The long-term impact of treatment with electroconvulsive therapy on discrete memory systems in patients with bipolar disorder

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Objective: Electroconvulsive therapy (ECT) has been controversially associated with long-lasting memory problems. Verbal learning and memory deficits are commonly reported in studies of people with bipolar disorder (BD). Whether memory deficits can be exacerbated in patients with BD who receive ECT has, to our knowledge, not been systematically examined. We aimed to examine whether long-term effects of ECT on discrete memory systems could be detected in patients with BD. **Methods:** We studied several domains of memory in 3 groups of subjects who were matched for age and sex: a group of healthy comparison subjects, a group of people with BD who had received ECT at least 6 months before memory assessment and another group with BD that had an equal past illness burden but had never received ECT. Memory was assessed with the California Verbal Learning Test, the Continuous Visual Memory Test and a computerized process dissociation task that examines recollection and habit memory in a single paradigm. **Results:** Compared with healthy subjects, patients had verbal learning and memory deficits. Subjects who had received remote ECT had further impairment on a variety of learning and memory tests when compared with patients with no past ECT. This degree of impairment could not be accounted for by illness state at the time of assessment or by differential past illness burden between patient groups. **Conclusions:** From a clinical perspective, it is unlikely that such findings, even if confirmed, would significantly change the risk–benefit ratio of this notably effective treatment. Nonetheless, they may highlight the importance of attending to cognitive factors in patients with BD who are about to receive ECT; further, they raise the question of whether certain strategies that minimize cognitive dysfunction with ECT should be routinely employed in this patient group.

Objectif : On a associé l'électrochoc à des problèmes de mémoire de longue durée, mais cette question demeure controversée. On signale couramment des déficits de l'apprentissage verbal et de la mémoire dans des études portant sur des personnes atteintes de trouble bipolaire (TB). Sauf erreur, on n'a pas cherché systématiquement à déterminer si l'électrochoc peut exacerber les déficits de la mémoire chez les patients atteints de TB. Nous voulions déterminer s'il était possible de détecter les effets à long terme de l'électrochoc sur les systèmes discrets de la mémoire chez des patients atteints de TB. **Méthodes :** Nous avons étudié plusieurs domaines de la mémoire chez trois groupes de sujets jumelés en fonction de l'âge et du sexe : un groupe de sujets témoins en bonne santé, un groupe de personnes atteintes de TB et ayant reçu des électrochocs au moins six mois avant l'évaluation de la mémoire et un groupe de sujets atteintes de TB et ayant un fardeau morbide antérieur égal mais n'ayant jamais reçu d'électrochoc. On a évalué la mémoire au moyen du test d'apprentissage verbal de la Californie, du test de mémoire visuelle continue et d'une tâche de dissociation de processus par ordinateur qui étudie la mémoire de rappel et d'habitude en un seul paradigme. **Résultats :** Comparativement aux sujets témoins en bonne santé, les patients avaient des déficits de l'apprentissage verbal et de la mémoire. Les sujets ayant reçu des électrochocs dans le passé présentaient d'autres déficits, révélés par un éventail de tests d'apprentissage et de mémoire, comparativement aux patients qui n'ayant pas reçu d'électrochoc dans le passé. L'état morbide au moment de l'évaluation ou le fardeau morbide antérieur différentiel entre les groupes de patients ne pouvait expliquer un déficit de cette ampleur. **Conclusions :** Dans une optique clinique, il est peu probable que de telles constatations, même si elles étaient confirmées, changent considérablement le ratio risque-avantage de ce traitement dont l'efficacité est reconnue. Elles pourraient néanmoins mettre en évidence l'importance de s'occuper des facteurs de la cognition chez les patients atteints de TB qui sont sur le point de recevoir des électrochocs. Elles soulèvent de plus la question de savoir s'il faudrait appliquer de routine à ces patients certaines stratégies qui minimisent le dysfonctionnement cognitif à la suite d'électrochocs.

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Introduction

Electroconvulsive therapy (ECT) is effective for both the manic and depressed phases of bipolar disorder (BD) and is included as an option for refractory BD in the algorithms of several published guidelines.[1–6] A major concern regarding ECT as a treatment option is generally not whether it is effective but whether it is associated with long-term cognitive changes, particularly in various memory systems. The effect of ECT on memory continues to be studied,[7–17] discussed and debated.[18–24] Perhaps the most controversial issue is whether ECT results in long-term (usually defined as greater than 6 months) changes in anterograde or retrograde memory performance; this is also an issue of clinical relevance.

Recent studies of patients' perceptions of memory impairment after ECT are notable. Rose and colleagues[25] summarized the results of 7 studies reporting on perceived memory loss and found that between 29% and 55% of respondents believed they experienced long-lasting or permanent memory changes. Complaints persist long after ECT treatment.[26]

Our understanding of the cognitive effects of ECT is largely confined to studies of patients with unipolar depression. There are, however, substantial differences between BD and unipolar depression on several cognitive dimensions.[27,28] Several,[29–33] although not all,[34] studies suggest that people with BD are generally more likely to have cognitive deficits when euthymic than are people with unipolar depression. It is not known whether the cognitive changes in BD are pathophysiologically distinct from the cognitive changes in unipolar depression. Further, memory is not a unitary construct, and it is possible that discrete memory systems could be differentially affected by ECT and other forms of treatment. Thus extrapolating from studies of unipolar depression is not a reliable way to make conclusions regarding the impact of ECT on memory for people with BD. The objective of this study, therefore, was to determine whether long-term effects of ECT on discrete memory systems could be detected in BD patients.

Methods

Participants

The study was approved by the Research Ethics Board of St. Joseph's Healthcare in Hamilton, Ontario. Patients were recruited from the outpatient service of the mood disorders program, and healthy control subjects were recruited from hospital staff and from the community, following hospital guidelines. After a complete description of the study protocol, all subjects provided written informed consent to participate in the collection of demographic, clinical and neuropsychological variables. Inclusion criteria included (1) age between 30 and 65 years, (2) ability to give informed consent and (3) diagnosis of BD confirmed by the Structured Clinical Interview for DSM-IV (SCID-IV[35]). Patients in the previous ECT group had at least 1 lifetime course of ECT (described in more detail below) but no exposure to ECT in the 6 months before testing, whereas patients in the non-ECT group had never been exposed to ECT.

Exclusion criteria for all groups included (1) substance abuse within the last 6 months or a lifetime history of substance dependence; (2) treatment with transcranial magnetic stimulation; (3) history of closed head injury resulting in loss of consciousness; (4) evidence of a reading deficit as assessed by performance on the vocabulary portion of the Wide Range Achievement Test; (5) untreated active medical illness (e.g., diabetes, hyperthyroidism, hypertension); (6) current symptoms of mania as measured by a Young Mania Rating Scale (YMS[36]) score > 6; and (7) current episode of depression as determined by the SCID-IV, with a 17-item Hamilton Depression Rating Scale (HAM-D[37]) score ≥ 16. In addition, healthy control subjects were excluded if they had a current or past history of any psychiatric illness as assessed by the SCID-IV.

Diagnostic and symptom evaluation

Subjects received the SCID-IV for diagnostic clarification and to rule out comorbidity. Information from the SCID-IV was used in conjunction with clinical records and family interviews, where possible, to ascertain the number of past episodes and other aspects of past illness burden. The National Adult Reading Test (NART[38]) was administered as an index of premorbid intelligent quotient (IQ). On the day of cognitive assessment, the HAM-D, the YMS and the Global Assessment of Function Scale (GAF[39]) were also completed. Ratings were completed by 2 clinicians who had established interrater reliability and who were not aware of the patients' ECT history at the time of assessment.

Memory assessment

Subjective

Subjects completed the Cognitive Failures Questionnaire (CFQ[40]). This simple 25-item questionnaire provides a measure of individual's self-perception of memory impairment by asking subjects to estimate the frequency (never [0] to always [4]) of common memory errors, such as forgetting items to be purchased at a store. High scores on the CFQ indicate a greater degree of perceived memory impairment, and we have shown that subjects with a history of depression have elevated CFQ scores that are not a function of current mood state.[41]

Objective

The California Verbal Learning Test (CVLT[42]) is used as a standard neuropsychological tool to assess immediate and delayed verbal memory; it is sensitive to temporohippocampal dysfunction.[43] Briefly, the task assesses memory of 16 items presented in 5 learning trials, followed by an assessment of memory after each trial. An interference list is presented after the fifth trial, followed by the assessment of memory recall from the interference trial and an immediate short delay free recall. Delayed recall and recognition are then assessed after about 20 minutes.[44] The CVLT is widely

used to assess verbal learning memory in patients with mood disorders and other neuropsychiatric conditions.[42]

We also used a computerized task, the process dissociation task, to examine recollection and habit memory integrity within a single task.[45,46] This task has been recognized as a valid method of examining recollection memory processes independent of habit memory in a single paradigm.[47] The task is sensitive to recollection memory impairment in subjects with unipolar depression across a variety of mood states[41,48] and employs stimuli that have been extensively studied in nonpsychiatric populations. Briefly, 18 stimulus words are paired with 2 associative responses that occurred with equal frequency in published norms (e.g., door-knobs, door-knock). Stimuli are presented on an IBM compatible computer monitor with Micro-Experimental Software.[49] Character size is approximately 3 × 4 mm, and subjects sit about 75 cm from the monitor.

The first phase of the procedure consists of training, during which, a habit is created by repeated association of the word pairs. Word pairs are presented every 2 seconds as an incomplete pair (door-kno_ _), then for 1 second as the complete pair (door-knobs). Subjects guess completions that are semantically related to the stimulus word. Unknown to subjects, the word pairs occur with specific frequencies; one pair (e.g., door-knobs) is presented as the correct response in 67% of trials while the other word pair (e.g., door-knock) is presented as the correct response in 33% of trials. Word pairs are presented in random order with the exception that no word pair occurred on more than 3 consecutive trials. The word pairs that are presented at high or low frequency are counterbalanced across subjects.

After this training phase, subjects immediately proceeded to a phase that presented 18 successive study test lists of 8 of the word pairs shown during training. Subjects read the word pairs and were told to remember them for a test that would follow. A mathematical distractor task was presented after the study list. The key test occurred immediately after the mathematical task when incomplete word pairs appeared on the screen at the rate of 1 pair every 3 seconds (door-kno_ _). Subjects completed the pair with the word on the immediately preceding study list and were told to guess if they did not remember.

Recollection scores were obtained by subtracting the probability of the incongruent trial (when study list pairs were the same as the low- frequency pair during training) from the congruent trial (where study list pairs were the same as the high-frequency pair during training) probability. An estimate of habit is obtained by the formula habit equals incongruent probability divided by 1 minus the recollection.[45]

The Continuous Visual Memory Task (CVMT) uses a visual recognition procedure to measure the acquisition of visual memory discriminations and a delayed multiple choice recognition procedure.[50] It comprises 112 complex, ambiguous drawings and irregular figures that are presented sequentially for 2 seconds each. In addition, it includes a 30-minute delayed recall trial and visual discrimination task. It uses a visual recognition procedure to measure acquisition of visual memory discriminations and a delayed multiple choice memory recognition component.[51] The construct validity of the CVMT has been demonstrated in healthy adults[50] and in patient samples.[51]

Sample size calculation

Previous studies of acute or subacute ECT treatment effects on cognition have reported moderate effect sizes on at least some components of verbal learning tasks. For example, one group of investigators found several differences in verbal recall measures for patients receiving ECT, compared with those treated with transcranial magnetic stimulation, with sample sizes of 14–16 people.[52] We found that the effect size for the recollection memory component of the process dissociation task is large and robust in repeated samples of subjects with mood disorders. Using published tables with $\alpha = 0.05$ and $\beta = 0.10$, we calculated that a sample of 20 subjects per group would have at least 90% power to detect a difference in patient and control groups at 5% significance with an estimate of moderate effect sizes.

Statistical analyses

We compared clinical and demographic characteristics with analyses of variance (ANOVAs) and between–group *t* tests (Welch-corrected for unequal variances). In addition, we used the chi-square test to compare the groups on BD type and substance abuse. Group differences in mood state and cognitive performance (process–dissociation task, CVLT, CFQ, CVMT) were evaluated with between–subjects 1-way ANOVA. Post hoc analyses were conducted with Newman–Keuls when significant main effects were present. Pearson's correlation coefficients were calculated to investigate relations between (a) subjective and objective neuropsychological test scores that demonstrated statistically significant group differences ($p < 0.05$), (b) burden of illness, (c) current mood state and (d) ECT details (e.g., number of ECT treatments), with a significance level of $p < 0.05$.

Results were expressed as a mean and a standard error of the mean. We considered a 5% significance level ($p \leq 0.05$) for all statistical analyses.

Results

Demographic and clinical variables

There were 20 participants in each group (see Table 1). The median total number of ECT treatments received was 12, with a range from 6 to 72. All participants in the ECT group had bilateral treatment, which is the convention at this treating centre. Two patients received some unilateral ECT but had bilateral ECT for the majority of treatment. The average interval between the last ECT treatment and participation in the current study was 45 months (standard deviation [SD] 21 mo).

There were no differences in age ($F_{2,57} = 0.47$, $p = 0.63$), educational achievement ($F_{2,57} = 1.01$, $p = 0.37$) or full-scale IQ as estimated by the NART ($F_{2,57} = 1.20$, $p = 0.31$) between pa-

tients with or without past ECT or with healthy control subjects (see Table 1).

There were no significant differences between the patient groups on any measure of illness burden (see Table 1). There were overall group differences at the time of testing between healthy control subjects and patients on scores of depression (HAM-D-17, $F_{2,57} = 15.6$, $p < 0.001$), but there were no significant differences in mania scores as reflected by the YMS ($F_{2,57} = 1.2$, $p = 0.298$). Post-hoc SNK tests revealed no significant differences in HAM-D scores between patient groups. There were also significant differences in GAF scores between the patient groups and healthy control subjects ($F_{2,57} = 31.3$, $p < 0.001$) but no significant differences between the ECT and non-ECT groups on GAF scores.

Table 1: Demographic and clinical variables for all groups

Variable	Group; mean (and SD)*		
	Healthy control subjects	BD with ECT	BD no ECT
Sex,% women	75	75	75
Age, yr	43.8 (1.8)	45.9 (1.8)	43.9 (1.6)
Years of education	15.7 (0.9)	14.4 (0.6)	14.8 (0.6)
FSIQ	115.9 (1.8)	113.4 (1.7)	112.4 (1.4)
Duration of illness, yr	NA	19.7 (2.3)	24.4 (2.3)
Age at illness onset, yr	NA	26.2 (3.1)	19.6 (2.1)
TLMTHILL,† mo	NA	112.9 (21.9)	114.0 (15.9)
DURMED,‡ yr	NA	11.9 (1.8)	13.2 (1.7)
HAM-D-17 score	2.2 (0.4)	13.4 (1.8)§	12.0 (1.7)§
YMS score	0.0 (0.0)	0.5 (0.2)	0.4 (0.3)
GAF score	86.3 (1.5)	62.5 (2.7)§	67.9 (2.3)§

SD = standard deviation; BD = bipolar disorder; ECT = electroconvulsive therapy; FSIQ = full-scale IQ; NA = not applicable; TLMTHILL = total no. of months ill (lifetime); DURMED = duration of medication use; HAM-D-17 = Hamilton Depression Rating Scale; YMS = Young Mania Rating Scale; GAF = Global Assessment of Function Scale.
*Unless otherwise indicated.
†Total reported lifetime number of months spent in mood episodes.
‡Number of years since first mood medication was started.
§ $p < 0.05$ difference from healthy comparison subjects.

Cognitive failures questionnaire

There was a significant difference between patient groups and healthy comparison subjects in their self-perceptions of memory deficits, as indicated by scores on the CFQ (see Table 2). There were significant differences between patient groups, compared with healthy control subjects and between the ECT and non-ECT groups. Notably, patients who received ECT perceived more memory impairment than did patients who had never received ECT (see Table 2).

Process–dissociation task scores

As shown in Table 2, recollection scores on the process dissociation task differed between groups. Patient groups differed from control subjects, but not from each other. The groups

Table 2: Performance of patients and healthy comparison subjects on subjective and objective assessment of memory

Measure	Group; mean (and SD)			ANOVA; F (*p* value)*	SNK post hoc test
	Healthy comparison subjects	BD with ECT	BD no ECT		
Process dissociation					
Recollection	0.44 (0.04)	0.28 (0.04)	0.32 (0.04)	5.19 (0.009)	ECT-BD, BD < C
Habit	0.55 (0.02)	0.57 (0.02)	0.59 (0.02)	0.79 (0.457)	
Guess	0.57 (0.02)	0.60 (0.02)	0.65 (0.02)	5.35 (0.007)	C, BD-ECT < BD
CVLT					
iFR-A, 1st	9.6 (0.4)	5.9 (0.4)	7.5 (0.6)	17.6 (0.001)	ECT-BD < BD < C
iFR-A, 5th	14.9 (0.4)	11.2 (0.6)	13.2 (0.6)	12.3 (0.001)	ECT-BD < BD < C
iFR-A, total	65.0 (1.9)	46.1 (2.4)	55.2 (2.6)	16.9 (0.001)	ECT-BD < BD < C
iFR-B	8.7 (0.4)	5.5 (0.5)	6.9 (0.5)	12.3 (0.001)	ECT-BD < BD < C
SdFR	13.9 (0.5)	8.8 (0.6)	11.0 (0.8)	15.6 (0.001)	ECT-BD < BD < C
sdCR, total	14.4 (0.4)	11.0 (0.7)	13.0 (0.6)	9.3 (0.001)	ECT-BD < BD, C
LdFR	14.3 (0.5)	9.8 (0.9)	11.9 (0.6)	11.1 (0.001)	ECT-BD < BD < C
ldCR, total	14.7 (0.4)	10.8 (0.7)	12.6 (0.6)	11.8 (0.001)	ECT-BD < BD < C
RG HITS	15.7 (0.2)	14.4 (0.5)	14.90 (0.3)	3.7 (0.032)	ECT-BD, BD < C
RG, % false alarms	0.5 (0.4)	4.6 (1.4)	4.6 (0.9)	5.6 (0.006)	C < ECT-BD, BD
RG, % false alarms-old	1.3 (1.3)	10.3 (2.8)	11.3 (2.7)	5.5 (0.006)	C < ECT-BD, BD
RG, % false alarms-new	0.3 (0.3)	2.3 (1.1)	2.0 (0.6)	2.4 (0.101)	—
CVMT					
CVMT total score	74.3 (2.1)	71.1 (1.4)	70.9 (1.9)	1.1 (0.353)	—
CVMT-RG	3.9 (0.5)	2.9 (0.4)	3.4 (0.4)	1.5 (0.224)	—
CFQ	30.0 (2.2)	58.8 (4.1)	49.3 (2.9)	21.8 (0.001)	C < BD < ECT-BD

SD = standard deviation; BD = bipolar disorder; ECT = electroconvulsive therapy; ANOVA = analysis of variance; SNK = Newman–Keuls; CVLT = California Verbal Learning Test; iFR-A = immediate free recall list A; SdFR = short delay free recall; sdCR = short delay cued recall; LdFR = long delay free recall; ldCR = long delay cued recall; RG = recognition; HITS = correct responses; CVMT = Continuous Visual Memory Task; CFQ = Cognitive Failures Questionnaire.
*$df = 2.57$.
Threshold for significance was $p < 0.05$. ECT-BD = patients with prior ECT treatment; BD = patients with no previous ECT treatment; C = healthy comparison subjects.

also differed significantly on the guessing variable. Post-hoc SNK revealed that the ECT group and the non-ECT group did not differ from each other, and similarly, the ECT group did not differ from the control group, yet the scores were significantly different for the non-ECT group, compared with the control group. The habit memory scores did not differ between groups. Although HAM-D and YMS scores were virtually identical between groups, we compared recollection memory performance for subjects when HAM-D scores were included as a covariate in analyses of memory function, with no change in the pattern of results. GAF also failed to contribute to recollection or habit scores when included in analyses as a covariate. Thus, it appears that differences in performance between groups on the recollection component of the process dissociation task cannot be accounted for on the basis of differential depression scores at the time of assessment or on the basis of age, education, illness duration or past illness burden, because these variables were matched.

California Verbal Learning Test

There were several group differences in performance on the CVLT (see Table 2). Consistent with performance on the recollection portion of the process dissociation task, the patients differed from the control subjects on virtually all aspects of immediate, short-delay and long-delay recall. For all immediate free-recall measures (trials 1–5), and for the short- and long-delay free recall, the patient groups performed significantly worse than the healthy control subjects, recalling fewer words across trials. Patients with remote ECT performed at lower levels than did patients with no past ECT treatment. Table 2 highlights the differences between the groups and where the ECT-BD group differs from the BD group without past ECT. Patient groups had significantly poorer performance on some recognition measures (recognition hits, percent of false alarms, percent of false alarm error of old items [B-list], discrimination, recognition d-prime), but not all (percent of false alarm error of new items [non-B list] and recognition response bias scores) than the comparison subjects. Post-hoc SNK tests found that, for all recognition measures, the patient groups differed significantly from the healthy participants, except for the recognition hits, where the ECT–BD group alone differed significantly from the control subjects. The ECT–BD and non-ECT–BD groups did not differ significantly from each other.

Continuous Visual Memory Task

Not all subjects were able to complete the CVMT; both patient groups had a total of $n = 18$ participants, whereas the healthy comparison group had $n = 14$. There were no significant differences between groups on measures of visual memory (see Table 2).

Correlations

We examined the Pearson correlations between several measures of past illness burden (including time since illness onset, time since first treatment, number of lifetime episodes, number of months hospitalization) and current mood state measures. No significant relations were observed between any measure of past illness burden and memory performance. This lack of association may reflect the relatively long duration of illness experienced by all patients. The ECT–BD group is a group of patients with a sufficient illness burden to have had remote ECT, and the non-ECT patients were specifically selected to have a past illness burden equivalent to that of the ECT–BD group. Thus, our ability to detect differences in memory as a function of illness burden might have been compromised by the relative homogeneity of the samples on this dimension.

Further, we performed correlations with current mood state measures and cognitive variables. Once again, no associations were observed, but as above, the samples were selected to have a restricted range of current mood symptoms, which likely reduced the probability of observing relations between symptoms and cognitive performance.

Finally, we examined the number of ECT treatments and the number of months between last ECT for relations with cognitive measures. Once again, no associations were observed. This was somewhat more surprising because participants had a wide range of past treatments and a variable duration from ECT to assessment. This lack of association may reflect a lack of power because of the relatively small number of subjects (only the past ECT group, $n = 20$) for whom this analysis was relevant. More interestingly, it may reflect a threshold effect, after which, an increased number of ECT treatments has little added impact on long-term cognitive function.

Discussion

A salient finding of this study is that both patient groups had significant impairment on measures of verbal learning and recollection when compared with age- and sex-matched healthy comparison subjects. Results from the process-dissociation task confirm previous reports that patients with BD have recollection memory problems; the deficits were striking and not accounted for by mood symptoms at the time of assessment. Results from the CVLT demonstrated deficits in immediate and short- and long-delay free recall and cued recall when patients were compared with control subjects. Comprehensive reviews of neuropsychological function in BD conclude that cognitive deficits in euthymic patients with BD are particularly prominent in the domains of verbal learning and memory and, more specifically, in the acquisition, encoding and retrieval of information, compared with retention.[31,53–58] The lack of performance differences between patient groups and comparison subjects on the CVMT is consistent with some[59–62] but not all studies.[63]

Long-term effects of ECT

There were differences in several aspects of learning and memory in patients who had or had not received ECT remotely, suggesting that there may be sustained impairment

in patients who have had ECT that exceeds that for patients with BD only. These findings are important, given the limited literature on the long-term effects of ECT on cognition and the dearth of literature examining the effect of ECT in people with BD.

ECT patients had a lower tendency to guess on the process dissociation task, although their habit or implicit memory was not lower than the non-ECT patients or healthy comparison subjects. It is difficult to know whether this reflects a different strategy in approaching the task. It is possible that the ECT group perceived that they had more memory problems and were therefore less likely to offer a guess than the non-ECT group.

The past ECT group had worse performance than that of the non-ECT group on immediate and short- and long-delay free recall and cued recall measures on the CVLT. Patients had further difficulty with encoding and retrieving information, compared with the non-ECT group, implicating medial temporal lobe structures and, possibly, aspects of the prefrontal cortex. The CVLT in particular identifies encoding-based memory deficits where free recall, short- and long-term memory and cued recall depend on proper encoding of the list and retrieval. Further, this list-learning task involves a component of strategic organization and is sensitive to executive dysfunction; it is possible that elements of executive function were particularly affected by ECT.

Perceived memory impairment

There were group differences on the CFQ, with patients having significantly greater perceived memory impairment than control subjects. Further, the ECT group had particularly high CFQ scores that exceeded those of the non-ECT group. Thus, even when such factors as diagnosis, illness burden, current symptoms and current medication use are comparable, patients with BD who have had ECT remotely perceive a greater severity and frequency of memory problems. This perceived impairment correlated with measured impairment, consistent with a previous study of patients with unipolar depression who were also assessed with the CFQ.[41] This finding is consistent with a recent report that patients who received ECT had memory complaints, even when they were interviewed on average 282 days after treatment concluded.[26] The results reviewed by Rose and colleagues[25] also support the notion that patients with ECT complain of long-lasting memory problems; however, to our knowledge, our study is one of few to compare memory complaints not only against healthy comparison subjects but also to a group of BD patients without ECT matched on other illness variables.

Factors influencing learning and memory deficits

Recognizing that there is no one preferred or even conventional method of reflecting past illness burden in BD, we attempted to reflect illness burden through several measures, including overall illness duration, lifetime number of months ill, number of depressive episodes and number of lifetime hospitalizations. Many subjects in this study have been observed in our clinic and, in most instances, we obtained supporting documentation, such as past chart records or consult notes regarding the illness burden. Despite the various ways of measuring illness burden, there was no evidence of an association between these measures and memory impairment.

The lack of association between clinical and demographic factors and performance on the cognitive tests may partly reflect the homogeneity of the sample. People with BD, similar to those with unipolar depression, tend to have ECT somewhat later in the course of illness. Because we intentionally matched the non-ECT group to control for illness burden, we have an overall patient sample with established, recurrent illness. Thus, it is possible that, if patients had been more heterogeneous, we would have observed associations with past illness burden, such as those described using the CVLT in predominately euthymic populations.[64–68]

Medication effects

Polypharmacy was common in this relatively refractory group; the group with past ECT averaged 2.5 medications per subject, and the non-ECT group averaged 2. Although it is impossible to rule out medication effects, there were no systematic differences in treatment between the 2 groups that would have predicted the current pattern of results. The atypical antipsychotic clozapine is the psychotropic medication with the greatest amount of data to support a salutary effect on cognition, and equal numbers of patients from each group were receiving clozapine (4 per group). Because clozapine is generally reserved for patients with refractory BD, the equal number of patients receiving this agent in each group suggests a rough equivalence in the refractoriness of the patient samples, supporting the fact that there was no difference in the illness burden for the patient groups. No patients were treated with first-generation antipsychotic medications or with other highly anticholinergic medications (tricyclic medications, antiparkinsonian medications) at the time of assessment.

Limitations

There are several limitations to this study. Ideally, patients would have been randomly assigned to receive ECT, thus minimizing the potential for systematic differences between patient groups. In reality, however, even recent studies that have examined the short-term effect of ECT on memory have used patient preference as the factor determining assignment to ECT.[52] For a study of the long-term effect of ECT on cognitive variables, even if it was possible to randomize patients to ECT or non-ECT, the treatments administered in the period between ECT and testing could not be rigidly prescribed. Many factors determine whether a patient receives ECT, including preference and accessibility; thus, there is no a priori reason to assume that, because the ECT group had ECT, they were de facto a more ill population. Nonetheless, it is impossible to confirm that there were no systematic demographic or illness variables other than treatment with ECT that accounted for the observed differences in the ECT versus the

non-ECT groups, although none of the current or past illness variables that we examined suggest this.

A second limitation is that retrograde memory impairment was not examined. This is also challenging to do in a study of long-term treatment effects, but it is an important issue, because patients sometimes complain of loss of memories acquired before ECT treatment.

Finally, although the sample sizes were larger than most studies examining cognition after ECT, it was not sufficient to allow us to examine the effects of some demographic and clinical variables in detail. For example, the samples were specifically chosen to be free of lifetime substance dependence, including alcohol dependence, which has an added negative impact on cognition in euthymic patients with BD[62] and could possibly exacerbate ECT-related cognitive changes. Similarly, participants were selected to be free of serious medical illness, although somatic diseases are common among people with BD. Larger and more diverse samples, with higher rates of comorbid conditions common to BD, would have allowed us to examine for any associations between treatment and condition.

Despite these limitations, our study provides preliminary data suggesting that the long-term effects of ECT in patients with BD warrant further investigation. The absence of long-term changes in cognition in people with unipolar depression treated with ECT is not sufficient to ensure that patients with BD will have the same long-term outcome. From a clinical perspective, it is unlikely that this would shift the risk–benefit ratio of ECT — a notably effective treatment — even if such long-term changes are confirmed in future studies. There are, however, several strategies being investigated for the treatment of cognitive problems, including short-term cognitive problems associated with ECT[69–72] and long-term cognitive problems in patients with BD. These data, if confirmed, will support the role for cognitive sparing agents in ECT and suggest that patients with BD who do have ECT are a group that must be flagged for monitoring cognitive complaints and, perhaps, a group that should be targeted for prophylactic intervention.

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