Original Article

Resolution of Cognitive Adverse Effects of Electroconvulsive Therapy in Persons with Schizophrenia: A Prospective Study

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ABSTRACT

Background: Cognitive impairments are among the most important adverse effects of electroconvulsive therapy (ECT). Although much is known about them in patients with depression, there is very little information about these in persons with schizophrenia. **Methods:** In this study, we examined the persistence of cognitive impairments in a subsample of patients (n = 49) with schizophrenia who had earlier participated in a clinical trial comparing the therapeutic and cognitive efficacy of bifrontal ECT (BFECT; n = 23) and bitemporal ECT (BTECT; n = 29) electrode placements. Total scores on Hindi Mental State Examination, processing speed, working memory, and verbal fluency were assessed in these patients at two points: first, at the end of their respective ECT course and at the follow-up (mean [standard deviation] = 98.7 [38.3] days). The course of cognitive impairments was assessed in all patients (n = 49) as a single group. Further, BFECT and BTECT patients were also compared with one another. **Results:** ECT-induced acute cognitive impairments in patients with schizophrenia had normalized by the end of 3 months' follow-up post-ECT. All the tested parameters in the realm of Hindi Mental Status Examination, speed of processing, sequencing, spatial and working memory and verbal fluency showed recovery. Further, across all tests, BFECT and BTECT ultimately had similar scores at the follow-up though BFECT performed relatively better with regards to the acute effects. In fact, worst performing BTECT group caught up to recover to comparable levels of performance by the end of follow-up. **Conclusions:** In patients with schizophrenia, most of acute ECT-induced cognitive impairments recover by the end of 3 months' post-ECT. Further, different electrode placements do not seem to make any difference regarding ultimate recovery of cognitive deficits. Future prospective studies are needed that could address the limitations of this study.

Key words: *Cognitive adverse effects, electroconvulsive therapy, resolution, schizophrenia*

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INTRODUCTION

Cognitive impairments related to electroconvulsive therapy (ECT) are among the most visible of its adverse effects. They are the ones most responsible for the controversies surrounding ECT. They have persisted despite the continuing refinement in treatment techniques including better waveforms, electrode placements, and altering pulse widths. Of course, many clinical and demographic factors influence their manifestation. Minimization of these side effects remains one of the major objectives for the ECT clinician.

The vast amount of literature exists on various dimensions of cognitive side effects. Most of these studies have occurred in depression. Many of these consist of unilateral ECTs. A succinct review by Ingram *et al.*[1] states the following: ECT affects cognition in general including the memory as well as nonmemory functions. Self-limiting short and long lasting confusional states have been described although the latter is rare. About memory per se, anterograde, as well as retrograde amnesias, are common occurrences. In anterograde memory, both the acquisition and retaining are affected though retaining takes longer to recover. Eventually though both aspects recover almost completely over a period of couple of weeks. The situation is not straightforward though for retrograde amnesia. What is clear is that retrograde amnesia commonly occurs and recovery is relatively slower. Probably, a temporal gradient also exists with nearer events showing greater vulnerability. However, the exact nature and degree of amnesia are not clear. A host of other cognitive functions also are known to get adversely affected by ECT. They include psychomotor speed, attention and concentration, working memory, and executive functions. The current consensus is that all these either recovers to premorbid levels or some may even improve after the ECT course. A more recent meta-analysis also affirms the above assertions
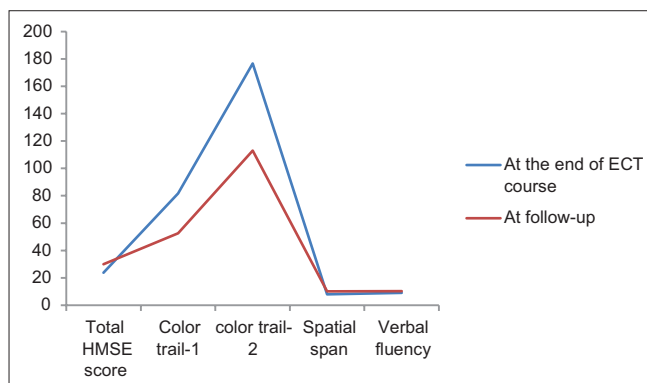
in depressed patients.[2] In sharp contrast to depression, cognitive side effects of ECT have received scant attention in persons with schizophrenia worldwide. This is understandable as ECT for schizophrenia is not a common indication across diverse settings. One study by Rami *et al.*[3] compared cognitive deficits among ten patients with schizophrenia during their maintenance ECT course (they had got an average 27 maintenance ECTs before this study) with those who had never got ECTs (n = 10) showed no significant differences in any of the tested cognitive measures between the two groups. Further, there was no correlation between numbers of previous ECT sessions and any of the cognitive measures.

In contrast, the clinical scenario in countries such as ours is entirely different. ECT forms one of the important therapeutic armamentariums for schizophrenia in our settings. In fact, schizophrenia is the most common diagnosis among all ECT receiving patients in India and other low- and middle-income countries.[4] Expecting faster recovery by keeping the in-patient stay to the minimum is one of the common reasons why schizophrenia patients receive ECT.[5] Despite this clinical reality, ECT in schizophrenia has received scant research attention. Thus, most schizophrenia patients continue to receive ECT with few attempts to optimize this treatment.[4] Since cognitive deficits from ECT are the most important concern, findings in this realm have the potential to inform clinical practice. A recent study has demonstrated the relative superiority of bifrontal electrode placement over the bitemporal counterpart.[6] However, this studied only the acute effects. In this paper, we describe cognitive functions of a sub-sample of Phutane *et al.*'s study[6] several weeks after the cessation of ECT course.

Figure 1: Mean cognitive performance immediately postelectroconvulsive therapy and at follow-up of the entire group (*n* = 49)
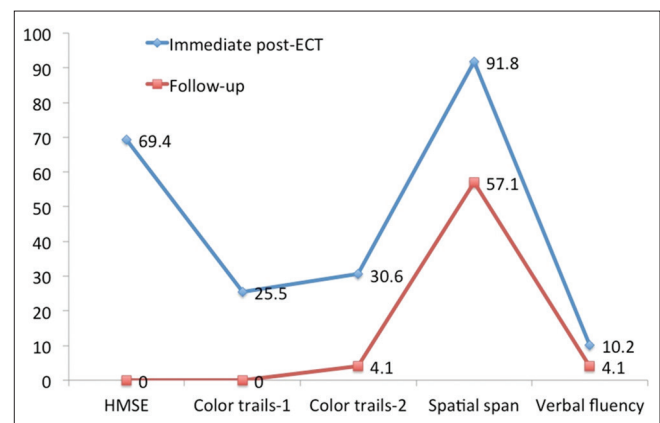

Figure 2: Proportion of patients with cognitive deficits immediately post ECT and at follow-up (*n* = 49). Note: there was reduction in proportion of subjects with deficits in all tests (*P* < 0.01) except verbal fluency (*P* = 0.25)
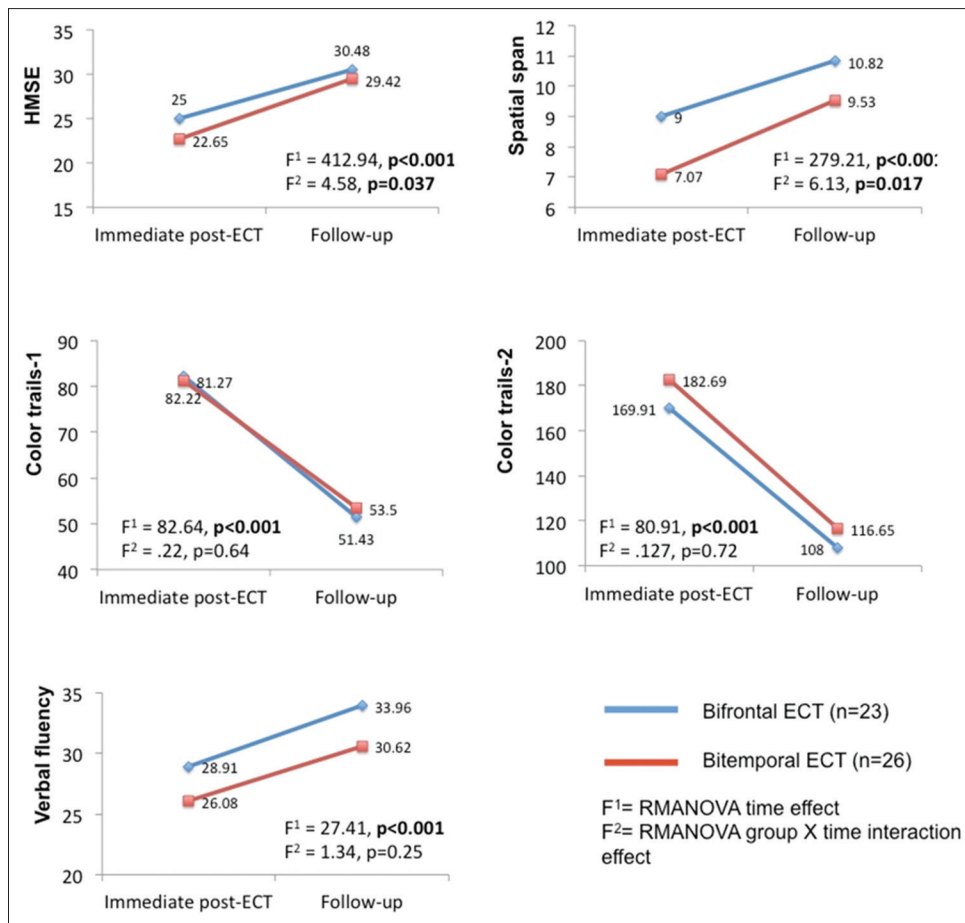
Figure 3: Mean cognitive performance immediately postelectroconvulsive therapy and at follow-up in patients receiving bifrontal and bitemporal electroconvulsive therapy. HMSE: Hindi Mental State Examination, RMANOVA: Repeated Measures Analysis of Variance

METHODS

Patients were from Phutane *et al.*'s study[6] which compared the clinical and cognitive efficacy of bifrontal ECT (BFECT) versus bitemporal ECT (BTECT) electrode placements in patients with schizophrenia or schizoaffective disorder referred for ECT. The study was conducted at the Department of Psychiatry, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, a state-run tertiary neuropsychiatric institute. Detailed methodology for the primary study has been described elsewhere[6] but for clarity, it is being described here in brief. ECT referred in-patients with schizophrenia/schizoaffective disorder were randomized to receive either BF ($n = 62$) or BT ($n = 60$) ECTs in a double-blind fashion. Patients of either sex, aged between 18 and 60 years were included in this study. The diagnosis was made per the ICD-10 criteria by two qualified psychiatrists, following independent clinical interviews. Mini International Neuropsychiatric Interview was used to confirm the diagnosis. Patients were excluded if they had mental retardation, substance use disorder (except nicotine) or major neurological

disorders. Those with a history of receiving ECT in past 2 months and those on nonbenzodiazepine anticonvulsants were also excluded. In all cases, clinical decision to refer for ECT was taken by their respective treating consultants. No patient was given ECTs solely for the study number of ECTs, antipsychotics and other medications were not controlled for during the study. ECT was administered thrice weekly using the NIVIQURE machine (Technonivilac, Bengaluru, India) with EEG monitoring. Brief-pulse square-wave stimulation with constant current at 800 mA, 125 bidirectional pulses per second with pulse width of 1.5 ms was used; duration of train was altered to adjust the stimulus dose. Anesthetic modification was with Thiopentone 2–4 mg/kg and succinylcholine 0.5–1 mg/kg. BT electrodes were placed 3 cm above the midpoint of a line joining the outer canthus of each eye with the ipsilateral external auditory meatus. BF electrodes were located 5 cm above the outer angle of orbit. Seizure threshold was determined during the first session by titration method. Further stimuli were at 1.5 times their threshold. Rater (VHP) and patients were blind to the electrode placement. Assessment tools included measures of symptoms, functioning, and

cognition. At the end of six ECTs, BFECT was superior both clinically and cognitively.[6] Participants of this study were assessed for their cognitive status by the same rater (VHP) during their first follow-up visit post-ECT to their respective consulting psychiatrists. He remained blind to the electrode placements during these follow-up assessments as well. Follow-up assessments were carried out till the end of 6 months after the last patient was recruited for the primary study. After that, follow-ups could not be completed due to logistical reasons. Till that time, 23 BFECT patients and 26 BTECT patients had their follow-up cognitive assessments completed. We report results from these patients in this paper. The following assessments were carried out twice: First at the end of their ECT course and second during their first follow-up visit. (a) Global cognitive screening: This was performed using the Hindi Mental Status Examination (HMSE), an adaptation of Mini-Mental Status Examination, which has been extensively used in ECT research. It briefly covers the domains of attention, orientation, memory (registration and recall), language (naming, repetition, comprehension, and sentence formation) and visuospatial construction. HMSE has been standardized for use in illiterate, rural population in India.[7] (b) Specific cognitive domains: Processing speed was evaluated using the color trails,[8] working memory was assessed using the spatial span test,[9] sustained attention and cognitive flexibility were examined by the color trails B.[8] Verbal fluency was assessed using the Controlled Oral Word Association (COWA).[10] We used the original consonants (F, A, and S) for those who were fluent in English; for those who were not fluent in English, we used consonants ka, pa, and ma as an Indian adaptation. The above tests have been adapted for use in the Indian setting[11] and have been used in earlier studies on psychiatric disorders in India.[12,13] Time taken to complete color trails A and B, number of forward and backward block sequences correctly performed on spatial span, and an average of the total number of acceptable new words generated in 1 min using the three consonants in the COWA were used for analysis. Age and gender-based norms for the local populations were available.[11] We noted whether each patient scored above or below the norm. Based on this, he/she was further categorized as being "normal" or "abnormal" for a test. Those who fell below 15th percentile score was categorized as "abnormal" while those who fell above the score of 15th percentile was considered "normal." This exercise was carried out for both baselines as well as the follow-up scores. For illiterate patients (those whose education spanned <10 years; *n* = 5), the next higher available norm was used for categorizing.

All patients/family members provided written informed consent for the ECT as well as the assessments. This study was provided ethical clearance by the Ethics Committee of NIMHANS, Bangalore, India.

Statistical analysis

Initially, all 49 patients were studied as a single group. While doing so, continuous variables were analyzed using the paired sample t-test; proportions were compared using the McNemar test. Later, the differential effect of BFECT and BTECT were tested using the Repeated Measures Analysis of Variance (RMANOVA).

RESULTS

Mean (standard deviation [SD]) age of the sample was 27.53 (7.3) years; 18 (36.7) were females. Mean (SD) duration of illness was 48.18 (44.3) months. Mean (SD) duration of education was 9.67 (4.6) years. Patients received an average of 7.92 (2.5) ECTs; mean (SD) motor seizure duration 52.69 (11.2) seconds. Mean (SD) time to first follow-up was 98.71 (34.3) days; median was 90 days. Tests of cognitive functioning are shown in Table 1. All patients improved considerably by the follow-up period across all tested domains [Figure 1]. Table 2 shows that proportion of patients with cognitive performance in the "abnormal" range had decreased significantly in all domains except verbal fluency [Figure 2]. It may be noted that in latter case, proportion of patients scoring below the norm was only 10% at the end of ECT course. Since this study deals with subsample analysis, we compared the cognitive functions of the "followed-up" group (*n* = 49) and the "not-followed up" group (*n* = 63) at the end of ECT course. Independent sample t-test showed no group difference across any of the tested functions (data not presented). Regarding the subgroups comparison, BFECT patients were significantly younger than BT counterparts. They were comparable across all other demographic and clinical variables [Table 3].

We did RMANOVA to understand the differential influence of BFECTs and BTECTs on the course of cognitive impairment [Figure 3]. Results showed

Table 1: Cognitive performance of the whole sample (*n*=49)§

	At the end of ECT course	At follow-up	*t*	*P*
Total HMSE score	23.76 (2.4)	29.92 (1.2)	−19.76	<0.01
Total time taken on color trail-1 test (s)	81.71 (28.3)	52.53 (8.2)	9.15	<0.01
Total time taken on color trail-2 test (s)	176.69 (60.6)	113.02 (19.6)	9.18	<0.01
Spatial span	7.97 (2.1)	10.14 (1.6)	−16.05	<0.01
Verbal fluency	9.14 (2.0)	10.30 (2.5)	−7.13	<0.01

§All values are in mean (SD). HMSE – Hindi mental status examination; ECT – Electroconvulsive therapy; SD – Standard deviation

that there were significant group effects across all the tests as per the following details: (a) HMSE: $df = 1$, $F = 412.9$, $P < 0.01$ (b) Color trail-1: $df = 1$, $F = 82.6$, $P < 0.01$ (c) Color trail-2: $df = 1$, $F = 80.9$, $P < 0.01$ (d) Spatial span: $df = 1$, $F = 279.2$, $P < 0.01$ (e) Verbal fluency: $df = 1$, $F = 178.3$, $P < 0.01$. The groups X time interaction effects are shown in Table 4. HMSE and spatial span scores showed significance favoring BTECT. In other words, though BTECT patients fared badly at baseline, they caught up with the BFECT patients to a significant extent by the end of follow-up period.

DISCUSSION

The most important result of this study is that ECT-induced acute cognitive impairments in patients with schizophrenia had normalized by the end of 3 months' post-ECT. All the tested parameters in the realm of sustained attention, speed of processing, sequencing, spatial and working memory, and verbal fluency showed recovery. This is not only reassuring but also an encouraging sign. Further, BFECT and BTECT ultimately had similar scores at the follow-up though BFECT performed relatively better with regards to the acute effects. In fact, worst performing BTECT group caught up to recover to comparable levels of performance. This may point to the fact that regardless of the electrode placements, there is ultimate recovery

Table 2: Proportions of patients at the end of electroconvulsive therapy course and at follow-up (*n*=49)§

	At the end of ECT course, *n* (%)	Follow-up, *n* (%)	*P*
HMSE			
Normal	15 (30.6)	49 (100)	Not-applicable
Abnormal	34 (69.4)	0	
Color trail-1			
Normal	37 (74.5)	49 (100)	Not-applicable
Abnormal	12 (25.5)	0	
Color trail-2			
Normal	34 (69.4)	47 (95.9)	<0.01
Abnormal	15 (30.6)	2 (4.1)	
Spatial span			
Normal	4 (8.2)	21 (42.9)	<0.01
Abnormal	45 (91.8)	28 (57.1)	
Verbal fluency			
Normal	44 (89.8)	47 (95.9)	0.25
Abnormal	5 (10.2)	2 (4.1)	

§Mc-Nemar test. HMSE – Hindi mental status examination; ECT – Electroconvulsive therapy

Table 3: Demographic and clinical details of the subgroups

	BFECT (*n*=23)	BTECT (*n*=26)	*t*/χ²	*P*
Mean age (years)	25.17 (6.4)	29.62 (7.6)	−2.2	0.03
Mean duration of education (years)	9.69 (4.7)	9.65 (4.6)	0.03	0.97
Sex, *n* (%)				
Males	12 (52.2)	19 (73.1)	2.3	0.1
Females	11 (47.8)	7 (26.9)		
Type of schizophrenia, *n* (%)				
Paranoid	13 (56.5)	11 (42.3)	2.7	0.43
Others	10 (43.5)	15 (57.7)		
Mean duration of follow-up (days)	101.57 (32.1)	96.19 (36.6)	0.54	0.59
Mean total duration of illness (months)	49.04 (45.5)	47.40 (44.1)	0.13	0.89
Mean total duration of motor seizures (s)	54.95 (12.3)	50.69 (9.9)	1.34	0.18
Mean total duration of EEG seizures (s)	73.95 (35.7)	58.75 (16.8)	1.72	0.09
Mean duration of follow-up (days)	101.57 (32.1)	96.19 (36.3)	0.54	0.59
Mean total ECTs received	7.57 (2.2)	8.23 (2.7)	−0.92	0.35

BFECT – Bi-frontal electroconvulsive therapy; EEG – Electroencephalogram; ECT – Electroconvulsive therapy; BTECT – Bi-temporal electroconvulsive therapy

Table 4: Differential effects of bi-temporal and bi-frontal electroconvulsive therapies on the course of cognitive impairments

	BFECT (*n*=23)		BTECT (*n*=26)		df/*F*	*P* value for group × time interaction effect
	At the end of ECT course	Follow-up	At the end of ECT course	Follow-up		
HMSE	25.00 (2.2)	30.48 (0.8)	22.65 (0.1)	29.42 (1.3)	1,47; 4.58	0.04
Color trail-1	82.22 (22.5)	51.43 (6.8)	81.27 (33.0)	53.50 (9.3)	1,47; 0.22	0.64
Color trail-2	169.91 (50.2)	108 (16.2)	182.69 (69.0)	116.65 (18.9)	1,47; 0.27	0.72
Spatial span	9.00 (2.0)	10.82 (1.5)	7.07 (1.8)	9.53 (1.4)	1,48; 6.13	0.02
Verbal fluency	28.91 (6.4)	33.96 (6.1)	26.08 (5.3)	30.62 (5.2)	1,47; 1.56	0.48

Baseline and follow-up cognitive performance depicted in mean (SD). HMSE – Hindi mental status examination; ECT – Electroconvulsive therapy; BTECT – Bi-temporal electroconvulsive therapy; SD – Standard deviation; BFECT – Bi-frontal electroconvulsive therapy

of the acute cognitive deficits induced by ECT. To the best of our knowledge, this is the first study in India to establish the cognitive safety of ECT in persons with schizophrenia. As discussed earlier, schizophrenia being the most common diagnostic indication for ECT prescription in India, these findings could help clinicians assure patients/family members about ECTs cognitive safety. One possible reason for improvement of cognitive functions could be the practice effect. While this effect cannot be ignored, it is reassuring that patients do not lose the ability to learn at the end of a mean number of about eight ECT sessions.

Our findings are roughly comparable to that of Rami *et al*.[3] to the extent that similar tests were used thereby testing similar cognitive dimensions. Even in that study, patients who had never received ECTs performed comparably to those who had received an average 27 ECTs. Difference is that our study did not have a no-ECT group. Another difference is about the timing of assessments of cognitive functions. Despite these differences, the same message comes across from both these studies.

Strengths of the study include the following: Diagnosis of schizophrenia/schizoaffective disorder was made by qualified psychiatrists and confirmed with a structured interview schedule; standard validated measures of cognition were used; a related issue is the availability of norms for normal population that made comparisons more valid; the rater who did the cognitive assessments remained blind to the electrode placement both at baseline and at follow-up. This avoided one level of bias.

We admit that a design of such nature lends itself to several limitations. They are: (a) it was a subsample analysis. We were seriously limited by the logistics of approaching patients for follow-up assessments as patients belonged to different clinical units and would come to follow-up at their convenience and it was difficult for us to be available at outpatient departments during their presence. This is one of the main reasons for not getting data from all patients who were randomized for a course of ECTs. Follow-up assessments were more likely when the patients' visits coincided with availability of the rater. This method yields itself to a follow-up sampling bias, resulting in acquiring data from a potentially distinct patient subgroup in terms of clinical and cognitive profiles. However, it may be noted that there were no "baseline" differences in cognitive status between the "followed-up" group and "not followed-up" groups (b) a related limitation is that there was no prior hypothesis about the safety or adverse effects of ECT (c) we did not test memory function in a systematic fashion. Although the baseline measures of memory were there, logistic issues precluded us from getting the follow-up

measures. Memory component was assessed as part of the HMSE. HMSE has components for testing new learning ability only. All participants did well on this aspect as shown by the total scores at follow-up. Both groups had reached maximum ceiling scores. Further, BTECT patients caught up with their BF counterparts in a significant fashion to regain comparative scores at follow-up. This could suggest that even memory deficits improve substantially during the follow-up period. Not assessing retrograde amnesia is an important limitation as this forms the most notable subjective complaint in some patients and needs to be addressed in future studies. However, it is to be noted that studying retrograde amnesia is more complex than an assessment of anterograde amnesia. Although both episodic and semantic components of autobiographical memory (viz., retrograde amnesias) are affected, these cannot be clearly separated from the reports of subjective memory loss. Other difficulties are the dearth of valid measures of retrograde amnesia and the effect of disorders *perse* on the measures of amnesia (d) there were no pre-ECT cognitive assessments for comparison. This is especially relevant to understand whether patients despite improvement fared better or worse than the pre-ECT state. However, conducting cognitive assessment pre-ECT was impossible given the nature of patients who got referred for ECT. They were too uncooperative by way of catatonic symptoms, refusing oral intake, violence or refusing to simply sit for a longer while for completing assessments.

CONCLUSION

This study in persons with schizophrenia shows that acute cognitive deficits induced by ECT tend to recover by the end of 3 months after the course. Further, different electrode placements do not seem to make any difference about ultimate recovery of cognitive deficits. Future prospective studies are needed that could address the above-mentioned limitations and yield more definitive information.

Conflicts of interest
There are no conflicts of interest.

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