

Effects of Electroconvulsive Therapy and Magnetic Seizure Therapy on Acute Memory Retrieval

Julia D. Polster, MS,* Sarah Kayser, MD, MSc,* Bettina H. Bewernick, PhD,* René Hurlemann, MD, PhD,* and Thomas E. Schlaepfer, MD*†

Objectives: Electroconvulsive therapy (ECT) is currently the most effective treatment for severe depression. However, it is frequently associated with negative cognitive side effects. Magnetic seizure therapy (MST) depicts an alternative, although experimental, convulsive treatment for major depression. Initial results suggest comparable antidepressant effects accompanied by a better side effect profile. However, no studies up to now have addressed acute retrieval disruption after MST in comparison to ECT. Therefore, we intended to broaden insight into the side effect profile of MST compared to ECT by examining the disruption of acute verbal memory processes after treatment.

Methods: Twenty depressed patients were randomly assigned to either MST (10 patients) or ECT (10 patients) treatment. On 2 treatment days and 2 treatment-free days, the patients memorized words using a controlled learning paradigm derived from the Batchelder and Riefer storage retrieval model. Four hours after memorization, the patients were asked to retrieve words freely (delayed recall) and a second time with the help of an additional cue constructed out of a hypernymic category (cued recall). By comparing memory performance on treatment days to control days, treatment-induced memory disruption was evaluated.

Results: After ECT, delayed recall was disturbed, whereas after MST, it was not. However, this difference in performance was no longer apparent upon cue application (cued recall).

Conclusions: This study demonstrates that ECT-induced acute memory disruption measured by delayed recall is absent after MST, confirming its superior side effect profile. We hope that confirming advantages of MST over ECT will improve therapy options for patients with severe depression.

Key Words: magnetic seizure therapy, electroconvulsive therapy, storage process, retrieval process, delayed recall, cued recall

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Major depression is one of the leading causes of invalidity and disability worldwide.¹ Depressive patients are affected in crucial and life-threatening ways² not least due to cognitive

and, in particular, memory deficits.³ Common treatments for depression such as pharmacotherapy and psychotherapy have made significant progress in the past decades but still fail to cure one third of patients.⁴ For these cases, which are therefore diagnosed with treatment-resistant depression (TRD),⁵ electroconvulsive therapy (ECT) remains the most effective treatment.⁶ In ECT, electrically induced generalized seizures under general anesthesia are used to attenuate depression. However, ECT is frequently associated with negative cognitive side effects.⁷ Besides prolonged reorientation and confusion,^{8,9} anterograde¹⁰ and retrograde amnesia commonly occur after treatment.^{11,12} Of these, retrograde amnesia is the most frequently reported adverse effect.¹¹ However, amnesia can be attenuated to some degree by constraining the location of stimulation: right unilateral ECT stimulation leads to less cognitive adverse effects compared to bilateral ECT stimulation⁹ but confers inferior antidepressant effects. Although the adverse effects previously mentioned seem to be reversible for the most part, they continue to contribute to the stigmatization of ECT. Hence, the use of ECT has been assigned to a treatment of last resort.¹³

Magnetic seizure therapy (MST) is an experimental alternative convulsive brain stimulation method that uses alternating magnetic fields to induce generalized seizures under general anesthesia for therapeutic purpose.¹⁴ A first proof-of-concept study demonstrated the safety and feasibility of MST and indicated a better cognitive side effect profile compared to ECT.¹⁵ The impedance of the skin and the skull does not influence the magnetic field in MST, allowing a more localized stimulation in comparison to ECT. Thus, the medial temporal areas, such as the hippocampi, which participate in memory function,¹⁵ are spared from stimulation. However, after ECT, they are often affected, leading to the aforementioned cognitive adverse effects.¹⁶ In previous clinical trials, MST-treated patients recovered their orientation more quickly than those treated with ECT.^{17–19} In addition, retrograde and anterograde amnesia have been reduced using MST in both nonhuman primates^{20,21} and humans.^{15,18} Moreover, initial studies have demonstrated equivalent robust antidepressant effects of MST and ECT.^{17,18,22,23}

One central question concerning the memory impairment caused by ECT²⁴ has been the nature of the impairment itself. Memory impairment has been widely suggested to be caused either by disruption of storage or of retrieval.^{25–27} In contrast to the complete deletion of a memory (storage process), disturbance of retrieval function implicates that memories are not deleted but rather temporarily not accessible.²⁸ Although reversibility of amnesia and restoration of memory contents over time point to a disruption in retrieval procedures after ECT,²⁹ a definite answer to this question is hard to provide and additional evidence is required. An interesting methodology for differentiation of storage or retrieval impairment is the application of external hints to facilitate the memory process (“cued recall”).^{24,30} Cue-induced memory is not believed to be deleted but rather temporarily inaccessible. Thus, in keeping with previous human studies³¹ and studies with rats,^{32,33} we included a cued recall measurement in addition to the free recall.

From the *Department of Psychiatry and Psychotherapy, University Hospital, Bonn, Germany and †Departments of Psychiatry and Behavioral Sciences, The Johns Hopkins University, Baltimore, MD.

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Reprints: Thomas E. Schlaepfer, MD, Department of Psychiatry and Psychotherapy, University Hospital, Sigmund-Freud-Straße 25, 53105 Bonn, Germany (e-mail: schlaepf@jhmi.edu).

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Julia D Polster and Sarah Kayser MD, MSc, shared first authorship.

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Although several studies have suggested a better cognitive and memory outcome of MST compared to ECT,^{18,19,34} MST has never been evaluated for acute memory disruption. The purpose of this study was to examine possible differences in acute verbal memory processes after MST treatment compared to ECT treatment. For the first time, a controlled learning and recall performance was assessed in either MST- or ECT-treated patients with a diagnosis of TRD and in healthy controls. To differentiate between the disruption of storage or retrieval after treatment, based on a modified storage retrieval model,³⁵ we included both a free recall and a cued recall measurement. In keeping with previous studies with a favorable side effect profile,^{18,19,34} we hypothesized that MST would induce far less acute memory disruption than ECT owing to the differences in stimulation technique.

MATERIALS AND METHODS

Study Design and Patients

The study was approved by the institutional review boards of the University of Bonn and was registered at ClinicalTrials.gov NCT00770783. It was a prospective, controlled, open-label, within-subject observational study. Patients signed the informed consent form after a waiting period of 2 weeks after receiving information about the study, depicted in an information sheet that they could take with them.

Twenty patients fulfilling the criteria for TRD and 10 healthy control subjects were included in the study. Treatment-resistant depression was defined as stage 2 of resistance according to Thase and Rush³⁶ for patients who are unresponsive to 2 different antidepressant treatments of adequate length and dosage during a current episode of depression. All patients and subjects were older than 18 years. The upper age limit was 69 years for patients, and one healthy control person was 82 years old. The primary inclusion criterion was an affective disorder with a current major depressive episode diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*,³⁷ with a clinical indication for MST/ECT. In addition, patients were required to have a minimum score of 20 on the 28-item Hamilton Depression Rating Scale (HDRS₂₈)³⁸ measured at baseline (2 weeks before treatment). Moreover, for patients with MST, the absence of former ECT treatments was required. None of the female patients were pregnant, and, if necessary, they received adequate birth control. The primary exclusion criteria were diagnoses of cognitive disorders or signs of dementia, delirium, amnesia, or nonaffective psychotic disorders. Alcohol or substance dependence within the previous 12 months or substance-related addiction within the past 6 months (except nicotine) also led to exclusion. Further exclusion criteria were anesthesiologically relevant cardiac diseases, any head injuries relevant to MST/ECT, other diseases of the central nervous system, and implanted medical devices and magnetic material in the head or body.

Patients were given a full treatment course (ranging from 10 to 12 treatments) of either MST (n = 10) or ECT (n = 10) from June 2009 to December 2012 and were tested for treatment-induced memory disruption during the same period at the Department of Psychiatry and Psychotherapy, University Hospital of Bonn. Additionally, they were rated using the Beck Depression Inventory (BDI)³⁹ at baseline.

Magnetic Seizure Therapy and Electroconvulsive Therapy

Antidepressant medication was kept stable 1 month before and during the entire course of treatment. Magnetic seizure therapy or ECT treatments were given twice a week (for 5–6 weeks), with

the total number varying between 10 and 12 treatments. Both brain stimulation treatments were conducted under general anesthesia with intravenous propofol (1.5 mg/kg; mean dose, 100 mg) and oxygenation with 100% O₂. Intravenous succinylcholine (1 mg/kg; mean dose, 70 mg) was administered as a muscle relaxant.

A MagPro (MagVenture A/S, Farum, Denmark) was used to perform MST. Seizures were induced via a biphasic waveform. A twin coil with 2 individual 13-cm-wide coils was used. The pulse had a dampened cosine wave shape. The center of the coil was placed at the vertex, and a peak magnetic field of approximately 4 T at the coil surface induced seizures. For each patient, an ascending titration was done with 100, 200, 300, etc, pulses in train upon the first trial. The minimum number of pulses required to activate a tonic-clonic seizure defined the individual seizure threshold. For subsequent trials, seizures were induced by stimulation seizure threshold, denoted high-dose MST.¹⁹ The other main stimulation parameters were the following: amplitude, 100%; frequency, 100 Hz; and a train duration averaging from 5 to 8 seconds.

A Thymatron IV (Somatics LLC, USA and Canada) was used for ECT treatments. The following stimulus parameters were applied: bipolar waveform, square wave, brief pulse current, and pulse width (0.5 ms). Frequency and duration of stimulation (5–8 seconds) depended on the energy set. All patients were treated with right unilateral stimulation. For each patient, an ascending titration determined the seizure threshold during the first treatment. Following stimulations were performed at 5-fold over seizure threshold.

Memory Performance

To compare possible memory disturbances after MST and ECT, we used a learning model using the reciting of memorized word lists (explained in the following text and in Fig. 1). On each of the 2 treatment control days and 2 treatment-free control days, the patients were given 3 consecutive learning trials in the morning to learn 40 words. Words were clustered into pairs and assigned to a hypernymic category for additional differentiation between storage or retrieval disruption of memory according to Batchelder and Riefer.³⁵ For example, “joy” and “fear” were assigned to the hypernymic category “emotions”. This enabled the recording of a cued recall providing information about the category. After treatment, patients were initially asked to remember all 40 of the words by themselves (“delayed recall”). Subsequently, they were provided with the name of each hypernymic category to enable them to recall all 40 words independently from delayed recall, again. In the aforementioned example, the patients were given the information that 2 emotions were among the words to be recalled and then asked to recall them another time (cued recall). It is generally believed that if patients extraordinarily benefit from these cues, this is indicative of a retrieval-based rather than a storage-focused memory disruption.^{24,30}

Words were assigned to categories according to the published norms of German linguistic usage provided by Hager and Hasselhorn.⁴⁰ To avoid long-term memory effects, a different word list was used on each of the 4 test days with randomly selected successions for each patient. Additionally, the order of the words was different for each of the 3 learning trials with the additional requirement that word pairs belonging to the same category had to be separated by 1 to 3 other words. These requirements were intended to facilitate memorizing of the actual words and prevent the simple memorization of word order. Words were presented on PowerPoint and using the font Arial in character size 40 on the computer screen for 2 seconds. After each of the 3 learning trials, the patients were asked to recall words. The patients were subjected to treatment immediately after the

08:30 Learning trials			13:00 retrieval	
Trial 1	Trial 2	Trial 3	Delayed recall	Cued recall

Each day:

	1. day	2. day		3. day	4. day
08:30	learning trials	learning trials	<i>weekend</i>	learning trials	learning trials
13:00	(control) retrieval	MST/ECT retrieval	<i>break</i>	(control) retrieval	MST/ECT retrieval

FIGURE 1. Procedure of learning and retrieval. Patients were given 3 trials to learn 40 words in the morning. Afterward, they received either MST or ECT or no therapy (control days). At noon, patients were asked to retrieve all words they remembered by themselves (delayed recall) and were subsequently provided with the hypernymic category of all words as an external cue (cued recall). On each of the 4 testing days, a different word list was used. For the 3 learning trials given on 1 day, 3 different word orders were used.

3 learning trials were over, or left untreated on control days. The break between treatment and retrieval tests was at least 2 hours to ensure full recovery from anesthesia.⁴¹ After this, the patients were asked to remember all possible words (delayed recall) and then helped by naming each category as a cue (cued recall).

To enable evaluation of treatment caused effects on a particular subject, the patients were treated with MST or ECT on 2 of the 4 testing days, whereas the other 2 days served as control. These conditions created 4 different experimental groups: MST control, MST therapy, ECT control, and ECT therapy. Clinical therapy required treatment 3 times a week, which took place on Mondays, Wednesdays, and Fridays. On two of these days within 2 weeks, memory effects of treatment were evaluated for this study. A control for memory without treatment was recorded twice within the same 2 weeks but not on the days before or after memory impairment due to treatment was assessed. Usually, patients were tested within 2 weeks. Generally, testing started at the beginning of the treatment course (MST/ECT), varying between the first (titration) and the third treatment. One patient with MST was tested at the end of a treatment course. One ECT patient and 5 MST patients started participating on a day with treatment, whereas all other patients started on a day without therapy owing to organization. At the end of the last testing day, the patients were asked to evaluate their subjective memory ability on a Likert scale,⁴² which we depict as memory evaluation (ME), ranging from 1 point (very bad) to 10 points (very good).

To differentiate which part of the performance might be due to depressive symptoms, the memory performances of 10 healthy people without a treatment were assessed once per person. Healthy controls were recruited by using notices at the Department of Psychiatry and Psychotherapy at the University of Bonn.

Statistical Analysis

For statistical evaluation of demographic and clinical variables, a χ^2 test was used for sex and unpaired *t* tests were used for age; duration of current episodes; number of antidepressant medication; and HDRS₋₂₈, BDI, and ME scores. Owing to the small sample, instead of analysis of variance (ANOVA), memory performance was compared using unpaired *t* tests between different treatments (MST and ECT) and paired *t* tests within conditions (between treatment and control). Owing to the large standard deviation within the ECT treatment group at delayed recall, additional nonparametric tests were used and values were tested for normal distribution. For an extended view on possible

different benefits from externally applied cues, we used a repeated-measures ANOVA with type of recall (delayed or cued) and treatment versus control as within-subject factors and MST versus ECT as a between-subjects factor. The level of significance for all calculations was set at 0.05.

RESULTS

Demographic and Clinical Characteristics

Detailed demographic and clinical characteristics are given in Table 1. The MST and ECT groups did not differ regarding the number of medications, duration of depressive episodes, and degree of treatment resistance (treatment resistance according to Thase and Rush).³⁶ The degree of depression as measured by HDRS₋₂₈ and BDI at baseline did not differ between the patients with MST and those with ECT. Both patient groups and the healthy control group did not differ significantly in their age, sex, or the self-evaluation of memory (ME).

Memory Performance

Learning Trials and Immediate Recall

The number of recalled words increased in all of the groups after each learning trial with the overall significantly best performance after the third trial (Fig. 2). However, 1 patient with MST, 3 patients with ECT, and 1 healthy control remembered marginally more words after the second trial. Therefore, the best performances were used for baseline values. Overall differences in performance during learning trials were found between ECT (14.3 ± 5.8 words, of 40 words) and MST (20.4 ± 6.2 words, of 40 words) (*P* = 0.03) as well as between ECT and healthy controls (23.3 ± 8.5 words, of 40 words) (*P* = 0.01). To prevent the interference of these differences with our analysis of memory recall, the number of recalled words after treatment was normalized for each person to his or her maximum number of memorized words at baseline (Fig. 3).

Delayed Recall

Values in all groups were normally distributed. The patients with MST and ECT remembered fewer words compared to their maximum performance at baseline (*P* < 0.001). Furthermore, the patients remembered less than the healthy controls did (*P* < 0.01). Within-group analysis revealed that the patients with MST recalled similar numbers of words on treatment and control days (mean treatment, 51.1% ± 21.8% vs mean control,

TABLE 1. Patients' Demographic and Clinical Characteristics

Variable	MST (n = 10)	ECT (n = 10)	Healthy Controls (n = 10)
Age, yrs*	43.7 (11)	54.7 (13)	53.8 (13)
Sex, % female*	30	60	60
Duration of current episodes, yrs*	4.1 (4)	3.1 (3)	ND
No. antidepressant medication during current episode*	5.8 (4)	5.1 (2)	ND
Degree of treatment resistance*†	TRD stage 2	TRD stage 2	ND
HDRS ₋₂₈ *	25.3 (7)	23.2 (8)	ND
BDI*	27.7 (8)	24.3 (11)	ND
ME‡	4.3 (2)	4.9 (1)	5.1 (1)

Data are presented as mean (SD).

*At baseline.

†Modified by Thase et al 2003 (Thase and Rush 1997).

‡After the fourth testing day.

ND indicates not determined.

56.4% ± 24%; $P =$ not significant [ns]). However, the patients with ECT performed worse on treatment days compared to control days (treatment, 23.2% ± 24.6%; and control, 46.7 ± 21.6%; paired t test, $P = 0.037$; nonparametric tests, $P < 0.05$; Fig. 4). Additionally, intergroup analysis showed that whereas both patient groups performed equally on control days (MST, 56.4% ± 24% vs ECT, 46.7% ± 21.6%; $P =$ ns), patients with ECT performed significantly worse than the MST group on treatment days (MST, 51.1% ± 21.8% vs ECT, 23.2% ± 24.6%; unpaired t test, $P = 0.015$; nonparametric tests, $P < 0.05$). As expected, the healthy controls did not decline at delayed recall when compared to baseline values (87.3% ± 23.4%; $P =$ ns; Fig. 3).

Cued Recall

After independent recall, participants were provided with the hypernymic categories for the memorized words as external cues. Unsurprisingly, all participants profited from these cues ($P < 0.05$). Whereas the healthy controls performed better upon cue than their maximum level of performance during the learning trials (135%), the patients could only reach levels similar to their performance during baseline (ECT treatment, 86.3%; ECT control, 104.5%; MST treatment, 104.8%; MST control, 98.9%) (Fig. 5). Notably, patients with ECT performed more poorly on treatment days (86.3%). However, the difference in the performance of the patients with ECT between control and treatment days was not statistically significant. To investigate if patients with ECT on treatment days benefited more from cues

compared to other experimental groups, a repeated-measures ANOVA using type of recall and treatment versus control as within-subject factors and MST versus ECT as a between-subject factor was used and showed no significant difference in benefits from external cues in either group. The healthy controls differed significantly from the patients (to MST on control days, $P = 0.007$; to MST on treatment days, $P = 0.015$; to ECT on control days, $P = 0.013$; and to ECT on treatment days, $P = 0.008$).

DISCUSSION

In this study, we investigated acute memory disruption by MST and ECT and report that MST demonstrates a better side effect profile. To our knowledge, this is the first approach comparing patient groups that received either MST or ECT but not both successively and including a within-subject control for each treatment. When asked to recall words memorized before treatment, patients performed equally well on days with treatment and on days without. In contrast, patients with ECT performed significantly worse on treatment days than on control days. This indicates that ECT negatively affects the acute memory of newly acquired knowledge. We would like to conclude that well-known disturbances of acute memory induced by ECT are absent after MST. This is consistent with former studies on side effect profiles of ECT and MST: It is known that disturbance of acute memory occurred both after unilateral and bilateral ECT with a stronger effect after the latter⁹ and particularly for memory contents learned shortly before ECT.^{11,43} In addition, the better

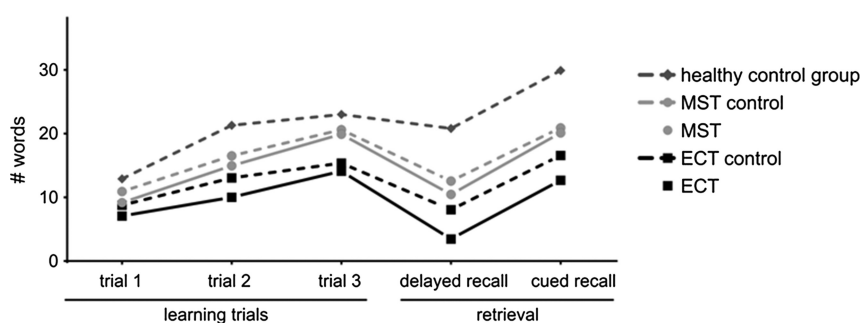


FIGURE 2. Raw data of memory performance. Absolute number of words memorized in learning trials (trials 1, 2, and 3) and retrieval (delayed and cued recall) with a possible maximum of 40 words. Days with therapy and days without (control) are depicted for each patient group (MST and ECT) plus the healthy control group.

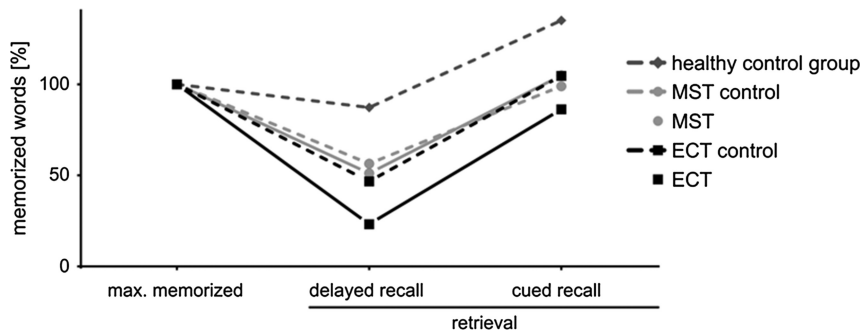


FIGURE 3. Percentage of words recalled. Depicted are results after normalization to the maximum memorized words in the morning set as 100%. Retrieval is demonstrated as delayed and cued recall.

side effect profile of MST in various acute memory tests has already been shown in nonhuman primate studies²⁰ and in humans, receiving first MST and ECT afterward.¹⁵ However, to our knowledge, we are the first to report weaker side effects on acute memory of sole MST treatment compared to ECT treatment within 2 independent patient groups.

Although MST and ECT are both brain convulsive therapies, only ECT causes acute memory disturbances. This indicates that the acute memory effects might not be caused by generalized seizures or anesthesia but rather by the stimulation technique itself. Consistent with this observation, the type and strength of ECT stimulation also correlate with the severity of cognitive adverse effects: bilateral ECT and high-dose treatment both induce more severe memory disturbance than unilateral ECT and low-dose treatment.⁹ In contrast, MST uses a more focused stimulation and displays no impairment of acute memory, as reported here. As previously reported, its magnetic stimulation does not reach the medial temporal lobes (MTL) containing the hippocampi,^{15,44} which are connected with memory consolidation and retrieval.^{16,45,46} Sparing of the hippocampi could explain why MST does not interact with associated memory processes. In contrast, ECT can interfere with those vulnerable structures.⁴⁷ Interestingly, the older memories are, the less they rely on the hippocampi; and, accordingly, deficits in acute memory are more pronounced than disruption of older memories after ECT.²⁷ In summary, we hypothesize that observed absence of acute memory disruption after MST compared to ECT might be due to its more targeted and thus gentler stimulation.

We designed the memorization and interrogation procedures to include cues to enhance memory retrieval. A disproportionately large benefit from this cue could have hinted at

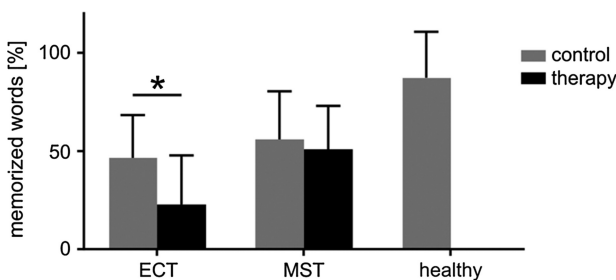


FIGURE 4. Memory performance at delayed recall. Percentages of words recalled without cue are shown normalized to the maximum memorized words in the morning set as 100%. The mean and standard deviation of each condition are depicted. Control refers to testing days without treatment. Therapy refers to testing days with interfering treatment. Healthy, healthy controls; * $P \leq 0.05$ (paired t test).

disrupted memory retrieval instead of failed memory consolidation.^{24,30} All but one of the patients was able to retrieve more information upon cue, independent of condition, indicating that the cue itself worked. Although we report a profound effect of ECT on free-recall performance, this effect was no longer significant after cuing. By implication, patients with ECT could have benefited more from cuing after treatment than on control days. However, using repeated-measures ANOVA, we found that the benefit induced by the cue was not significantly enhanced in patients treated with ECT compared to the other groups. Thus, no valid conclusion can be drawn, and the question whether ECT-induced memory impairment is rather storage or retrieval based remains unanswered.

As another conclusion from this study, we think memory testing using controlled learning and cued recall should be implemented in future research on convulsive brain stimulation methods like ECT and MST. Not only do patients profit emotionally from cues when they see their improvement, but additional information could also be gained about the memory processes possibly compromised after brain stimulation.

Whereas the discussion about the nature of ECT-induced memory disruption cannot benefit from our data, the results concerning the side effect profile of MST are still compelling. As previous reports have suggested, given the equal therapeutic effects on depressive symptoms,^{17,18,22,23} MST might become a promising alternative in treating TRD without the adverse effects of ECT.

Limitations and Outlook

As with most studies on experimental clinical therapies, an obvious limitation of this report is its small sample size. However, the attenuated side effect profile shown by MST in

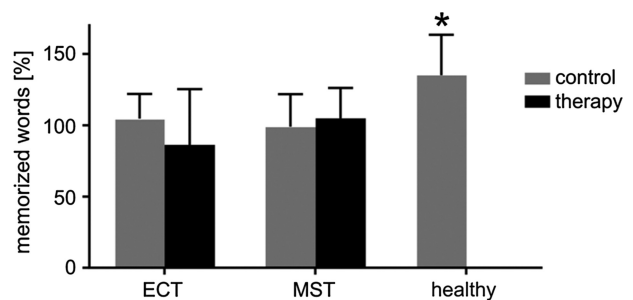


FIGURE 5. Memory performance at cued recall. Performance of the whole patient sample and the healthy control group is shown at cued recall. The hypernymic categories of words were given as cues. * $P \leq 0.05$ (unpaired t test).

comparison to ECT was so remarkably strong that even in this small group of patients, effects could demonstrate significant differences. Since we found a large standard deviation in the ECT treatment group compared to the mean, we confirmed the data set to be normally distributed. Additionally, nonparametric tests for group comparisons were also significant. For organizational reasons, neither patients nor testing persons could be blinded to the treatment method (MST or ECT) or the condition (therapy or control). Thus, we cannot exclude bias due to the investigator and influenced by his expectations. Ideally, a double-blind randomized study should be pursued to verify our results. In addition, the study is limited in that it does not take the possible influences of anesthesia, concomitant drugs, or the comorbidities of patients into account. Similarly, we limited the patient sample to patients with a diagnosis of unipolar depression. It remains to be seen if our findings transfer to other forms of depression (eg, bipolar). Despite these limitations, our results confirm and extend a favorable side effect profile of MST compared to ECT with regard to acute memory function. We hope that the confirmed advantages of MST will improve therapy options for patients with severe depression.

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