Predictors of Retrograde Amnesia Following ECT

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Objective: Substantial progress has been made in identifying how the treatment parameters used in ECT impact on cognitive side effects. However, there is limited information regarding individual differences in vulnerability to these side effects. The authors examined patients' pretreatment global cognitive status and postictal orientation recovery time as potential predictors of the magnitude of retrograde amnesia for autobiographical memories after ECT. *Method:* Seventy-one inpatients with major depressive disorder were randomly assigned to four ECT conditions that varied in electrode placement (right unilateral versus bilateral) and stimulus dosage (low versus high intensity). Orientation recovery time was assessed at virtually every session during the course of ECT. Global cognitive status was assessed with the modified Mini-Mental State examination before treatment, during the week after termination of treatment, and 2 months after treatment ended. Retrograde amnesia was assessed at these same time points with the Autobiographical Memory Interview. *Results:* Pre-ECT global cognitive status and the duration of postictal disorientation were strong predictors of the magnitude of retrograde amnesia in the week after the course of ECT and at 2-month follow-up. In general, these relationships were maintained regardless of technical parameters in the administration of the ECT. *Conclusions:* Patients who manifest global cognitive impairment before treatment and patients who experience prolonged disorientation in the acute postictal period may be the most vulnerable to persistent retrograde amnesia for autobiographical information.
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Administration of ECT results in characteristic cognitive side effects. Immediately after termination of the seizure, patients are disoriented (1–3). During the acute postictal period, patients may also manifest attentional disturbance and transient neurological or sensorimotor abnormalities (4, 5). A few days after completion of the treatment course, depressed patients typically show improved performance, relative to their pre-ECT baseline performance, on tests of attention, immediate learning, and intelligence; the improvement often covaries with the extent of symptom reduction (6–9). In contrast, at this time point, patients typically manifest deficits in the retention of newly learned information (anterograde amnesia) and in the recall of information learned prior to the treatment course (retrograde amnesia) (7, 10–12). The anterograde disturbance resolves rapidly, and it has been difficult to document deficits in this domain more than a few weeks after ECT (9). Retrograde amnesia may be more persistent, and loss of memory for personally relevant, autobiographical information may be a particularly robust iatrogenic effect (10, 11, 13, 14). Indeed, it is thought that ECT can result in permanent gaps in memory for events that occurred in the months surrounding the course of treatment (15).

The magnitude of the acute and short-term cognitive side effects of ECT is highly sensitive to treatment parameters. In general, these side effects are more severe or persistent with the use of bilateral as opposed to right unilateral electrode placement, with the use of high-intensity as compared to low-intensity electrical dosage, and with shorter intervals between treatments (2, 11, 12, 16–18). For example, the time to recover orientation after termination of the seizure may vary from a few minutes to several hours depending on the combination of these treatment variables (1, 2, 12, 16). Nonetheless, within any given form of ECT, there are considerable individual differences in the magnitude of acute and short-term cognitive changes, and little is known about the factors that distinguish patients in their vulnerability to these adverse effects. There is some evidence that older patients are more at risk (19–21). There is also initial evidence that acute delirium

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during ECT is particularly likely in patients with lesions in the basal ganglia (22).

The major aim of this study was to test two possible predictors of short- and long-term retrograde amnesia. We hypothesized that impaired cognitive status prior to ECT is linked to greater vulnerability to persistent amnestic side effects. Surprisingly, despite considerable speculation, the issue of whether preexisting cognitive impairment constitutes a risk factor has not been addressed empirically (23). We also hypothesized that the duration of disorientation during the acute postictal period predicts the magnitude of retrograde amnesia for autobiographical memories. This hypothesis was based on the view that acute disorientation for person, place, and time may itself be a gross and rapidly shrinking form of retrograde amnesia (3, 24). The discovery of predictors of persistent retrograde amnesia could be of clinical value in identifying the patients who are most vulnerable to adverse cognitive side effects and require particularly careful adjustment of treatment parameters. From a theoretical perspective, identifying behavioral predictors of persistent retrograde amnesia might also provide useful leads regarding the mechanisms that underlie memory impairment following ECT.

METHOD

The patients included in this study were referred consecutively by community physicians to a research protocol examining the affective and cognitive consequences of ECT (12). The study group consisted of 71 patients, 30 (42%) male and 41 (58%) female, who met the Research Diagnostic Criteria (25) for major depressive disorder, endogenous subtype, and who had pretreatment scores of 18 or higher on the 24-item Hamilton Depression Rating Scale. Patients with a history of schizophrenia, schizoaffective disorder, other functional psychosis, rapid-cycling bipolar disorder, organic mental syndrome, neurological disorder or insult, alcohol or drug abuse within the past year, ECT within the past 6 months, or severe medical illness were excluded. Informed consent was obtained from all study patients after the procedures had been fully explained. Other than lorazepam (up to 3 mg/day p.r.n.), patients were free of psychotropic medications at least 5 days prior to neuropsychological assessment or ECT; the mean pre-ECT washout period was 16.6 days (SD=7.9; 30-day upper limit).

ECT

ECT was administered three times per week with a customized brief-pulse, constant-current device (MECTA SR-1). Patients were randomly assigned to four treatment groups (12); either the standard bifrontotemporal (bilateral) or the d'Elia (right unilateral) electrode placement was used, and electrical dosage was either low or high. Seizure threshold was quantified at the first treatment with the use of the empirical titration procedure (26). In the low dosage groups, electrical intensity was kept just above each patient's seizure threshold throughout the treatment course. Patients randomly assigned to the high dosage groups received electrical intensities that were 2.5 times their initial seizure threshold (in units of charge). For all patients, seizure threshold was redetermined at the last treatment. Anesthetic medications included atropine (0.40 mg i.v.), methohexital sodium (0.75 mg/kg), and succinylcholine (0.50 mg/kg), and patients were given oxygen (100% O_2, positive pressure) until the resumption of spontaneous respiration. Physiological monitoring included pulse oximetry, ECG, and two channels of EEG. The durations of motor and EEG seizure manifestations were assessed, and conservative criteria were used to guarantee adequate seizure duration at each treatment (12).

The number of treatments administered was determined by a clinical evaluation team blind to treatment assignment. A minimum of 10 treatments was required before a patient was classified as a nonresponder. This criterion was reduced to eight treatments in cases of clinical urgency. No minimum or maximum number of treatments was imposed on patients who showed clinical benefit. Nonresponders to the double-blind, randomized treatment conditions were offered a second, open course of ECT. This course used high-dose (2.5 times threshold) bilateral treatment. Other than lorazepam, patients were free of psychotropic medications until 1 week after the termination of all ECT. Following this, patients received uncontrolled continuation pharmacotherapy.

Neuropsychological Assessment

The technicians who administered the neuropsychological procedures were blind to treatment assignment. Global cognitive status was assessed with the modified Mini-Mental State examination (27, 28) before treatment, during the week following the end of the randomized phase, and 8 weeks after the completion of all ECT. This test, with a maximum score of 57 (normal range=52–57), contains the original Mini-Mental State items (29) as well as additional items assessing confrontation naming and digit span. The reliability and validity of the modified Mini-Mental State examination, as well as its strong relation to the original version, have been established (28, 30). Change in modified Mini-Mental State scores was quantified as a percentage relative to baseline ([1–posttreatment score/pretreatment score]×100). Alternative versions of the modified Mini-Mental State examination were used at each testing occasion, with different versions for five items (word registration, attention, calculation, addition, and digit span). Valid modified Mini-Mental State data were available for 67 of the 71 patients at the baseline and short-term time points and for 44 of 45 patients at 2-month follow-up. At baseline, the average pretreatment modified Mini-Mental State score was 48.85 (SD=6.61, range=27–57), indicating mild to moderate cognitive impairment.

During the randomized phase, postictal orientation recovery was assessed at virtually every ECT session (2, 31). Following the resumption of spontaneous respiration, a technician requested that the patient open his or her eyes. When this was done, continuous assessment of orientation recovery ensued. The patient was asked to state his or her name, where he or she was (New York State Psychiatric Institute or Columbia-Presbyterian Medical Center), age, date of birth, and the day of the week. These requests continued until correct responses were given or for up to 90 minutes. The criterion for orientation recovery was correct responses to four of the five questions. Any patient who failed to meet this criterion within 90 minutes was given a score of 100 minutes. This ceiling value was given to four patients on a total of 11 occasions. Postictal orientation was not assessed if psychotropic medication was administered during the postictal period to control emergent delirium or for any other reason (2.1% of 675 sessions). The orientation measure used here was the mean time to recovery across treatment sessions, dropping the first and last sessions, in which all patients received low-dose treatment. All statistical analyses were performed on log-transformed scores.

Retrograde amnesia for personal information was assessed with the Autobiographical Memory Interview (12), an expanded adaptation of the Personal Memory Questionnaire developed by Weiner et al. (11). It is a structured interview involving 281 inquiries about recent and remote personal memories. It focuses on illnesses, employment history, places of residence, travel and entertainment activities, emotionally significant events, and everyday events in the lives of patients, their families, and their friends. Of these inquiries, 185 items require a descriptive response (providing a name, location, or description of an event). Responses to these items were used to derive retrograde amnesia scores. At retest, patients were administered only those items for which they had given a definite answer at the pretreatment assessment. At baseline, patients averaged 115.6 (SD=25.8) responses to the 185 inquiries. For short-term testing, amnesia was quantified as the ratio of the number of items in which the 1-week post-ECT

response was consistent with baseline response relative to the total number of factual responses produced at baseline ([1–posttreatment consistency score/pretreatment total items]×100). For long-term testing, patients were credited with consistency if the response at 2-month follow-up matched either the baseline or the 1-week post-ECT (short-term) response. Statistical analyses were conducted after arc sine transformation of these amnesia ratio scores. Seventy-one patients completed the Autobiographical Memory Interview before treatment and during the week following the randomized phase; 45 patients completed the Autobiographical Memory Interview at all three time points. Seventeen of these patients had received a second, crossover course of ECT following the randomized phase.

Statistical Analyses

The comparability of treatment groups in baseline characteristics and treatment parameters was tested with analyses of variance (ANOVA) (electrode placement by dosage condition) on continuous measures and log-linear analyses on dichotomous variables. We next examined the effects of the treatment conditions on the cognitive measures. An analysis of covariance (ANCOVA) was performed on the orientation recovery times, with electrode placement and dosage condition as between-subject factors and age as a covariate. Similar ANCOVAs were conducted on the short-term (1 week post-ECT) change in modified Mini-Mental State and retrograde amnesia measures. Post hoc comparisons of group differences contributing to significant interaction effects were based on t tests conducted on least squares adjusted means. For the subgroup studied at 2-month follow-up, repeated measures ANOVAs were conducted on the change in modified Mini-Mental State and retrograde amnesia scores to examine changes over time and the effects of treatment conditions. The dependent measures were the cognitive scores at the short-term and long-term time points; the between-subject factors were electrode placement during the randomized phase and having received one course of ECT (randomized phase) or two courses (randomized and crossover phases).

The associations between baseline modified Mini-Mental State scores, orientation recovery, and short-term retrograde amnesia scores were tested with Pearson product-moment correlations. At the short-term time point, a simultaneous regression analysis was also conducted to predict the retrograde amnesia scores on the basis of baseline modified Mini-Mental State scores, orientation recovery time, age, dosage condition (low versus high), absolute electrical dosage (log-transformed charge), average EEG seizure duration (log-transformed), and number of ECTs. Since electrode placement exerted marked effects on the short-term retrograde amnesia scores, this regression analysis was also conducted separately for patients treated with right unilateral and bilateral ECT. Similar correlational and regression analyses were performed to determine whether baseline modified Mini-Mental State scores or postictal orientation recovery predicted the magnitude of retrograde amnesia at the 2-month follow-up. All tests of significance were two-tailed.

RESULTS

Table 1 presents demographic and clinical characteristics and treatment variables for the group of 71 depressed inpatients. The ANOVAs and log-linear analyses indicated that there were no significant differences among the treatment groups.

Effects of Treatment Condition on Cognitive Measures

The ANCOVA on orientation recovery time yielded a main effect of electrode placement ($F=80.69$, $df=1, 66$, $p<0.001$), a main effect of stimulus intensity ($F=5.37$, $df=1, 66$, $p=0.02$), and a significant interaction between the two ($F=5.32$, $df=1, 66$, $p=0.02$). As shown in table 2, the two bilateral ECT groups had equivalent recovery times, while all other comparisons among the treatment groups showed significant differences (all p values ≤0.002). The ANCOVA on modified Mini-Mental State scores yielded only a main effect of electrode placement ($F=10.42$, $df=1, 62$, $p=0.002$). Patients treated with right unilateral ECT had unchanged modified Mini-Mental State scores following ECT (paired $t=0.12$, $df=28$, n.s.), while patients treated with bilateral ECT had reduced scores (paired $t=4.89$, $df=37$, $p<0.001$). Similarly, the ANCOVA on the short-term retrograde amnesia scores yielded a main effect only for electrode placement ($F=21.43$, $df=1, 66$, $p<0.001$). Retrograde amnesia was greater with bilateral than right unilateral ECT (table 2).

The repeated measures ANOVA conducted on the short-term and follow-up modified Mini-Mental State scores yielded a main effect of electrode placement during the randomized phase ($F=6.52$, $df=1, 40$, $p=0.01$), a main effect of time point ($F=17.78$, $df=1, 40$, $p<0.001$), and an almost significant interaction between these factors ($F=3.65$, $df=1, 40$, $p=0.06$). At 2-month follow-up, there was no impact on modified Mini-Mental State scores of having received a crossover course of high-dose bilateral ECT. The study group showed significant improvement in modified Mini-Mental State scores at 2-month follow-up relative to both the week following

TABLE 1. Demographic and Clinical Characteristics of 71 Inpatients With Major Depressive Disorder Who Received ECT

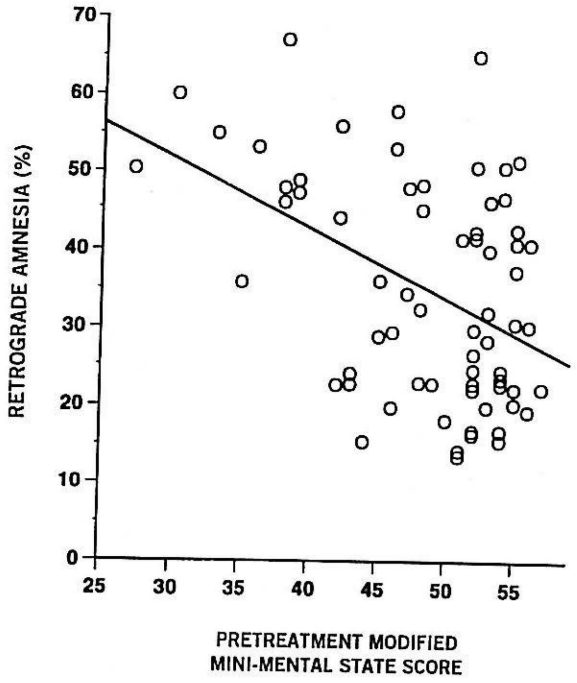
Variable	Value	
	Mean	*SD*
Demographic		
Age (years)	53.56	14.07
Education (years)	13.35	3.18
Socioeconomic status	2.39	1.12
Verbal IQ	103.63	16.22
	N	*%*
Clinical		
Psychotic depression	32	45.07
Bipolar depression	24	33.80
History of previous ECT	28	39.44
	Mean	*SD*
Duration of current episode (weeks)[a]	44.03	33.37
Number of previous affective episodes[b]	3.59	3.32
Number of previous psychiatric hospitalizations[b]	2.24	2.91
Age at onset of affective illness (years)	36.63	17.14
Pretreatment Hamilton depression scale score	32.96	8.14
ECT (randomized phase)		
Number of treatments	9.51	2.41
Electrical charge per session (mC)[c]	206.65	154.11
Methohexital dose per session (mg)[c]	56.47	15.16
Succinylcholine dose per session (mg)[c]	40.49	14.44
Motor seizure duration per session (seconds)[c]	45.93	12.62
EEG seizure duration per session (seconds)[c]	58.90	16.29

[a]Maximum of 104 weeks counted.
[b]Maximum of 10 episodes or hospitalizations counted.
[c]Average for sessions in which postictal orientation testing was conducted.

TABLE 2. Performance of Four Groups of Inpatients With Major Depressive Disorder on Orientation and Short-Term Cognitive Tests After Receiving ECT

Variable	Low-Dose Right Unilateral ECT		High-Dose Right Unilateral ECT		Low-Dose Bilateral ECT		High-Dose Bilateral ECT	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Orientation recovery (minutes)	11.1	7.9	19.2	10.5	40.0	22.7	37.2	13.5
Percent change in Mini-Mental State score	−1.9	6.7	1.6	10.8	8.8	13.0	9.7	12.9
Retrograde amnesia (% of items inconsistent with baseline)	29.8	10.8	26.8	12.8	47.0	11.7	38.5	15.7

FIGURE 1. Relation Between Pretreatment Modified Mini-Mental State Scores and Retrograde Amnesia for Autobiographical Memories During the Week After a Course of ECT (N=67)



ECT (paired t=5.51, df=43, p<0.001) and the pre-ECT baseline (paired t=3.91, df=50, p<0.001). At 2-month follow-up, the improvement in scores among patients originally treated with bilateral ECT (mean=–4.58%, SD=7.39%) was comparable to that of patients treated with right unilateral ECT (mean=–3.67%, SD=6.85%) (t=0.42, df=42, n.s.). In contrast, during the week following ECT, bilateral ECT had produced a clear-cut deficit in scores (mean=10.07%, SD=10.81%) relative to right unilateral ECT (mean=1.24%, SD=5.83%) (t=3.22, df=42, p<0.005).

In the repeated measures ANOVA conducted on the short-term and follow-up retrograde amnesia scores, there were main effects of electrode placement (F=7.58, df=1, 41, p<0.01) and time point (F=7.39, df=1, 41, p< 0.01), as well as a significant interaction between crossover status and time point (F=4.70, df=1, 41, p< 0.05). Patients originally randomly assigned to bilateral ECT had greater retrograde amnesia across the time points. Patients who received one course of ECT showed marked improvement in follow-up amnesia scores compared to short-term amnesia scores (paired t=4.03, df= 27, p<0.001), while patients who received crossover treatment were unchanged (paired t=0.14, df=16, n.s.). These analyses indicated that the magnitude of retrograde amnesia at 2-month follow-up was influenced by whether or not patients had received crossover treatment with high-dose bilateral ECT. Therefore, subsequent analyses of 2-month follow-up data included only the 28 patients who received one course of ECT.

Prediction of Retrograde Amnesia

Short term. Across the study group, patients with lower baseline modified Mini-Mental State scores had greater retrograde amnesia 1 week after the course of ECT (r=–0.41, df=65, p<0.001) (figure 1). More prolonged acute disorientation was also associated with greater retrograde amnesia (r=0.57, df=69, p<0.001) (figure 2). A multiple regression analysis was conducted to predict the short-term retrograde amnesia scores on the basis of pre-ECT modified Mini-Mental State scores and posticta orientation recovery time, controlling for age, dosage condition, absolute electrical dosage, seizure duration, and the total number of treatments administered. Both baseline modified Mini-Mental State scores (t=–2.86, df=59, p<0.01) and orientation time (t=5.51, df=59, p<0.001) were significant predictors.

These results could have been an artifact of the marked differences among the treatment groups in orientation recovery time and retrograde amnesia (table 2). Therefore, the regression analysis was repeated, separately for patients treated with right unilateral ECT and those treated with bilateral ECT. For right unilateral ECT, the magnitude of short-term retrograde amnesia was related to orientation recovery (t=3.28, df=21, p<0.005), but not to baseline modified Mini-Mental State scores (t=–0.31, df=21, n.s.). For bilateral ECT, both baseline modified Mini-Mental State scores (t=–1.79, df=30, p=0.08) and orientation recovery time (t=2.79, df=30, p<0.01) showed predictive relationships.

Long term. Among the 28 patients who received only one course of ECT, poorer global cognitive status at baseline was associated with greater retrograde amnesia 2 months after ECT (r=–0.46, df=26, p=0.01). Longer duration of acute disorientation was also associated with greater persistent retrograde amnesia (r=

0.47, df=26, p=0.01). For the 19 patients who received bilateral ECT during the randomized course, these correlations were r=–0.45, df=17, p=0.05, and r=0.50, df=17, p<0.05, respectively. Across the 28 patients, a multiple regression analysis indicated that when considered together, both the baseline modified Mini-Mental State scores (t=–1.80, df=25, p=0.08) and orientation recovery time (t=1.85, df=25, p=0.08) tended to predict long-term retrograde amnesia.

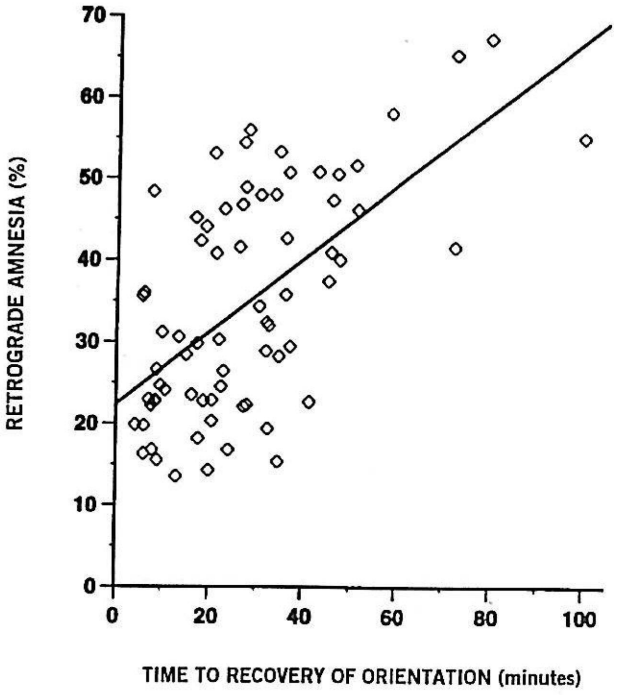
Specificity of the Predictive Relationships

The findings indicated that baseline global cognitive status and postictal orientation recovery each predicted the magnitude of retrograde amnesia for autobiographical information at both the short-term and long-term time points. Given these results, it was important to determine whether these predictive relationships were specific to the measure of retrograde amnesia or pertained more generally to global changes in cognitive status.

Across the study group, there was no association between baseline modified Mini-Mental State scores and the change in these scores during the week following ECT (r=–0.21, df=65, n.s.). This correlation was not significant within the subgroups treated with right unilateral and bilateral ECT. In contrast, patients who had longer periods of postictal disorientation had greater decrements in modified Mini-Mental State scores (r=0.55, df=65, p<0.001). This association was significant among patients treated with either right unilateral ECT or bilateral ECT. Greater retrograde amnesia during the week following ECT was also associated with a greater drop in modified Mini-Mental State scores (r=0.43, df=65, p<0.001). This association was also significant for each electrode placement.

In contrast to the findings for the week following ECT, there was an association between baseline modified Mini-Mental State scores and the change in these scores at 2-month follow-up (r=0.71, df=26, p<0.001). Patients with greater global cognitive impairment at baseline showed the greatest improvement in modified Mini-Mental State scores at long-term follow-up. Similarly, patients who had more prolonged postictal disorientation showed greater improvement in the global cognitive measure at 2-month follow-up (r=–0.47, df=26, p=0.01). At this time point, there was no relation between retrograde amnesia scores and change in global cognitive status (r=–0.25, df=26, n.s.). This pattern of correlations was maintained in the subgroup treated with bilateral ECT. Consequently, global cognitive impairment at baseline and prolonged postictal disorientation were each predictive of greater retrograde amnesia, but improved global cognitive status, 2 months after ECT.

FIGURE 2. Relation Between the Duration of Acute Postictal Disorientation and Retrograde Amnesia for Autobiographical Memories During the Week After a Course of ECT (N=71)



DISCUSSION

Consistent with a large body of research (9), ECT technical parameters substantially influenced cognitive side effects. Postictal orientation recovery was sensitive to both electrode placement and dosage condition, while global cognitive status and retrograde amnesia during the week after ECT were influenced by electrode placement. Long-term retrograde amnesia was significantly influenced by whether or not patients had received a second, crossover course of ECT. Nonetheless, within each of the ECT treatment conditions, there was also considerable variability among patients in the magnitude of cognitive side effects. This study suggests that both global cognitive function before treatment and orientation recovery time during the acute postictal period predict the extent of short-term and persistent retrograde amnesia for autobiographical memories.

The significance of these findings is contingent on the validity of the measure of retrograde amnesia. The Autobiographical Memory Interview was unusually detailed, producing a large item pool of personal memories. However, a core difficulty in assessing memory for personally relevant events is the inability to verify the accuracy of recall. When patients were retested, inconsistencies with their baseline reports were taken to be instances of amnesia, although the "correct" memories could not be identified unequivocally. Nonetheless, confidence in these findings is strengthened by the fact that there were consistent effects of electrode placement on short-term amnesia scores and of crossover treatment on long-term amnesia measures. Using a shortened version of this interview, Weiner et al. (11) observed persistent amnestic effects 6 months after bilateral ECT.

Some specificity was demonstrated in the associa-

tions of baseline global cognitive status and duration of postictal disorientation with cognitive side effects. Each variable was associated with the magnitude of retrograde amnesia both 1 week and 2 months after ECT. These relationships could have simply indicated that both variables were sensitive to a nonspecific, general cognitive decline. Indeed, we found that a longer duration of postictal disorientation was also associated with a greater decrement in modified Mini-Mental State scores, assessed during the week following ECT. However, at the 2-month follow-up, modified Mini-Mental State scores were substantially improved. Despite evidencing greater persistent retrograde amnesia, patients with lower baseline global cognitive function or longer postictal disorientation also showed greater improvement in their follow-up modified Mini-Mental State scores. This dissociation was due partly to a ceiling effect. By definition, patients with little or no baseline global cognitive impairment could manifest little or no improvement at follow-up, while patients with marked baseline impairment had the possibility of substantial improvement. Nonetheless, this dissociation demonstrated that the predictions of persistent deficit applied specifically to retrograde amnesia and not to change in global cognitive status. In contrast, it is unknown whether similar results would have been obtained had we examined other types of retrograde or anterograde amnesia. As noted, anterograde deficits typically resolve within a few weeks after ECT (9), so prediction of persistent effects would seem unlikely. Future research might focus on prediction of retrograde amnesia for public information. The extent of covariation in retrograde amnesia for autobiographical and public events after ECT has never been established (9).

The findings have theoretical as well as clinical implications. Some authors have suggested that the disturbance of consciousness, reflected in disorientation, is indivisible and is neither dependent on nor a reflection of other cognitive processes (32). Alternatively, some have contended that disorientation is at least partly a form of retrograde amnesia (3, 33, 34). This view is supported by the finding that, like many classic amnesia syndromes (10, 33), postictal disorientation following ECT "shrinks," with recovery of information from the remote past (e.g., name) occurring sooner than recovery of information learned more recently (e.g., place or time) (1–3, 27). Our findings provide additional support for the view that the durations of disorientation and retrograde amnesia are overlapping phenomena. We suggest that retrograde amnesia is most severe immediately after seizure induction, with substantial recovery as the time since treatment increases, and that the duration of disorientation marks either the rate or extent of the recovery of personal memories. The degree to which disorientation and retrograde amnesia reflect overlapping phenomena might be examined in neurobiological studies. It is thought that the retrograde amnesia associated with ECT reflects disruption of storage and/or retrieval processes dependent on the integrity of the hippocampus, parahippocampal gyrus, and related diencephalic structures (10, 35, 36). It remains to be determined whether alteration in the functional activity of a unitary neural system is related to both the duration of disorientation and the magnitude of retrograde amnesia. Another approach would be to determine whether pharmacological modifications of ECT that reduce amnestic effects also shorten the period of disorientation (37). In general, it does appear that alterations of ECT technique that lessen amnestic effects also speed orientation recovery (11, 12).

The findings relating baseline global cognitive impairment to persistent retrograde amnesia are novel. Cognitive impairment in the context of severe depression and normal neurological findings is typically regarded as a transient phenomenon, attributable to the patient's abnormal mood state (38). Indeed, in this study patients with the greatest degree of baseline impairment showed the greatest improvement in global cognitive status at follow-up. At issue, however, is why these patients were especially vulnerable to persistent retrograde amnesia. The findings raise the possibility that, either as a state or trait phenomenon, patients whose depressions manifest with substantial cognitive impairment are particularly vulnerable to the disruptive effects of seizures on the storage or retrieval of recent memories. More discrete characterization of the baseline neuropsychological impairments responsible for this predictive relationship might prove valuable. Furthermore, our findings underscore the possibility that cognitive impairment in the context of major depression may be associated with a distinct pathophysiology (39, 40).

Clinically, it may be useful to assess global cognitive function prior to ECT and to note the occurrence of prolonged postictal disorientation during the course of ECT. Our findings suggest that patients with preexisting cognitive impairment and/or prolonged postictal disorientation are the most vulnerable to developing persistent retrograde amnesia. For such patients, treatment alterations that minimize cognitive side effects (15), such as the use of right unilateral ECT, lowering electrical dosage, or increasing the interval between treatments, might be considered.

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