutic outcome.

The ictal EEG findings in the present study have implications regarding the neurophysiology of ECT seizures. The observed T versus 2.5T ictal EEG differences reinforce the concept that ECT seizures are graded rather than all-or-none phenomena.<sup>5</sup> These differences appear to reflect a greater ability of 2.5T ECT to induce neuronal synchronization and to elicit endogenous inhibitory reactive processes within the brain. Neuronal synchronization, although poorly understood physiologically, is felt to play a central role in generating observed EEG and clinical epileptic activity<sup>37</sup> and would be expected to be greater in seizures that have greater amplitude and coherence, such as we have found with 2.5T ECT. Ictal slow waves have been associated with subcortical (particularly thalamic) processes that inhibit cortical function and have been hypothesized to be involved in mediating the antidepressant effect of ECT.<sup>1,5,19,37,38</sup> The greater midictal amplitude and earlier polyspike and slow-wave phase onset (shorter T SLOW) observed with 2.5T compared with T ECT suggest that these subcortical processes are activated earlier and more potently by this more effective form of treatment. This observation is also consistent with the

hypothesized antidepressant role of the inhibitory subcortical processes that are postulated to be generated by the electrically induced seizure,<sup>5</sup> as is the finding of greater postictal suppression with 2.5T ECT. Postictal suppression has been found to be highly correlated with midictal slow-wave activity<sup>5,19</sup> and is believed to reflect the extent to which widespread inhibitory processes are elicited by the seizure.<sup>37</sup>

The absence of any significant differences in ictal EEG interhemispheric asymmetry between the T and 2.5T groups is consistent with reports that suggest that factors other than the degree of asymmetry best reflect the extent of seizure generalization. In this regard, we previously found greater ictal EEG asymmetry (right > left) in 2.25T as compared with T UL ECT, where the more intense stimuli were accompanied by significantly greater ictal amplitude and coherence and postictal suppression.<sup>19</sup> Also, the degree of generalization of generalized tonic-clonic seizures is reported to be better reflected by the extent of development of the tonic and clonic phases than the extent of asymmetry.<sup>37</sup>

Although additional work is needed to determine the relationship of ictal EEG variables and therapeutic response and to develop a clinically useful ictal EEG algorithm for determining ECT therapeutic adequacy, this report joins a growing body of evidence suggesting that ictal EEG indices differ among types of ECT that vary in therapeutic response. By developing an ictal EEG model of relative stimulus intensity, this study has taken a significant step toward alleviating the present clinical uncertainty in ascertaining ECT treatment adequacy. These results suggest that an algorithm based on ictal EEG indices holds substantial promise of clinical usefulness for the determination of ECT seizure therapeutic adequacy.

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