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Seizure Threshold in Electroconvulsive Therapy

Effects of Sex, Age, Electrode Placement, and Number of Treatments

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• **In a random-assignment trial to unilateral right and bilateral electrode placements, electroconvulsive therapy (ECT) stimulus intensity was titrated to just above seizure threshold for each of 52 depressed patients. Seizure threshold was quantified in units of charge. There was a 12-fold range in the minimum electrical intensity necessary to produce seizure. Sex, age, electrode placement, and the cumulative number of treatments were each associated with seizure threshold. Bilateral ECT had both a higher initial seizure threshold and a greater cumulative increase in seizure threshold compared with unilateral ECT. Clinical and research implications are discussed with respect to dosing strategies in ECT.**

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There is evidence that the cognitive side effects of electroconvulsive therapy (ECT) are related to the dosage, waveform, and current paths of the electrical stimulus. Higher levels of stimulus intensity,[1,2] stimulus waveforms that are relatively inefficient in seizure-eliciting properties,[3,4] and bilateral in contrast with unilateral right-sided electrode placement[4-6] are associated with greater posttreatment confusion and amnesia. While it frequently has been claimed that electrical dosage in excess of seizure threshold contributes to cognitive side effects,[1,2,7,8] it has also been asserted that, independent of dosage, the elicitation of a generalized seizure is necessary and sufficient for the antidepressant properties of the treatment.[2,7,8] Increasingly, however, this latter claim has been questioned.[9-11] Indeed, there is initial evidence that dosage and waveform characteristics may contribute to the efficacy of the treatment.[12-14]

Despite the indications that the dosage or intensity of the ECT stimulus has an impact on the efficacy and side effects of the treatment, there are no extant data on the range and variability encountered in the seizure threshold of depressed patients. Traditionally, in clinical and research practice it is standard to use a fixed electrical dosage across patient samples. These fixed dosages typically are sufficiently intense so that subconvulsive administrations are rare. Depending on the range that characterizes seizure threshold and the inefficiency of the electrical waveform, it is conceivable that traditional practice results in the administration of electrical intensities that exceed the seizure threshold of some patients by several thousand percent.

Limited information is available with respect to whether patient variables, such as sex and age, or treatment variables, such as electrode placement (bilateral vs unilateral), are predictive of seizure threshold.[15] The identification of significant predictors may be clinically useful in designing more electrically efficient dosing strategies. From a research perspective, the absence of information on predictors of seizure threshold raises an additional set of concerns. If, for instance, unilateral and bilateral ECT differ in the minimum electrical intensity necessary to produce seizure, the standard fixed-dosage technique may seriously confound comparisons of the electrode placements. Dosage will exceed seizure threshold to a greater extent in the modality characterized by a lower seizure threshold. This may compromise comparisons of relative efficacy and side effects.

To examine these issues, we designed a titration procedure to adjust the intensity of the ECT stimulus to just above seizure threshold. We report on the range in seizure threshold encountered in patients who have major depressive disorder and on the relations between seizure threshold and sex, age, electrode placement, and cumulative treatment number. Seizure threshold was quantified in

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Table 1.—Demographic and Psychiatric Characteristics of the Sample*

	Total (n=52)	Bilateral ECT (n=27)	Unilateral Right ECT (n=25)	Sex	
				M (n=18)	F (n=34)
Age, y	61.33 (13.14)	60.78 (10.69)	61.92 (15.33)	64.00 (11.26)	59.91 (13.83)
HAM-D score	30.99 (7.84)	30.53 (7.17)	31.48 (8.48)	29.45 (9.17)	31.73 (6.99)
Affective disorder					
Previous episodes, No. (maximum of 10 permitted)	3.85 (3.13)	4.48 (3.48)	3.16 (2.53)	4.24 (3.14)	3.66 (3.11)
Current episode duration, wk (maximum of 104 wk permitted)	36.77 (29.61)	39.07 (32.65)	34.28 (25.70)	39.18 (37.13)	35.60 (25.08)
Previous psychiatric hospitalizations, No.	2.39 (2.79)	2.63 (3.31)	2.12 (2.05)	2.29 (3.25)	2.43 (2.53)
Age at first affective episode, y	44.02 (16.13)	43.26 (13.98)	44.84 (18.13)	42.18 (13.23)	44.91 (17.30)

*All values are the mean (SD). HAM-D indicates Hamilton Depression Scale (pretreatment).

units of charge (millicoulomb). This dosage unit was selected since both theoretical and empirical evidence suggest that, at least with brief-pulse, constant-current stimulation, it provides a more reliable and sensitive index of seizure threshold than the more commonly used unit of watt-seconds (joules).[11,16] In addition, unlike the unit of watt-seconds, the unit of charge has the advantage of more directly reflecting the actual settings of ECT stimulus parameters when using brief-pulse, constant-current stimulation. Comparison of the units of charge and of watt-seconds regarding the findings reported herein will be the subject of a future report.

PATIENTS AND METHODS

Patients

To enter the study, patients, on the basis of Schedule for Affective Disorders and Schizophrenia[17] interviews, had to meet the Research Diagnostic Criteria[18] for primary, major depressive disorder, have a minimum pretreatment score of 18 on the 24-item Hamilton Depression Rating Scale,[19] and provide informed consent. Patients were excluded who had received ECT within the past year, had a history of organic brain syndrome or substance abuse, or had a serious medical condition (Table 1).

This research was conducted in the context of a double-blind, random-assignment trial contrasting the relative efficacies and cognitive consequences of bilateral and right unilateral ECT. Demographic and psychiatric variables are presented in Table 1 for the sample as a whole (N=52) and as a function of the treatment modality (27 bilateral, 25 unilateral) and sex (18 male, 34 female). There were no significant differences between the groups.

Treatment Parameters

At least five days before the first treatment, all psychotropic medications, except lorazepam (1 mg every 12 hours as required), were withheld. Fifteen patients were maintained on nonpsychotropic medications (diuretic/antihypertensive, n=7; antiarrhythmic, n=3; antidiabetic, n=3; antibiotic, n=1; anti-inflammatory, n=1; antibacterial, n=1; thyroid supplement, n=1; and tuberculosis preparation, n=1). Either thiopental sodium or methohexital sodium was used as the anesthetic, with within-patient random assignment to an agent at each treatment session. In the first session with an anesthetic agent, the doses were 1.9 mg/kg and 0.75 mg/kg for thiopental sodium and methohexital sodium, respectively. In subsequent sessions, the dose was titrated as a function of anesthetic response (thiopental sodium: mean=119.67 mg, SD=40.35; methohexital sodium: mean=52.37 mg, SD=14.68). These doses were lower than those often used in ECT so as to minimize anesthetic effects on seizure threshold and on cognitive functioning. Succinylcholine chloride was administered as a muscle relaxant (first session, 0.5 mg/kg; titrated mean=35.18 mg; SD=14.01). Atropine sulfate (0.4 mg intravenously) was administered approximately two minutes before the anesthetic. Patients were oxygenated from after the administration of the muscle relaxant to the recovery of spontaneous respiration following the seizure. The standard bifrontotemporal[15] and d'Elia[20] electrode placements were used for bilateral ECT (ten male and 17 female patients) and right-sided unilateral ECT (eight male and 17 female patients), respectively. Skin was first prepared by cleansing it with acetone. A ground-quartz abrasive paste (Redux) was used to reduce impedance, and a conductive gel (Redux) served as the electrolyte on electrodes. Electrodes were hand held and were 4.8 cm in diameter.

The device used to elicit seizures (MECTA) produces a bidirectional, square-wave, brief-pulse stimulus. During each pulse, an 800-mA constant current is passed. The frequency and width of pulses may be varied, as well as the duration of the pulse train.

A method-of-limits procedure was designed to titrate dosage to just above the seizure threshold. In the first session, a dosage (pulse frequency, 20 Hz; pulse width, 1.5 ms; and duration, 1 s) was used that rarely elicited a seizure (eight of 52 patients, 15.38%). Following a subconvulsive administration, a minimum interval of 40 s was required before readministration at increased intensity. The settings for subsequent readministrations were a 40-Hz frequency with 1-s duration, 70-Hz frequency with 1-s duration, and 70-Hz frequency with 2-s duration; all were at a pulse width of 1.5 ms. In all patients a generalized seizure was elicited by the fourth stimulation. The electroencephalogram (EEG) (left frontal lead) and electrocardiogram were monitored throughout. The tourniquet method[21] was used to block the distribution of the muscle relaxant from a limb. The duration of motor and EEG seizure manifestations were assessed. The criterion for an adequate seizure was at least 25 s of motor manifestation.

In the second treatment session the dose that previously resulted in a seizure was again administered. If again a seizure was produced at that dose, the charge was decreased at the next session. This procedure was followed throughout the treatment course. The frequency of pulses was the primary variable manipulated to vary dosage (charge). However, in patients with high thresholds, the duration of the pulse train was also varied. The general aim was to produce subconvulsive administrations at approximately 40% to 50% of sessions to quantify and track seizure threshold, to minimize the dose at convulsion, and to contrast acute cognitive effects of sessions involving single convulsive administrations and sessions involving convulsive administrations preceded by subconvulsive administrations.

On the average, patients received 1.55 electrical administrations (SD=0.28) per treatment session. The average percent of treatment sessions with one or more subconvulsive administrations was 44.40% (SD=17%). The motor manifestations of seizures appeared to be all or none to the extent that nongeneralized jacksonian seizures or seizures lasting less than 25 s in motor manifestations occurred in less than 3% of sessions. In such cases a 90-s interval was required before restimulation. Less than 1% of sessions required additional administration of anesthetic or muscle relaxant. These sessions were discarded in the data analyses.

Electroconvulsive therapy was administered on a schedule of three times per week. The length of the course of ECT was determined on a double-blind basis by a clinical evaluation team and was based on therapeutic response. A minimum of ten treat-

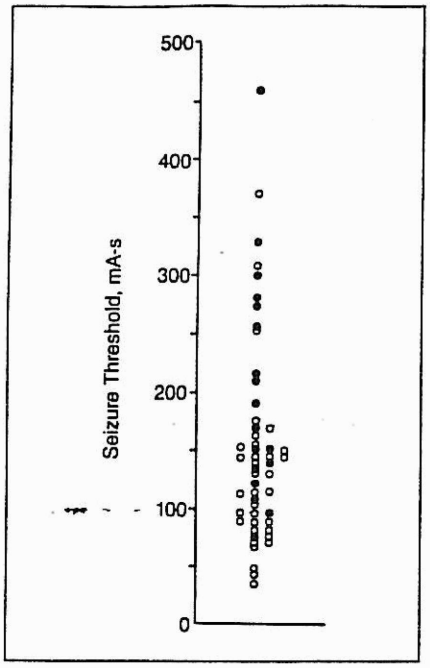

Fig 1.—Seizure threshold in unit of charge for individual male (closed circle) and female (open circle) subjects. Threshold values were averaged for each patient across all treatments.

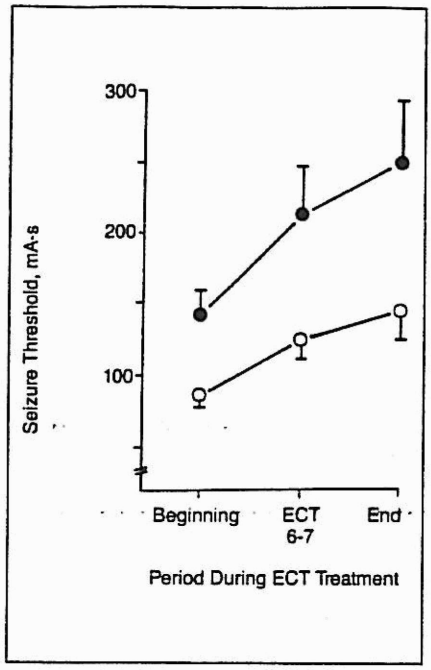

Fig 2.—Seizure threshold in unit of charge at selected time points during electroconvulsive therapy (ECT) as function of sex. Closed circles indicate male subjects; open circles, female subjects.

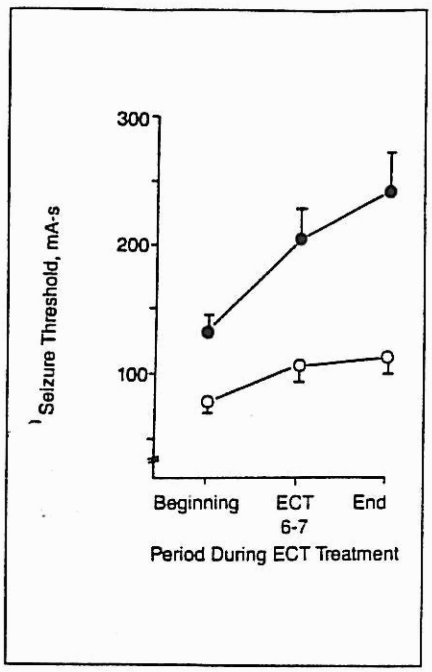

Fig 3.—Seizure threshold in unit of charge at selected time points during electroconvulsive therapy (ECT) as function of electrode placement (bilateral [closed circles] or right unilateral [open circles] ECT).

ments was required for patients to be classified as nonresponders to a particular modality. The modalities did not differ in average number of treatments (bilateral ECT: mean = 9.30, SD = 2.52; right-sided unilateral ECT: mean = 9.40, SD = 2.26). Seizure length was also equivalent, with motor manifestations averaging 48.69 s (SD = 13.66) for bilateral ECT and 46.84 s (SD = 13.18) for unilateral ECT. Seizure length as assessed by EEG averaged 61.44 s (SD = 18.94) and 59.55 s (SD = 20.91) for the bilateral and unilateral modalities, respectively.

Electrical Parameters

At each treatment session the charge that produced the seizure and the dynamic impedance to the passage of the current were quantified. The watt-seconds administered were computed on the basis of these values. Charge (milliampere-seconds) was calculated by determining the amount of time during which the 800-mA current was passed (800 mA × pulse frequency × 2 × pulse width × train duration). Dynamic impedance was calculated from the readings provided on the chart recorder. The current generator was regularly calibrated to ensure constancy of the 800-mA current output and of the stimulus parameters. Accuracy of the dynamic impedance values was likewise verified on a storage oscilloscope against a range (100 to 1200 Ω) of known impedance loads. As a further check, values were verified against a custom watt-second meter both with known charge and impedance loads and during actual administrations.

Statistical Analyses

Relations between continuous variables were examined with the Pearson product-moment correlation. The degree to which sex, age, and modality conjointly predicted seizure threshold was examined with a stepwise, multiple regression analysis. Differences between groups on single continuous variables were evaluated with *t* tests. Differences between groups on variables assessed on more than one occasion were evaluated with repeated-measures analyses of variance (ANOVA). An ANOVA was conducted that examined electrical parameters at the beginning of the ECT course, at the sixth or seventh treatment, and at the final treatment. In those cases in which six or fewer treatments were administered (n = 8), data from the final treatment were used for the last two time points. All significance levels are for two-tailed tests.

RESULTS

Range in Seizure Threshold

The mean charge required to elicit a generalized seizure was computed for each of the 52 patients across all of their treatment sessions (mean = 154.31 mA-s, SD = 86.84). Figure 1 displays the data for individuals, separated by sex. In this sample, the range of mean charge was approximately 12-fold (36 to 459 mA-s). This indicated that the patient with the highest seizure threshold required an intensity to produce seizure that was at least 12 times that of the patient with the lowest threshold. In addition to being characterized by marked variance, the values for mean charge were not normally distributed. The distribution displayed significant positive skew ($P<.001$) and kurtosis ($P<.01$). After logarithmic transformation, the distribution was normal and subsequent statistical analyses were based on transformed values.

Cumulative Treatment Effects

It is a well-established phenomenon that seizure threshold increases during a course of ECT.[23-24] An increase in seizure threshold is also observed in animals following electrical or chemical induction of seizures.[25-27] We have suggested that the increase in seizure threshold be viewed as one of several anticonvulsant properties of ECT.[28,29] The minimum charge necessary to elicit seizure was determined in all patients for the beginning of the ECT series (lowest level in sessions 1 to 3), at the sixth or seventh treatment, and at the end of the course. Figure 2 presents the seizure threshold data at these time points separately for male and female patients. The sample as a whole averaged a 64.60% ± 7.48% increase in seizure threshold from the beginning of the course to the final treatment ($P<.001$, paired *t* test). The percentage increases were comparable in male and female patients (68.77% in male and 62.4% in female patients).

Sex Differences

It is evident in Figs 1 and 2 that a dramatic sex difference was obtained in the charge necessary to elicit seizure. Across all treatments, the charge administered to male patients averaged 158.34% of that administered to female patients ($t=3.32$; $df=50$; $P=.002$). The finding that a lower average charge was needed in female patients is in accord with the recent reports of higher average rates of cortical gray matter blood flow, and presumably neurometabolism, in adult female subjects.[30,31] Increased neurometabolic rates may result in enhanced neural excitability with a consequent low threshold for seizure.[32] However, individual differences in neural excitability is only one of a set of factors that contribute to the seizure-threshold measure. With respect to the sex difference in seizure threshold, we may presume that a smaller skull thickness, smaller neural mass, and epidermal differences in impedance, due possibly to fatty deposits, each contribute to the lower seizure threshold in female subjects by resulting in less shunting and/or greater current density in the brain. A smaller head circumference in female patients, with a consequently smaller interelectrode distance, would contribute in the opposite direction, by increasing shunting and thereby lowering current density in the brain.

Age

Some investigators have reported moderate associations between age and seizure threshold.[15,33-36] In our sample, the correlation with age was .32 ($P<.05$). Higher dosage levels were necessary to produce seizure in older patients.

Electrode Placement

It has been suggested that with standard clinical procedures, missed seizures are more likely with right-sided unilateral ECT than bilateral ECT.[37] This would imply that the stimulus intensity needed to produce seizures is higher with unilateral than bilateral placements. As Weiner's[15] review indicated, studies using constant voltage, sine wave, and related stimulus configurations obtained either no difference[15,20,38-40] or a higher seizure threshold with the unilateral placement.[41-43] In contrast, however, studies using constant-current, pulse waveforms have generally observed a lower seizure threshold with unilateral or vertex placements.[15,44-47] Data concerning modality differences in seizure threshold necessarily have been approximate, since rigorous titration of dosage to just above threshold had not been done previously.

Figure 3 presents the charge necessary to produce seizures at the three time points as a function of modality. A repeated-measures ANOVA (modality × sex × time point) disclosed the main effects of modality ($F=21.93$; $df=1,48$; $P<.001$), sex ($F=12.13$; $df=1,48$; $P=.002$), and time point ($F=81.31$; $df=2,96$; $P<.001$), and an interaction between modality and time point ($F=7.16$, $df=2,96$; $P=.002$). The sex difference was described above. There was no significant interaction involving sex. At all three time points, higher charge was required to produce seizures with bilateral than unilateral ECT (all $P<.001$). Despite starting at a higher level, both the absolute and proportional increase in seizure threshold was greater with bilateral than with unilateral ECT. On the average, seizure threshold increased 87.1% (SD = 58.9%) from the beginning to the end of the course with bilateral ECT and only 40.3% (SD = 32.4%) with unilateral ECT ($t=3.66$; $df=50$; $P=.001$).

Predicting Seizure Threshold

To examine how much of the variance in seizure threshold could be accounted for when charge was averaged across all treatments, a stepwise multiple regression was computed, with sex, age, and treatment modality serving as predictors. As shown in Table 2, 47.1% of the variance was accounted for ($F=14.24$; $df=3,48$; $P<.001$), with each predictor significant. This analysis also indicated that, while the predictors each made important independent contributions, the majority of the variance in seizure threshold was still unaccounted for.

Table 2.—Multiple-Regression Analysis Predicting Seizure Threshold on the Basis of Electrode Placement, Sex, and Age

Variable	Standardized Coefficient	*t* Test*	Significance	Cumulative Variance
Electrode placement (unilateral/bilateral)	.47	4.50	<.001	.23
Sex, M/F	−.36	−3.36	.002	.39
Age	.29	2.69	.01	.47

*$df=48$.

COMMENT

Our findings indicate that there is a considerable range in the minimum electrical intensity necessary to elicit generalized seizure and that patient and treatment variables are reliably predictive of seizure threshold. The findings pertain to brief-pulse, constant-current forms of ECT administration. Whether similar relations apply to constant-voltage forms of administration is a matter for investigation. Furthermore, the extent to which the unexplained variance in seizure threshold was a function of benzodiazepine administration, a relatively brief washout period for psychotropic medication prior to ECT, and/or the use of nonpsychotropic medications in some patients is unknown.

The findings have important implications for both the clinical and research use of ECT. As indicated earlier, the typical procedure in both contexts has been to administer the same electrical dosage to virtually all patients, regardless of sex, age, modality, or other factors, often using forms of stimulation that are inefficient in seizure-eliciting properties. The dosage used is rarely subconvulsive. Maxwell[48] reported that with constant-voltage, sine wave administration, a dosage of 112 W-s (748 mA-s assuming 200 Ω dynamic impedance) was necessary to elicit seizures in approximately 60% of a series of unselected patients. Typical reported values in the research literature range from 40 to 100 W-s (approximately 447 to 707 mA-s) for constant-voltage devices. In a sample of relatively older patients with major depressive disorder, we observed an approximately 12-fold range in the dosage necessary to elicit generalized seizure. Using the same treatment procedures in patients with different diagnostic, age, and medication status, we have observed that this range is further extended, with a greater representation of patients with lower seizure thresholds.[49] Some patients consistently have adequate seizures at intensities as low as 10 mA-s. An outcome of this variability is that when a standard high dosage is used, patients with low thresholds can receive in each treatment session stimulus intensities that may be several thousand percent in excess of their thresholds. To the extent that a dosage above threshold contributes to adverse cognitive side effects, the traditional practice may unnecessarily increase the magnitude of these side effects.

In ECT research, the most common procedure has also been to administer a standard fixed dosage. Our findings indicate that, with a standard stimulus intensity and brief-pulse, constant-current administration, dosage in excess of threshold will be greater in female patients, younger patients, and patients treated with a unilateral electrode placement. It has not been established whether the absolute dosage, per se, or a dosage in excess of the threshold is more related to the therapeutic and adverse effects of ECT. We suspect that the latter condition is more critical, particularly since much of the variance in dosage necessary to elicit seizure is due to anatomic variability (eg, degree of shunting), independent of the functional state of the brain. Presuming that the critical variable is the degree to which dosage exceeds seizure threshold, with a traditional fixed-dosage procedure, differences between treatment modal-

ities, sex differences, and age effects may be artifactual. For example, with a single electrical intensity administered to all patients, dosage relative to threshold will be greater in unilateral than bilateral ECT. This may bias efficacy results in favor of unilateral administration. Therefore, on both research and clinical grounds there are reasons to consider implementation of some form of a titration procedure for determining ECT dosage.

Whatever benefits might be achieved by titrating ECT dosage, they must be weighed against the risks and possible adverse effects of the titration procedure and the relative efficacy of low-dosage techniques compared with more traditional forms of ECT administration. In this study, we deliberately administered subconvulsive intensities to determine the dosage necessary to elicit seizure. The safety of subconvulsive administrations, assessed by comparison of the physiological and neuropsychological effects of single convulsive sessions and sessions involving prior subconvulsive administrations, will be the subject of future reports. It should be noted that for research purposes the frequency of subconvulsive administrations was kept high so that seizure threshold could be quantified sensitively and tracked. For clinical purposes, by taking advantage of knowledge of the predictors of seizure threshold (eg, sex, modality, and age) and giving relatively few subconvulsive administrations, adequate adjustment of ECT dosage may be achieved. Likewise, the development of organic states in patients may suggest reductions in dosage to levels closer to threshold.

We suspect that ultimately the issue of efficacy will be more consequential in determining ECT dosing strategies than the issue of safety. There are preliminary indications that low-dosage techniques may not be as efficacious as traditional forms of ECT administration, particularly with unilateral electrode placement.[9-14] Unfortunately, no information is presently available concerning the extent that dosage should exceed seizure threshold to maintain strong therapeutic results. If and when a therapeutic dosage window is determined, titration strategies may be designed to administer doses that exceed the threshold by fixed amounts (eg, 50%). The possibility that dosage in excess of threshold is associated with therapeutic outcome is also problematic for the traditional fixed-dosage technique. With this practice, one may not know whether the dosage administered to the individual patient is grossly above the threshold or just marginally above the threshold.

The modality differences in seizure threshold observed herein merit special consideration. In accounting for the sex difference in the dose required to produce seizure, we emphasized anatomic factors that influence the degree of current shunting. Such factors are less likely to account for the difference between the two modalities in seizure threshold at the beginning of the treatment course and cannot account for the modality difference in the magnitude of the increase in threshold during the treatment course. Seizure threshold was consistently lower with right-sided unilateral ECT. The current paths of bilateral and right unilateral ECT are distinct. In the cortex, current density with bilateral ECT is greatest in anterofrontal regions. With unilateral ECT, current density is more evenly distributed over the hemisphere ipsilateral to administration.[50-53] There is evidence that seizure threshold is higher in anterofrontal relative to more posterior regions, particularly the motor and parietal cortices.[54,55] This may be related to the higher intensity necessary to elicit seizures with bilateral ECT.

The increase in seizure threshold observed over the course of treatment was a highly consistent finding. The increase reflects a cumulative change in the functional state of neural tissue.[11] Elsewhere,[11,28] we have suggested that the threshold increase is related to the neurometabolic suppression, ie, the decrease in cerebral blood flow[29,56,57] and glucose metabolism[58] observed following ECT. We found here that the threshold increase was greater with bilateral than with right-sided unilateral ECT, when both were administered just above threshold. This suggests a major difference in the subacute neurophysiological consequences of bilateral and right-sided unilateral ECT. In animals, electroconvulsive shock raises the threshold for chemical convulsants that act through antagonism of gamma aminobutyric acid (GABA), but does not seem to raise the threshold for convulsants that act on the glycine or 5-hydroxytryptamine systems.[25] It has also been shown that electroconvulsive shock results in increased GABA concentrations in several neural regions[59,60] and in increased density of $GABA_B$ receptors.[61] The difference between modalities in the relative increase in seizure threshold may reflect differences in altering GABA-ergic transmission.

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