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Cognitive training to improve memory in individuals undergoing electroconvulsive therapy: Negative findings

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Abstract

Although electroconvulsive therapy (ECT) remains the most effective treatment for severe depression, some patients report persistent memory problems following ECT that impact their quality of life and their willingness to consent to further ECT. While cognitive training has been shown to improve memory performance in various conditions, this approach has never been applied to help patients regain their memory after ECT. In a double-blind study, we tested the efficacy of a new cognitive training program called Memory Training for ECT (Mem-ECT), specifically designed to target anterograde and retrograde memory that can be compromised following ECT. Fifty-nine patients with treatment-resistant depression scheduled to undergo ultra-brief right unilateral ECT were randomly assigned to either: (a) Mem-ECT, (b) active control comprised of nonspecific mental stimulation, or (c) treatment as usual. Participants were evaluated within one week prior to the start of ECT and then again within 2 weeks following the last ECT session. All three groups improved in global function, quality of life, depression, and self-reported memory abilities without significant group differences. While there was a decline in verbal delayed recall and mental status, there was no decline in general retrograde memory or autobiographical memory in any of the groups, with no significant memory or clinical benefit for the Mem-ECT or active control conditions compared to treatment as usual. While we report negative findings, these results continue to promote the much needed discussion on developing effective strategies to minimize the adverse memory side effects of ECT, in hopes it will make

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ECT a better and more easily tolerated treatment for patients with severe depression who need this therapeutic option.

Keywords

electroconvulsive therapy; cognitive training; memory; depression

1. Introduction

The efficacy of electroconvulsive therapy (ECT) has been robustly established in many psychiatric disorders within clinical trials and community practice (Prudic et al., 2000; Sackeim et al., 2007). It is most commonly prescribed for severely depressed patients who have not responded to antidepressants or have had difficulty tolerating several courses of medications (McClintock et al., 2014). Given the prompt clinical response and high response rates, ECT is also considered an early or first-line treatment for severely agitated or acutely suicidal patients, or in circumstances where medical concerns are paramount (Weiner and Prudic, 2013). Despite its unparalleled efficacy for depression, ECT carries a risk of memory difficulties for some people who undergo this treatment, and the American Psychiatric Association (APA, 2001; McDonald et al., 2013) and the FDA have long been concerned about the potential cognitive side effects of ECT (FDA Medical Devices Advisory Committee, 2011).

The adverse cognitive effects can be primarily transient in nature for most people (Kellner et al., 2016a). A recent large meta-analysis by Semkowska and McLoughlin (2010) that examined 2981 patients from 84 studies found cognitive problems to be generally most pronounced within 3 days after ECT, with most cognitive abilities recovering to pretreatment levels within 14 days. That being said, some people who undergo ECT report persistent memory problems that impact their quality of life and their willingness to consent to further ECT (McDonald et al., 2013). Retrograde amnesia remains the most serious adverse side effect, with more persistent deficits in remote knowledge about the world compared with autobiographical information, though impairments in anterograde memory are also present (Lisanby, 2004, 2007). Variations in ECT technique such as right unilateral ultrabrief pulse (RUL UB) ECT have reduced this risk (Prudic, 2008), while efforts to improve the cognitive side effect profile of ECT with pharmacological agents have shown promise (Matthews et al., 2013) including the use of thyroid hormone T3 (Tremont and Stern, 2000) and carbamylated erythropoietin (Kellner et al., 2015). However, the risk has not been eliminated. To date, no intervention to effectively mitigate ECT treatment-induced cognitive deficits has been developed. This is a serious oversight, as memory loss is considered by patients to be the most disturbing and serious side effect of ECT (Fraser et al., 2008). It adversely impacts their everyday life and their willingness to consent to receive needed treatment to obtain or maintain symptom remission.

Cognitive remediation is a behavioral treatment which has been used to improve cognitive function in brain injury, stroke, dementia, epilepsy, schizophrenia, and other psychiatric populations (Choi and Twamley, 2013; Fiszdon et al., 2016; Cicerone et al., 2011; Wykes et

al., 2011). Emerging literature on the recovery of memory deficits in seizure disorder is the most pertinent to the use of CR with ECT (Mangaoang and Lucey, 2007), since the pattern of memory impairments associated with ECT can be similar to the memory loss associated with temporal lobe epilepsy (Ponds and Hendriks, 2006). Although moderately successful in reducing cognitive impairments associated with temporal lobe epilepsy (Shulman and Barr, 2002), strategies for memory training in seizures have never been applied to help patients regain their memory after ECT. In 2011, we reported the results from an initial open pilot (N=9) to test the feasibility of a new cognitive remediation (CR) treatment called Memory training for ECT (Mem-ECT) based on methodology from cognitive neuroscience experiments in recovering compromised memories following repeated seizures. We found Mem-ECT to be fairly well tolerated by depressed inpatients and easily implemented within ECT treatment services. In this single group study, overall results indicated that ECT recipients with major depression who received Mem-ECT demonstrated retrograde and anterograde memory recovery by maintaining memory scores within 0.50 SD of pre-ECT memory performance (Choi et al., 2011).

On the basis of these promising findings, we conducted a methodologically rigorous and larger study to determine whether this novel memory training program could help alleviate memory problems associated with ECT. To our knowledge, this was the first attempt to address ECT-related memory impairment in a fully powered and randomized controlled study using a behavioral strategy. We hypothesized that compared to an active control group and treatment as usual, ECT recipients with major depression who received Mem-ECT would demonstrate better memory immediately after ECT. We also explored the potential impact of changes in depressive symptoms (as opposed to receipt of Mem-ECT) on improvements in memory and/or quality of life.

2. Material and Methods

2.1 Participants

Participants were 59 inpatients, ages 18 to 60, diagnosed with Major Depressive Disorder and scheduled to undergo right unilateral ultrabrief pulse (RUL UB ECT) within 2 weeks at either New York State Psychiatric Institute (NYSPI) or New York Presbyterian Hospital - Columbia University Medical Center (CUMC). This investigation was reviewed by the local institutional review board, and it was carried out in accordance with the latest version of the Declaration of Helsinki, with informed consent obtained after the nature of the procedures had been fully explained.

Exclusion criteria were: (a) significant auditory/visual/English language impairment; (b) changes in antidepressant prescribed during course of the study; (c) chart diagnosis of any other medical or neuropsychiatric illnesses known to impair brain function (e.g. dementia, traumatic brain injury, schizophrenia); (d) mental status examination score below 40 (out of 57) on the Modified Mini-Mental State examination (mMMS); (e) benzodiazepines > 3mg/day, as 3mg/d or less is commonly administered as part of the clinical care and there is extensive ECT literature to show that 3mg/d or less has minimal cognitive impact; (f) severely catatonic, agitated or suicidal patients; (g) for participants with a past history of substance dependence (excluding nicotine and caffeine), use of illicit substances 1 month

prior to baseline and at any time during study participation; (h) history of ECT in past 6 months since recent ECT may confound performance on cognitive outcome measures; (i) non-response to RUL UB ECT and subsequent switch to bilateral ECT.

2.2 Procedures

This was a double blind randomized clinical trial. Informed consent of the participants was obtained after the nature of the procedures had been fully explained. Following informed consent and baseline evaluation, participants were randomized to either Mem-ECT, an active control group (ACG), or “treatment as usual.” Block randomization was used with group assignment occurring within blocks of 6. Participants in Mem-ECT received memory training before and after their ECT course while participants in the ACG worked on commercially available memory puzzles at the same pre and post ECT sessions. Mem-ECT or ACG consisted of 2 pre-ECT sessions conducted a few days prior to ECT, and 5 post-ECT sessions starting as soon as the patient was willing to attend to materials but not extending beyond a 2 week post-ECT timeframe (Fig 1). The ACG was matched for the same dose and duration as Mem-ECT along with the puzzle exercises carefully matched to Mem-ECT exercises in appearance in order to provide better equipoise (described below). Post-testing was conducted by a research assistant blind to randomization. The RA and participant completed a best guess rating form to assess adequacy of the blind and treatment masking. Participants in the “treatment as usual” group were not administered any memory training or puzzles but along with participants in the other two groups, received standard clinical care throughout the duration of the study. All participants were inpatients and all memory training/active control and assessment procedures were conducted while the participants were on the hospital unit. The study was approved by the local institutional review board and conducted in accordance with the Helsinki Declaration as revised in 1989.

2.2a Electroconvulsive therapy (ECT)—While bilateral (BL) ECT may have been the more appropriate choice to test the cognitive training intervention given that it carries a higher risk for cognitive side effects (Sackeim et al., 2000), the administration of UB RUL ECT at six times seizure threshold is the standard first line treatment given to clinical patients at CUMC. Therefore, BL ECT was not a feasible option, and RUL ECT was administered as clinically indicated. Non-responders to RUL were re-examined for ECT threshold and appropriate adjustments made to treatment parameters including cross over to high dose RUL standard pulse width or switching to bilateral treatment and subsequent exclusion from the study. We emphasize that ECT and procedures related to its’ administration were *not* part of the experimental design or manipulations, as patients were referred for ECT as part of their clinical care. No variation in clinical practice occurred including anesthetic approaches, medications, and technical aspects of ECT due to study involvement. For the duration of the ECT course, patients were maintained on stable doses of psychotropic medications as clinically indicated. The length of the ECT course and ECT parameter adjustments were determined by Dr. Prudic, senior investigator on the study and Director of ECT services, in collaboration with the patients’ attending psychiatrists.

2.2b Memory training for ECT (Mem-ECT)—Similar to cognitive strategies used in cognitive remediation programs for people with epilepsy (Engelberts et al., 2002), the pre-

ECT sessions were designed to provide psychoeducation about possible memory difficulties associated with ECT, and then teach and practice memory strategies which may be helpful in recovering episodic memories and memory skills following a generalized seizure episode (Choi et al., 2011). The goal of pre-ECT sessions was to teach more resilient memory encoding strategies prior to ECT to enhance retrieval mechanisms for soon-to-be-forgotten information while at the same time strengthening memory skills to learn and relearn new information. The post-ECT sessions were designed to quickly accelerate the recovery of pre-ECT memory abilities in addition to quickly re-learning or reviewing memory retrieval paradigms that were taught in pre-ECT sessions. Accelerating memory recovery to learn new information has been shown by itself to improve the retrieval of overall memory pre-ECT, and allows for the retention of learned strategies which can help consolidate new information (Mangaoang and Lucey, 2007; Sobin et al., 1995).

Generally, each memory session paired a paper-and-pencil memory task with a computerized cognitive exercise specific to the targeted memory mechanism. Initial paper-and-pencil tasks at the beginning of each session attempted to prime the targeted memory skill, isolate the acquiring mechanism, and prepare for the rehearsal of an identified memory processing pathway on computers. In this way, the paper-and-pencil exercises assisted in the learning or review of retrieval strategies while the computerized exercises allowed for the drill and practice of various memory strategies and skills. The exercises were adapted from recent animal and human studies focused on the cognitive neuroscience of recovering compromised memories following repeated seizures (Bayley et al., 2006; Moscovitch et al., 2006). Each session consisted of approximately 60-75 minutes of training for a total of 8.75 hours of training.

2.2c Active Control Group (ACG)—The active control group worked on various commercially available computer and paper-and-pencil puzzles (BrainAge[®], Hoyle Puzzles[®], Sudoku[®]). Participants worked on the games in comparable structural format at the same times pre and post ECT as the Mem-ECT group. Treatment dosage and intensity was matched to the Mem-ECT group.

2.2d Treatment as usual—The “treatment as usual” group did not work on memory training or puzzles but received the usual psychiatric care provided to all patients within ECT services at CUMC. This included case management by a social worker, individual and/or group psychotherapy by a psychiatrist, psychologist, or other mental health professional, and medical referrals to appropriate hospital departments as deemed necessary by their mental health or primary care providers.

The treatment as usual arm allowed us to examine the contributions of non-specific mental stimulation while the active control was designed to mask group assignment and control for clinician contact. We believe it was essential to try and isolate the memory training separate from potential psychological benefits that can be provided to depressed patients via a placebo effect or merely by contact with clinicians. As memory training programs are implemented throughout the country, it is imperative to demonstrate that neuroscience-based cognitive treatments are, at a minimum, more efficacious than mentally stimulating puzzles

available to the general public. This is especially true given recent press about commercial puzzle games to “improve” memory ability.

2.3 Instruments

Given the inpatient population, measures were carefully selected to reduce patient burden. All measures were standard instruments widely used in ECT outcome research.

Diagnosis or provisional diagnosis of major depression, severe, was confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV; First et al., 1995). An estimation of Pre-morbid IQ was based on the North American Adult Reading Test (NAART; Johnstone, 1996) while gross cognitive status was assessed via the Modified Mini-Mental State examination (mMMS; Stern, 1987). Anterograde verbal learning and memory was assessed using the Buschke Selective Reminding Test (BSRT; Buschke, 1973). Retrograde memory for autobiographical information was tested using the Columbia University Autobiographical Memory Interview-Short Form (AMI-SF; McElhiney et al., 1995), while retrograde memory for impersonal information or general knowledge about the world was measured with the Goldberg Remote Memory Questionnaire (GRMQ; Goldberg, 1985). Participant perception of cognitive problems was assessed with the Cognitive Failures Questionnaire (CFQ; Broadbent et al., 1982) and the Squire Subjective Memory Questionnaire (SSMQ; Squire et al., 1979). Health-related quality of life was measured by the Medical Outcomes Study-Short Form 12 item (MOS SF-12; Ware et al., 1992, 1993). Overall social, occupational, and psychological functioning was rated on the Global Assessment of Functioning (GAF; Spitzer et al., 1996). Depression was assessed with the Hamilton Rating Scale for Depression-24 item (HRSD; Hamilton, 1960; Williams, 1988).

2.4 Data analyses

Our primary aim was to compare cognition at baseline and post ECT between Mem-ECT, active control and treatment as usual. Primary outcome measures for cognition were mMMS total score, total list learning and delayed recall on the BSRT, GRMQ total score, and AMI-SF total score at baseline and the percent retained at post. In order to examine the potential impact of symptoms on functioning, we examined the relationship between depression (HRSD), overall functioning (GAF), health-related quality of life (MOS SF-12), and subjective cognitive performance on the SSMQ and CFQ. For each outcome, we fitted a linear mixed effects model using all available repeated measures of an outcome. We included treatment group, time, interaction between treatment and time, and baseline demographic (age and gender) as covariates. Participant-specific random intercepts were included to account for the correlations between measures from the same participant. We first compared mean post treatment scores across treatment groups based on the parameters estimated from the model. Next, we also compared the difference in post score from baseline between groups. Lastly, to examine the overall time trend in cognition, clinical symptoms, and quality of life, we combined the three treatment groups and compared the difference of post scores from baseline in all the participants. All tests were two-sided with a significance level of 0.05. SAS 9.4 was used for all analyses.

3. Results

Demographic information and baseline characteristics of each group are summarized in Table 1. There were no significant demographic differences between groups ($p > 0.07$). A majority of the sample was Caucasian, female, with some level of college education or a degree, which is consistent with past ECT studies for severe depression in New York City and other metropolitan areas (McCall et al., 2013; Weiner and Prudic, 2013). Compared to other study samples (Prudic et al., 2001, 2013), the current sample as a whole was not as depressed at baseline and had somewhat higher baseline GAF. Except for higher GRMQ baseline performance in the active control group ($p = 0.04$), there were no other significant group differences at baseline ($p > 0.13$).

There was no difference at post across treatment groups in any of the outcome measures, nor was there a treatment effect for the memory training or the active control on pre-post change scores (Table 2). In fact, compared to both the active control and memory training groups, the treatment as usual group reported better health-related quality of life on the MOS SF-12 and attenuated subjective memory problems at post on the SSMQ (Table 2).

When looking at the sample as a whole, participants improved significantly in clinical, symptom, and subjective memory measures, with no significant decline on the AMI-SF (sample retained 81.76% of pre-ECT information, which is consistent with healthy control performance; Sackeim, 2014), BSRT total list recall, GRMQ, or CFQ (Table 3). The GAF improved by 17.51 (CI: 12.86, 22.17, $p < 0.0001$), the MOS SF-12 improved by 8.75 (CI: 4.981, 12.58, $p < 0.0001$), and there was significant improvement on the HRSD as depression decreased by 12.27 ($p < 0.0001$). Interestingly, while delayed recall on the BSRT and the mMMS decreased by significant margins (1.05 and 1.17, respectively, $p < 0.009$), participants reported much improved memory on the SSMQ (15.26, $p = 0.012$), with fewer reports of everyday cognitive problems on the CFQ approaching statistical significance ($p = 0.060$).

4. Discussion

Overall, we found no significant memory or clinical benefit for the Mem-ECT or active control conditions compared to treatment as usual. The results were actually contrary to implementing any type of cognitive training or mental stimulation tasks, as those in the treatment as usual group reported better quality of life and subjective memory following ECT. Consistent with other RUL ECT trials (Prudic, 2008; Sackeim et al., 2006), the sample as a whole significantly improved in global function, quality of life, depression, and self-reported memory abilities, with no decline in general retrograde memory or autobiographical memory.

The decline in verbal delayed recall and mental status was surprising given the improvement in subjective memory performance and quality of life indicators, as well as the lack of decline in other cognitive domains. These results stand in sharp contrast to our pilot in 2011 that found promising results, albeit in only 9 participants. The current sample was younger (mean age of 43 versus 49 years old) with intact global cognitive function and much better baseline anterograde and remote memory and less depression than the pilot sample. There

exists the possibility that the current sample possessed greater cognitive reserve, and therefore, may not have needed a cognitive training intervention. That is, the most straightforward interpretation of the lack of significant effects for Mem-ECT is that patients in this trial had no quantifiable need for a cognitive training given that most benefited from this method of RUL ECT, reporting substantial reduction in depression, better quality of life, and very positive memory performance following ECT. The method of ECT used in this study, ultra-brief pulse RUL ECT, has been established as an effective treatment in-and-of-itself in severe depression (Lisanby, 2007; Prudic, 2008), with fewer or less severe cognitive side-effects than BL ECT, including mounting evidence for its use with depressed older adults (Kellner et al., 2016b). This is particularly true when ultrabrief stimulus is compared against bilateral electrode placement, which can result in more severe and persistent cognitive deficits (Sackeim et al., 2000, 2008). In retrospect, a signal for the memory training approach may have emerged in a bilateral ECT study. However, this was not feasible since RUL ECT is the standard first line treatment provided to all patients at the sites.

That being said, while there was no decline on most cognitive outcome measures due to the effectiveness of the ECT used in this trial, the decline in verbal delayed recall and mental status is disappointing since that is what we found the memory training to target in the pilot. The memory training should have, at minimum, impacted those two outcome measures given that the theory and technique behind the post-ECT training sessions is to accelerate mental status and anterograde memory recovery following ECT. Indeed, in this fully powered study, we now see that the memory training did not provide any clinical utility in making ECT more tolerable to patients by targeting anterograde memory and general mental status. Furthermore, while the next step would be to examine the memory training and its components in a BL ECT rather than RUL ECT, the technique and basis of the memory training may be inherently flawed in that the premise of the treatment is based on cognitive training for epilepsy and recovering episodic memories and memory skills following a generalized seizure episode. Emerging ECT literature published after the start of this study now suggests that cognitive deficits related to BL ECT or ECT in general may not be so similar to generalized seizures, after all (McClintock, 2014).

Nevertheless, while we report negative findings, these results continue to promote the much needed discussion on developing effective strategies to minimize the adverse memory side effects of ECT, especially BL ECT. The ultimate goal of this line of discussion is to make ECT a better and more easily tolerated treatment for patients with severe depression who need this therapeutic option.

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Figure 1.
Study procedures

Table 1

Demographics and baseline measures by treatment groups

Variable	Mean(SD)			Test statistic	P value
	Mem-ECT (N=21)	Active Control (N=18)	Treatment as Usual (N=20)		
Age	39.30(12.72)	48.22(10.82)	41.7(14.44)	5.31	0.07
Ed	16.7(2.25)	16.44(3.26)	15.95(2.54)	0.87	0.65
Male, N(%)	9(42.86)	10(55.56)	8(40)	1.03	0.6
Race/Ethnicity, n(%)					0.75
White	19(90.48)	17(94.44)	17(85)		
Black	1(4.76)	1(5.56)	1(5)		
Hispanic	0(0)	0(0)	2(10)		
Asian	1(4.76)	0(0)	0(0)		
NAAART	44.81(8.66)	45.83(9.12)	40.1(14.16)	1.4	0.50
mMMS	53.14(3.85)	52.17(4.9)	52.25(3.21)	1.88	0.39
BSRT Total List Recall	53.00(9.36)	49.17(15.17)	51.55(9.75)	0.45	0.80
BSRT Delayed Recall	8.43(2.84)	7.67(3.83)	7.65(2.85)	0.83	0.66
AMI	52.48(5.13)	51.33(6.49)	51.5(4.72)	0.63	0.73
GRMQ	43.55(14.35)	55.17(14.48)	44.78(20.22)	6.27	0.04
CFQ	49.25(13.68)	53.88(24.04)	45.86(8.07)	0.68	0.71
SSMQ	20.19(16.29)	23.00(23.06)	20.71(27.00)	0.26	0.88
SF-12	29.83(11.74)	25.33(6.53)	25.85(6.21)	1.38	0.50
GAF	42.15(10.46)	41.57(11.13)	46.45(12.26)	2.85	0.24
HRSD	25.14(7.69)	26.33(6.32)	24.95(6.61)	1.09	0.58

NAAART (North American Adult Reading Test); mMMS (Modified Mini-Mental State examination); BSRT (Buschke Selective Reminding Test); AMI-SF (Columbia University Autobiographical Memory Interview-Short Form); GRMQ (Goldberg Remote Memory Questionnaire); CFQ (Cognitive Failures Questionnaire); SSMQ (Squire Subjective Memory Questionnaire); SF-12 (Medical Outcomes Study-Short Form 12 item); GAF (Global Assessment of Functioning); HRSD (Hamilton Rating Scale for Depression-24 item)

Table 2
Mean differences between treatment groups in post treatment scores and pre-post change scores

Outcome	Arm	Descriptives of post-treatment scores			Compare post-treatment scores across treatment groups				Compare pre-post change scores across treatment groups			
		N	Mean	SD	Estimate	p-value	Lower CI	Upper CI	Estimate	p-value	Lower CI	Upper CI
mMMS	Mem-ECT	18	51.89	2.95								
	Active control	15	51.6	4.47	Diff1 *	0.801	-2.9	2.25	Diff1 **	0.109	-3.8	0.4
	Trt as usual	18	51.33	3.71	Diff2 †	0.521	-1.62	3.16	Diff2 ††	0.467	-2.74	1.27
BSRT Total List Recall	Mem-ECT	18	54.56	13.9								
	Active control	15	46.13	14.1	Diff1	0.213	-3	13.12	Diff1	0.424	-4.71	11.04
	Trt as usual	18	50.83	10.2	Diff2	0.442	-4.59	10.36	Diff2	0.831	-6.74	8.35
BSRT Delayed Recall	Mem-ECT	18	7.44	2.48								
	Active control	15	6.07	3.43	Diff1	0.46	-1.56	2.47	Diff1	0.804	-1.7	2.18
	Trt as usual	18	6.94	3.13	Diff2	0.36	-1.51	2.23	Diff2	0.524	-2.45	1.26
AMI-SF	Mem-ECT	18	41.83	7.56								
	Active control	15	40.80	7.79	Diff1	1.15	-3.23	5.53	Diff1	0.749	-4.65	3.37
	Trt as usual	18	44.17	5.48	Diff2	0.283	-6.25	1.87	Diff2	0.05	-7.68	0
GRMQ	Mem-ECT	18	46.42	12.5								
	Active control	15	55.43	14.5	Diff1	0.391	-13.91	5.54	Diff1	0.709	-1.76	2.57
	Trt as usual	18	47.19	19.8	Diff2	0.6	-6.66	11.4	Diff2	0.794	-1.79	2.33
CFQ	Mem-ECT	8	48.13	18.6								
	Active control	9	49.33	21.4	Diff1	0.83	-18.14	19.8	Diff1	0.291	-14.38	4.58
	Trt as usual	7	45.86	7.99	Diff2	0.991	-18.3	18.1	Diff2	0.214	-17.11	4.11
SSMQ	Mem-ECT	8	-6	7.56								
	Active control	9	-11.8	19.7	Diff1	0.683	-16.55	24.65	Diff1	0.821	-24.14	30.04
	Trt as usual	7	-3.14	17.9	Diff2	0.795	-23.95	18.62	Diff2	0.71	-33.75	23.48
SF-12	Mem-ECT	18	34.42	6.19								
	Active control	14	34.24	7.14	Diff1	0.82	-7.99	6.36	Diff1	0.349	-13.93	5.02

Outcome	Arm	Descriptives of post-treatment scores			Compare post-treatment scores across treatment groups				Compare pre-post change scores across treatment groups							
		N	Mean	SD		Diff2	Estimate	p-value	Lower CI	Upper CI		Diff2	Estimate	p-value	Lower CI	Upper CI
GAF	Trt as usual	18	37.9	16.1		Diff2	-3.57	0.279	-10.14	2.99		Diff2	-7.44	0.106	-16.52	1.65
	Mem-ECT	18	58.94	15.5												
	Active control	14	65.5	11	Diff1		-6.98	0.147	-16.5	2.55	Diff1		-7.7	0.192	-19.4	4.01
	Trt as usual	18	58.61	14.9	Diff2		0.01	0.998	-8.64	8.66	Diff2		3.92	0.468	-6.87	14.71
HRSD	Mem-ECT	18	14.56	10.4												
	Active control	14	11.5	5.95	Diff1		3.43	0.218	-2.1	8.95	Diff1		4.67	0.189	-2.38	11.73
	Trt as usual	18	13.17	6.86	Diff2		1.59	0.529	-3.46	6.64	Diff2		1.71	0.612	-5.01	8.42

* Estimated difference between active control and Mem-ECT

[†] Estimated difference between treatment as usual and Mem-ECT

** Estimated pre-post treatment change scores between active control and Mem-ECT

^{††} Estimated pre-post treatment change scores between treatment as usual and Mem-ECT

Table 3

Baseline and post-treatment scores and change scores in the entire sample.

Outcome	Baseline			Post			Adjusted difference			
	N	Mean	SD	N	Mean	SD	Estimate	p-value	Lower	Upper
mMMS	59	52.54	3.97	51	51.61	3.64	-1.17	0.0077	-2.01	-0.32
BSRT Total List Recall	59	51.34	11.46	51	50.76	12.97	-0.54	0.7351	-3.71	2.64
BSRT Delayed Recall	59	7.93	3.15	51	6.86	3.01	-1.05	0.0097	-1.83	-0.27
AMI	59	51.8	5.38	51	42.35	6.98	-9.52	<0001	-11.14	-7.9
GRMQ	59	47.51	17.11	51	49.34	16.16	0.6	0.173	-0.27	1.47
CFQ	23	49.83	16.5	24	47.92	16.8	-3.96	0.0605	-8.11	0.20
SSMQ	23	-21.33	21.31	24	-7.33	15.82	15.26	0.0124	3.74	26.78
SF-12	57	27.08	8.74	50	35.62	10.95	8.75	<0001	4.91	12.58
GAF	54	43.59	11.33	50	60.66	14.23	17.51	<0001	12.86	22.17
HRSD	59	25.44	6.84	50	13.2	8.06	-12.27	<0001	-15.11	-9.43