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Patient, treatment and anatomical predictors of outcome in electroconvulsive therapy: *A prospective study*

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Abstract

Background: Baseline predictors of effectiveness and cognitive adverse effects of electroconvulsive therapy (ECT) were prospectively examined.

Methods: Before and after ECT, the Montgomery-Åsberg Depression Rating Scale (MADRS) and Mini-Mental State Examination (MMSE) were assessed. Before ECT, a magnetic resonance imaging of the head was performed. Outcome predictors were investigated using multivariable regression analyses.

Results: Of 83 patients (mean age ± SD, 59.2±15.3 years; 39% men), 28% had a psychotic depressive disorder, 16% had a bipolar depression, 30% had had previous ECT course(s), and 66% used concomitant antipsychotics. Presence of psychotic depression (β=-0.25; *P*=0.04) and having had previous ECT (β=-0.35; *P*=0.003) predicted lower post-ECT MADRS score. Baseline magnetic resonance imaging characteristics were not predictive of post-ECT MADRS and MMSE scores. The use of concomitant antipsychotics predicted a lower post-ECT MMSE score (β=-0.21; *P*=0.02), whereas presence of bipolar depression at baseline predicted higher post-ECT MMSE score (β=0.23; *P*=0.01). The post-ECT MADRS score seemed to be a confounder for the post-ECT MMSE score (β=-0.20; *P*=0.02).

Conclusions: Effectiveness of ECT was better in the patients with a baseline psychotic depression and those who had had ECT before. Cognitive outcome was better in patients with baseline bipolar depression but worse in those who used antipsychotics during ECT and those who showed more persistent depressive symptoms after ECT.

Introduction

Electroconvulsive therapy (ECT) is a fast, effective and safe treatment for severe pharmacotherapy-resistant depression and shows remission rates up to 80%.[1-3] Occurrence of particularly memory disturbances during and after a course of ECT is a main adverse effect and may limit acceptance and use of this treatment.[2] During a course of ECT, consecutive seizures are elicited by administering an electrical stimulus above the seizure threshold (ST) under generalized anaesthesia, muscle relaxation, and continuous oxygen supply.[2]

Many attempts have been made to determine whether certain patient, treatment and brain anatomical characteristics may predict effectiveness and cognitive adverse effects of ECT.[2,4,5] Effectiveness of ECT was studied in relation to the type and specific symptoms of depression. It was shown that depression with disturbances in vegetative functions, psychomotor retardation, psychotic features, and shorter duration of the current episode was associated with a more positive outcome of ECT.[4,6,7] In addition, older patients,[8,9] patients with catatonic symptoms,[4] and patients without a comorbid borderline personality disorder had a better outcome of ECT.[10] The presence of bipolar depression was examined as a factor of influence for effectiveness in ECT but has not been shown a consistent predictor of outcome,[7,11,12] Effectiveness of ECT has also been associated with certain (technical) aspects of the treatment itself. Having been treated with ECT before predicted better outcome of ECT,[7] as well as treatment with higher electrical stimulus dosage above the ST[3] and concomitant nortriptyline use during the ECT course.[13] Bifronto-temporal (BL) electrode placement was shown to be equally effective to right unilateral ECT (RUL), if appropriate attention was paid to the technical aspects of dosing.[2,14] Regarding brain anatomical predictors of ECT effectiveness, measured with the Montgomery-Åsberg Depression Rating Scale (MADRS), a poorer response was suggested by increased amounts of subcorticofrontal gray matter hyperintensities[15] and by the presence of medial temporal lobe atrophy.[16]

Predictors of post-ECT cognitive adverse effects have more scarcely been studied.[17,18] Poorer pre-treatment global cognitive functioning, assessed with the Mini-Mental State Examination (MMSE) [19], seemed to be a strong predictor of persistent retrograde amnesia after ECT.[17,20] Furthermore, advanced age showed a robust association with greater memory deficits after a course of ECT,[21] but on the other hand, several studies showed an improvement of cognitive functioning after ECT.[18,22] Regarding technical treatment characteristics, administering more BL ECT sessions (but not RUL) during the treatment course predicted more cognitive adverse effects, as well as electrical stimulation with longer pulse widths and

treating patients in higher frequencies (e.g., 3 times a week compared to 2 times).[21,23] From an anatomical point of view, less hippocampal volume on magnetic resonance imaging (MRI) of the head was associated with poorer ECT-related memory outcomes in one small study,[24] but this result has not been replicated in studies associating anatomical head MRI characteristics and possible cognitive adverse effects of ECT. In this prospective study, we investigated in 83 patients undergoing ECT whether certain patient, (technical) treatment, and anatomical head MRI characteristics were predictive of effectiveness and cognitive adverse effects of ECT.

Materials and methods

Patients, demographic and clinical data acquisition

All consecutive patients indicated for ECT in Rijnstate Hospital (Arnhem, the Netherlands, a 36-beds psychiatric facility with a catchment area of 600,000 inhabitants), from December 1, 2009, until November 15, 2011, were asked to participate in a prospective MRI study relating anatomical and functional parameters and seizure threshold (trail registration number: NL24697.091.09).[25] Patients were excluded if age was younger than 18 years, no written informed consent was provided, or contraindications existed for dose titration (e.g., life-threatening condition of the patient, severe cardiovascular comorbidity) or for MRI (e.g., metals in the body, claustrophobic reactions, patients' inability to lie still in the scanner). Within 2 weeks before the first ECT session, a head MRI was obtained. The medical ethical committee of the hospital approved the study protocol, and written informed consent was obtained from all participants. Patient and head MRI characteristics of the study population are described in more detail elsewhere.[26] In this present open observational study, the relation between baseline characteristics and prospectively obtained outcome measures were analyzed.

Psychometric instruments

Severity of depression was scored by a trained research nurse (O.B.H.) in the week before the first ECT (baseline) and within 1 week after the last ECT session using the MADRS, a validated observer-rated scale that contains 10 items (scored 1-6 per item), with the sum score ranging from 0 to 60 and higher scores indicating more and a higher severity of depressive symptoms.[27]

Cognitive functioning at baseline and within 1 week after the last ECT session was assessed using the MMSE, a commonly used validated instrument to evaluate

cognitive functioning, with the total score ranging from 0 to 30, and lower scores indicating more cognitive dysfunction.[19]

Amount and severity of somatic comorbidity at baseline were rated using a modified Cumulative Illness Rating Scale (CIRS), consisting of 14 aspects of possible pathology and impairment of major organ systems, which are rated from 1 (no impairment to that organ/system) to 5 (impairment is life-threatening; treatment is urgent or of no avail; prognosis is grave), ranging from 14 to 70. The item 'Psychiatric/Behavioral (includes depression, anxiety, agitation, psychosis, not dementia)' was set at 5.[28]

Electroconvulsive therapy and measurement of ST

Electroconvulsive therapy was administered using a constant-current (0.9 Ampère), brief-pulse (0.25 milliseconds [ms] in RUL and 0.5 ms in BL ECT) device (maximum output, 1008 milliCoulombs [mC]; Thymatron IV; Somatics Incorporation, Lake Bluff, Illinois, USA) after induction of anesthesia intravenously with etomidate (1.5 mg/kg body mass), muscle paralysis with succinylcholine (0.5-1 mg/kg body mass) intravenously, and with appropriate oxygenation (100% oxygen, positive pressure) until the resumption of spontaneous respiration. Electrode placement was started RUL, except in patients at high risk for suicidality and/or somatic complications, or if previous ECT had successfully been administered bilaterally. Initial ST (IST) was measured at the 1st ECT session by an empirical titration method.[4] If the starting stimulus dose failed to elicit a seizure of at least 20 seconds of motor activity measured with the cuff method and/or 25 seconds or longer on electroencephalogram, stimulus charge was increased according to the titration schedule (for patients younger than 50 years: 25.2 mC, 50.4 mC, 100.8 mC, 201.6 mC, and 403.2 mC; for patients aged 50 years and older: 50.4 mC, 100.8 mC, 201.6 mC, and 403.2 mC), and the patient was restimulated after 30 seconds. At the second session, dosage was set at 6 times the IST in RUL ECT and at 2.5 times the IST for BL treatment. The patients were treated twice weekly. Right unilateral electrode placement was changed into BL during the ECT course, based on the clinical decision of experienced psychiatrists, mostly if the patient did not show (enough) improvement after 6 RUL sessions. If at the titration session the ST was reached and there was still sufficient sedation and muscle relaxation, the patient was restimulated at a therapeutic dose also in this session.

Magnetic Resonance Imaging data acquisition to explore anatomical characteristics

More details of the MRI data acquisition and analyses are described elsewhere.[25] Imaging was performed on a 1.5 Tesla Philips Medical Instruments (Best, the

Netherlands) MRI scanner. The scanning protocol included a high-resolution T_1-weighted image and a FLuid Attenuated Inverse Recovery (FLAIR) image. Structural MRI analyses were performed using the Oxford Centre for Functional MRI of the Brain Software Library (FSL) tools (http://www.fmrib.ox.ac.uk/fsl/). After visually checking for the presence of (motion) artifacts, brains were extracted and masks for white matter hyperintensities (WMH) were created manually using FLAIR. Each brain-extracted T_1-weighted image was segmented into partial volume maps of total cerebrospinal fluid (CSF), total gray matter and total white matter, and total WMH. All segmentations were visually inspected and showed no problems during the analysis. Volumes of total CSF, total gray and white matter, and total WMH were obtained in milliliters (mL).

Analysis of data

Data are presented as means ± standard deviations (SD), medians and interquartile ranges (IQR), or numbers and percentages when appropriate. Differences between the in- and excluded group were compared using t-tests for normally distributed variables (age and MADRS score), Mann-Whitney U tests for non-normally distributed continuous variables (CIRS score and baseline MMSE score), and chi-square tests for categorical variables (sex and diagnosis categories). Main outcome was effectiveness of ECT as determined by the post-ECT MADRS score. Response to ECT was defined as 50% or greater decrease of the MADRS score after the ECT course compared to baseline, and complete remission as the MADRS score 10 or less at endpoint. In addition, cognitive functioning as determined by the MMSE score after the ECT course was a main outcome variable.

Several groups were compared using (paired and unpaired) t-tests for continuous variables, and Wilcoxon signed ranks tests and Mann-Whitney U tests for nonnormally distributed variables. To explore whether patient, treatment and anatomical characteristics were predictive of ECT effectiveness and cognition after ECT, first univariate regression analyses, adjusted for the baseline MADRS scores and MMSE scores, respectively, were performed with the post-ECT MADRS and MMSE scores as dependent variables. Because the distribution of the MMSE scores were negatively skewed (because of the ceiling effect of 30), they were natural log transformed (i.e., -ln[31-MMSE score]) to obtain a near-normal distribution.[29] Patients' characteristics (sex, age, CIRS score, diagnostic categories), treatment characteristics (previous ECT course[s], use of concomitant pharmacotherapy and the level of IST), and anatomical characteristics (z-scores of total volumes of CSF, gray matter, white matter and WMH, respectively) were entered as independent variables. The variable 'level of IST' was adjusted for age and electrode placement because of their known associations.[26] Preliminary analyses were

conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity and homoscedasticity. Next, only variables showing $P<0.10$ in these univariate analyses were entered in an overall multivariate analysis, adjusted for age, sex and baseline MADRS and MMSE scores, to explore whether they were independent predictors for the post-ECT MADRS and MMSE scores. In the multivariable analysis of post-ECT MMSE score, adjustment for electrode placement at the first ECT session was performed as well because the level of IST was entered as independent variable and is confounded by electrode placement.[26] All tests were two-sided, with $P<0.05$ denoting statistical significance, and were analyzed using SPSS for Windows (version 18.0; SPSS Inc., Chicago, Illinous, USA).

Results

Patient, treatment and anatomical MRI characteristics

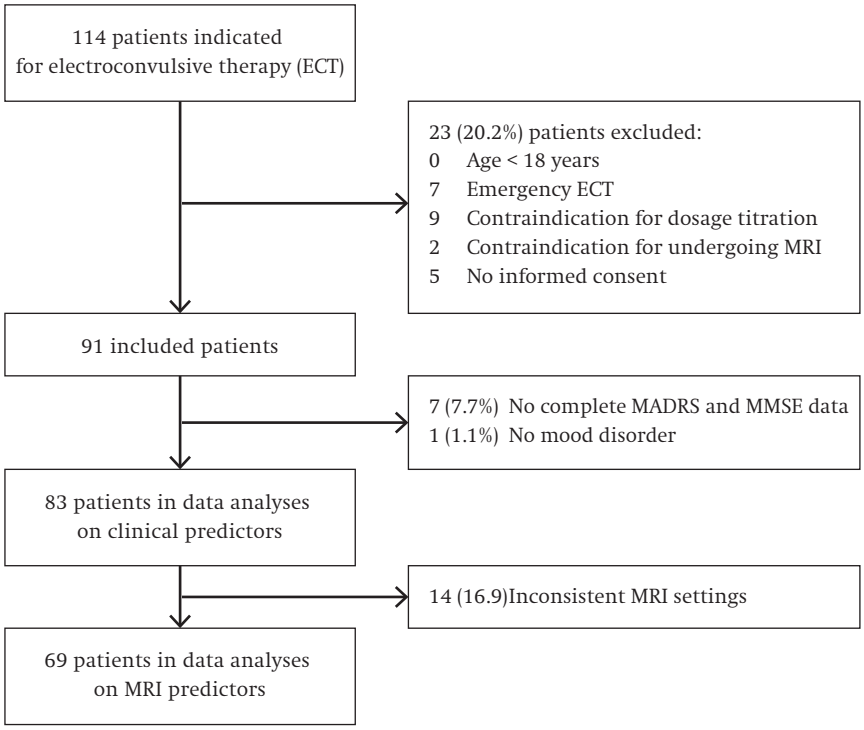
Of 114 patients indicated for ECT, 18 had to be excluded and 5 patients did not give written informed consent (Figure 1). Some baseline (n=2) and post-ECT measurements (n=5) of MADRS and MMSE scores were missing, one patient did not have a mood disorder, and in 14 head MRI scans, different settings of scanning parameters had been used. Therefore, of 83 (73%) patients, the patients' and treatment characteristics could be entered in the analyses, and of 69 (61%) patients, the anatomical MRI characteristics could be entered in the analyses. The excluded patients did not differ from the study group regarding mean age (P=0.20), sex (P=0.66), and mean MADRS score at baseline (P=0.56), although the excluded group of patients showed lower median MMSE score at baseline (P=0.03), higher median CIRS score (P=0.02), and comprised catatonic patients ($P<0.001$).

In Table 1, patient (n=83), treatment (n=83) and anatomical (n=69) characteristics are summarized. Mean age ± SD was 59.2±15.3 years, 39% was composed of men (n=32), and median CIRS score was 21 (IQR, 20-23). All patients were depressed (16% [n=13] bipolar depression), and most of them used concomitant medications (antipsychotics in 66% [n=55]). Thirty percent (n=25) had had ECT. Initial ST was 62.2±44.8 mC, 30% (n=25) of the patients started the ECT course with BL electrode placement, and 37% (n=31) switched electrode placement from initially RUL to BL during the course.

Outcome of ECT

In total, a mean ± SD of 17.4±7.4 ECT sessions was administered to the patients during a completed ECT course (Table 2). Patients who changed electrode placement (n=31) from RUL to BL during the ECT course were treated with more sessions

Figure 1 Flow diagram showing the patient selection process



MRI=magnetic resonance imaging

(*P*<0.001). After the ECT course, in the total group, the mean MADRS score was significantly lower than pre-ECT (*P*<0.001) and decreased with mean ± SD of 22.8±12.7 points. Patients who started ECT with RUL (n=27) and BL (n=25) electrode placement, as well as patients who changed from RUL in BL during the ECT course (n=31) showed significantly lower MADRS scores after ECT. Moreover, patients who changed electrode placement showed a significantly higher mean post-ECT MADRS score than those who did not change.

The bipolar depressed patients (n=13) showed a higher median post-ECT MMSE score (30; IQR, 28.5-30) than the unipolar patients (n=70; median 28; IQR, 26.8-29; Mann-Whitney U Test, 620.5; n=83; *P*=0.03), but did not differ regarding mean age (*P*=0.44), MADRS score at baseline (*P*=0.70) and after ECT (*P*=0.70), MMSE score at baseline (*P*=0.97), IST level (*P*=0.75), electrode placement (*P*=0.75), and mean total

Table 1 Patient, treatment and anatomical characteristics at baseline of patients (n=83) treated with electroconvulsive therapy (ECT)

Patients' characteristics	**Mean ±SD*; n (%); or median; IQR****
Male gender	32 (38.6)
Age, in years	59.2±15.3
Modified Cumulative Illness Rating Scale score	21; 20-23
Diagnostic category, according to axis 1 of DSM-IV-TR^:	
Depressive disorder without psychotic features	47 (56.6)
Depressive disorder with psychotic features	23 (27.7)
Bipolar disorder, depressive episode	13 (15.7)
MADRS*** score at baseline	36.1±8.6
MMSE**** score at baseline	28; 26-29
Treatment characteristics	
Had ECT before	25 (30.1)
Use of seizure threshold influencing concomitant pharmacotherapy:	
Benzodiazepines	51 (61.4)
Anti-epileptics	7 (8.4)
Antidepressants	50 (60.2)
Antipsychotics	55 (66.3)
Electrode placement is bifrontotemporal at first titration session	25 (30.1)
Initial seizure threshold, in milliCoulombs	62.2±44.8
Anatomical MRI# characteristics, in milliliters (n=69)	
Intracranial volume, including cerebrospinal fluid	1458±142
Total volume of cerebrospinal fluid	376±45
Total volume of gray matter	538±61
Total volume white matter	544±62
Total volume of white matter hyperintensities	3.0; 1.1-9.8

*standard deviation; **interquartile range; ^Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; ***Montgomery-Åsberg Depression Rating Scale; ****Mini-Mental State Examination; #Magnetic Resonance Imaging.

Table 2 Outcome measurements of patients (n=83) treated with right unilateral (RUL) and bifrontotemporal (BL) electroconvulsive therapy (ECT)

Group	n	Total number of ECT sessions	*P*-value	MADRS* score			MMSE** score		
				Pre-ECT	Post-ECT	*P*-value	Pre-ECT	Post-ECT	*P*-value
All patients	83	17.4±7.4		36.1±8.6	13.3±9.8	<0.001†	28; 26-29	29; 27-30	0.11††
Start with RUL	27	13.7±7.3	0.16‡	35.8±9.0	9.1±7.1$	<0.001†	28; 26-29	29; 27-30	0.02††
Start with BL	25	15.6±5.8		38.0±8.6	10.4±9.0	<0.001†	27; 25-29.5	28; 25-29	0.13††
Change in BL during course	31	22.0±6.4	<0.001‡‡	34.8±8.1	19.3±9.7$	<0.001†	29; 27-30	28; 27-29	0.51††
Unipolar depression	70	17.5±7.6	nsº	35.9±8.4	13.5±9.8	nsº	28; 25.8-29	28; 26.8-29	0.03º
Bipolar depression	13	16.9±6.5		36.9±9.7	12.3±10.5		28; 26-29.5	30; 28.5-30	
Nonpsychotic depression	60	17.6±7.1	nsºº	35.1±8.3	14.4±10.3	nsºº	29; 27-29.8	29; 28-30	0.01ºº
Psychotic depression	23	16.8±8.2		38.7±8.8	10.5±7.9		26; 25-27	27; 24-29	

*Montgomery-Åsberg Depression Rating Scale; **Mini-Mental State Examination; †Paired-samples tests used for comparing pre- and post-ECT scores; ††Wilcoxon signed ranks tests used for comparing pre- and post-ECT scores; ‡Comparing the patients who started with RUL and BL using t-test; $Comparing post-ECT MADRS scores of patients who did not (n=27; 9.1±7.1) and who did (n=31; 19.3±9.7) change electrode placement during the ECT course using t-test showed *P*<0.001; ‡‡Comparing patients who did not (n=52; 14.7±6.6) and who did (n=31; 22.0±6.4) change electrode placement during the ECT course using t-test; ºns= not significant, comparing unipolar and bipolar depressed patients; ººComparing nonpsychotic and psychotic patients.

ECT sessions (*P*=0.81). In addition, bipolar patients used concomitant antiepileptics more often (*P*=0.01) and antidepressants less often (*P*=0.02) compared to unipolar depressed patients.

Seventy percent (n=57) of the patients responded to ECT, and 48% (n=40) reached complete remission. In the total group, median post-ECT MMSE score was 29 (IQR, 27-30) and did not differ from the pre-ECT median MMSE score (*P*=0.11). In RUL-treated patients, the post-ECT median MMSE score was significantly higher than before ECT (*P*=0.02).

Predictors of post-ECT MADRS score

Using the multivariate regression analysis, with adjustment for age, sex and baseline MADRS score (Table 3), thereby entering only variables with *P*<0.1 at the first univariate analyses, lower post-ECT MADRS score (meaning better effectiveness) was independently predicted by a diagnosis of depressive disorder with psychotic features (β=-0.25; *P*=0.04; Figure 2A) and having had previous ECT course(s) (β=-0.35; *P*=0.003; Figure 2A). Baseline MMSE score was not associated with post-ECT MADRS score (*P*=0.55). None of the anatomical MRI characteristics were individually predictive of the post-ECT MADRS score and therefore not entered into the final multivariate analysis.

Predictors of post-ECT MMSE score

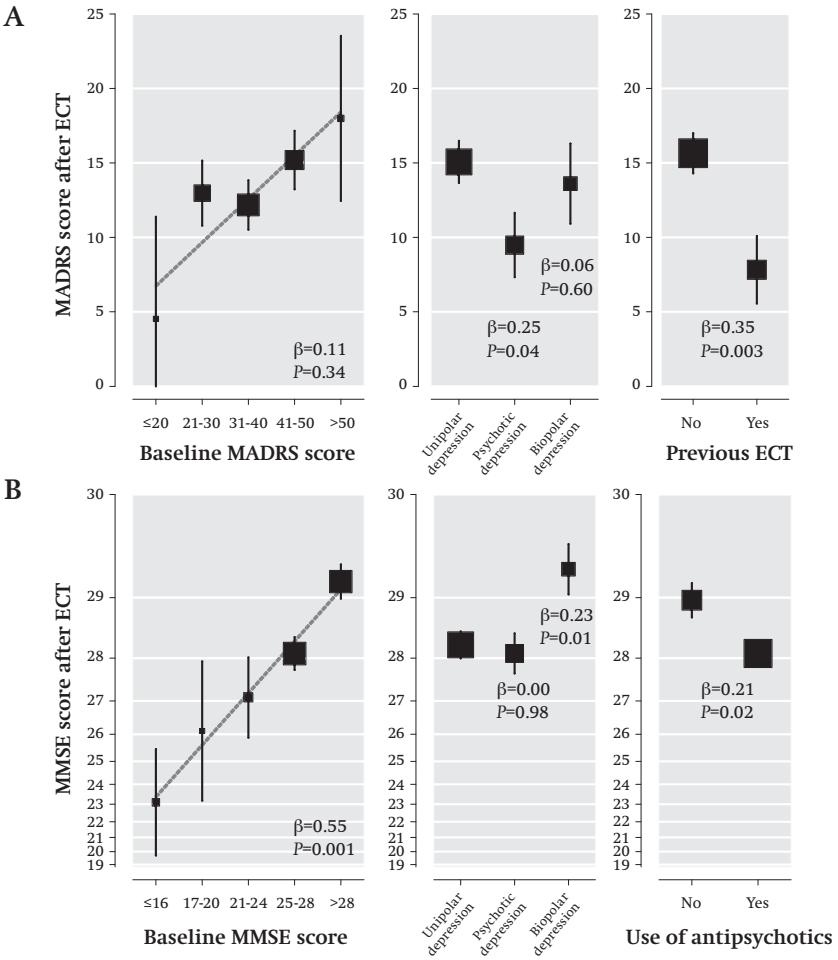
As expected, post-ECT MADRS was inversely associated with the post-ECT MMSE score (β=-0.20; *P*=0.02). Adjusted for age and sex, a higher baseline MMSE score was associated with a higher post-ECT MMSE score (β=0.55; *P*<0.001; Figure 2B). Using multivariable regression analysis (Table 4), with adjustment for age, sex, electrode placement and baseline MMSE, thereby entering only variables with *P*<0.1 at the first univariate analyses, higher post-ECT MMSE score (meaning better cognitive functioning) was independently predicted by having a bipolar depression at baseline (β=0.23; *P*=0.01; Figure 2B). Concomitant antipsychotics use during the ECT course was an independent predictor of a lower post-ECT MMSE score (β=-0.21; *P*=0.02; Figure 2B), meaning more cognitive dysfunction. In a sensitivity analysis, we additionally adjusted for the pre- and post-ECT MADRS scores, yielding similar results. The post-ECT MADRS score seemed to be a confounder for the post-ECT MMSE score (β=-0.20; *P*=0.02).

Table 3 Multivariate regression analyses to detect baseline patient, treatment and anatomical predictors of the Montgomery-Åsberg Depression Rating Scale (MADRS) score after electroconvulsive therapy (ECT) in 83 patients

	Univariate correlates of MADRS score at endpoint, adjusted for MADRS score at baseline		Multivariate correlates of MADRS at endpoint, only variable with *P*<0.1 in univariate analyses and adjusted for MADRS score at baseline, age and sex	
Patient variables	β-coefficient	*P*-value	β-coefficient	*P*-value
Male gender	0.07	0.57	0.01	0.93
Age	-0.12	0.30	0.04	0.71
Cumulative Illness Rating Scale score	0.08	0.50		
Diagnostic category, according to axis 1 of DSM-IV-TR[$] :				
Depressive disorder with psychotic features	-0.23	0.06	-0.25	**0.04**
Bipolar disorder, depressive episode	-0.11	0.35	-0.06	0.60
MMSE[*] score at baseline	0.07	0.55		
Treatment characteristics				
Had ECT before	-0.33	**0.002**	-0.35	**0.003**
Use of seizure threshold influencing concomitant pharmacotherapy:				
Benzodiazepines	-0.07	0.56		
Anti-epileptics	-0.05	0.65		
Antidepressants	-0.06	0.57		
Antipsychotics	0.04	0.72		
Initial seizure threshold	-0.15^	0.33		
Z-scores of anatomical MRI characteristics (n=69)				
Intracranial volume, including cerebrospinal fluid	0.05	0.69		
Volume of total cerebrospinal fluid	0.02	0.90		
Volume of gray matter	0.12	0.35		
Volume of white matter	-0.10	0.92		
Volume of white matter hyperintensities	-0.02	0.85		

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; [*]Mini-Mental State Examination (lnMMSE at baseline was used in analyses); ^also adjusted for electrode placement

Figure 2 Relationship between 83 patients who underwent electroconvulsive therapy (ECT), and (A) scores on the Montgomery-Åsberg Depression Rating Scale (MADRS) and (B) Mini-Mental State Examination (MMSE), with their baseline scores, diagnostic category, previous treatment with ECT and concomitant use of antipsychotics, respectively *



*Data are presented as adjusted means by ANCOVA, adjusted for (A) sex, age, baseline MADRS score, diagnostic category, and previous ECT, and (B) age, baseline MMSE score, diagnostic categories, IST level, and the use of antipsychotics when appropriate. The size of each square is proportional to the number of patients. Vertical lines indicate standard errors. Beta-coefficients and *P*-values are calculated by linear regression analysis.

Table 4 Multivariate regression analyses to detect baseline patient, treatment and anatomical predictors of the score of the Mini-Mental State Examination (MMSE)*

	Univariate correlates of MMSE score at endpoint, adjusted for MMSE score at baseline		Multivariate correlates of MMSE score at endpoint, showing *P*<0.1 in univariate analyses and adjusted for MMSE at baseline, age, sex and electrode placement	
Patient variables	β-coefficient	P-value	β-coefficient	*P*-value
Male gender	0.07	0.43	0.07	0.40
Age	-0.13	0.20	-0.18	0.09
Cumulative Illness Rating Scale score	-0.04	0.67		
Diagnostic category, according to axis 1 of DSM-IV-TR^ :				
Depressive disorder with psychotic features	-0.07[$]	0.50	0.003	0.98
Bipolar disorder, depressive episode	0.22[$]	**0.02**	0.23	**0.01**
MADRS** score at baseline	0.15	0.10		
Treatment characteristics				
Had ECT before	-0.03	0.75		
Use of seizure threshold influencing concomitant pharmacotherapy:				
Benzodiazepines	0.14	0.12		
Anti-epileptics	0.002	0.98		
Antidepressants	0.06	0.51		
Antipsychotics	-0.12	**0.048**	-0.21	**0.02**
Initial seizure threshold	0.27[$$]	**0.03**	0.20	0.09
Z-scores of anatomical MRI characteristics (n=69)				
Intracranial volume, including cerebrospinal fluid	0.16	0.14		
Volume of total cerebrospinal fluid	0.16	0.12		
Volume of gray matter	0.11	0.31		
Volume of white matter	0.13	0.23		
Volume of white matter hyperintensities	-0.15	0.15		

*MMSE scores were transformed in lnMMSE scores owing to nonnormally distribution;**Montgomery-Åsberg Depression Rating Scale; ^Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; [$]also adjusted for MADRS score at endpoint; [$$]also adjusted for known confounders (age and electrode placement)

Discussion

As has been shown before, our prospective study demonstrated that having had ECT before and presence of psychotic depression at baseline were independent predictors of increased effectiveness of ECT. Furthermore, we found that concomitant use of antipsychotics predicted poorer cognitive outcome, whereas a baseline bipolar depression predicted better cognitive outcome after ECT. These findings remained when we additionally adjusted for the severity of residual depressive symptoms.

In line with earlier results,[7] having had ECT course(s) before was a predictor of increased effectiveness. This finding is most probably due to confounding by indication, as a previously positive ECT outcome will increase the chance of being treated with ECT again. In addition, our results confirm earlier findings regarding enhanced effectiveness of ECT in psychotic depressed patients[6] but did not support the previously reported positive association with higher age and concomitant use of antidepressants.[8,9,13] Data about the length of the current depressive episode were not available in a standardized manner and could therefore not be related to effectiveness of treatment. Electroconvulsive therapy was equally effective with regard to depression in bipolar and unipolar patients, as was shown before.[30] Compared to other studies, the average number of total ECT sessions in our study was high.[2] A possible reason for this is that the use of ultra-brief pulse width in the larger group of initially RUL-treated patients caused the longer treatment duration compared to brief pulse BL-treated patients.[23,31]

None of the anatomical head MRI scan variables were predictive of effectiveness of ECT, which contrasts with earlier studies showing poorer outcome of treatment (with antidepressants) in patients with more subcortical gray matter hyperintensities and increased CSF volume.[15,32-34] Because we did not determine separate volumes of the hippocampus and medial temporal lobes, no further comparison with the literature can be made.[16,24]

In clinical practice, cognitive impairment is no contraindication for ECT.[4] Indeed, in our study, the baseline MMSE score was not associated with effectiveness of ECT, meaning that poorer cognitive functioning before ECT did not predict worse effectiveness. Otherwise, a higher MMSE score at baseline strongly predicted better post-ECT cognitive functioning, as has been reported before.[17,20] In the patients exclusively treated with RUL (using stimuli with ultrabrief pulse width) ECT, the median post-ECT MMSE score was one point higher than before ECT, which matches with earlier findings showing less cognitive adverse effects with ultrabrief RUL ECT.[23] That a higher post-ECT MADRS score was associated with a

lower post-ECT MMSE score was probably due to the presence of (residual) depressive symptoms that are associated with (persistent) memory impairment.[35,36] Moreover, due to less clinical response, more total ECT sessions were administered (a median of 21 sessions [IQR, 15.5-24.5] in the group of patients who showed less than 50% decrease of post-ECT MADRS score, compared to a median of 15 sessions [IQR, 10-21] in those who decreased by 50% or greater; P=0.02), as well as more often occurrence of electrode placement switch to BL (68% [n=17] in patients showing less than 50% decrease of post-ECT MADRS score, compared to 23% [n=13] in the better outcome group; P<0.001), which factors both may have led to a lower post-ECT MMSE score.[21]

A diagnosis of bipolar depression unexpectedly predicted better post-ECT cognitive function which, as far as we know, has not been reported before. Besides, the more often use of concomitant antiepileptics and less often use of antidepressants, no differences between the bipolar and unipolar depressed patients were found; especially not regarding the expected predictors of the post-MMSE score age, use of BL electrode placement, and duration of the ECT course.[21,23] Presence of bipolar disorder and the use of lithium and antiepileptics were associated with more cognitive impairment.[37] This remarkable finding is new and should be replicated before drawing further conclusions.

Although psychotic depression predicted better effectiveness of ECT, the consequent use of antipsychotics during the ECT course predicted more cognitive dysfunction. An explanation for this result may be that patients who use antipsychotics during the ECT course might be a distinct group with more severe depression and a probably higher risk for cognitive adverse effects. In addition, the presence of persisting psychotic features or (postictal) delirium may have been the reason for the continuing use of antipsychotics during the ECT course. In general, anticholinergic activity of psychotropic medications negatively affects cognitive functioning, especially in older adults,[38] which may have been another cause of poorer post-ECT cognitive functioning in our study. In addition, antipsychotic medication may have slightly decreased the patients' ST compared to nonusers (without being noticed because of the rather crude titration protocol), resulting in administration of electrical stimuli a little too well above the ST.[39] Because not the absolute electrical stimulus dose but the dose relatively exceeding the ST was suggested to predict cognitive adverse effects of ECT,[40] this may explain more cognitive dysfunction in ECT patients using concomitant antipsychotics. On the other hand, in a few randomized controlled trials no differences were shown in memory effects of ECT between patients with and without concomitant antipsychotics use, but these studies included mainly patients with schizophrenia.[41,42]

Several limitations should be addressed. First, of the 114 patients only, 83 patients (and for the MRI analyses, 69 patients) could be included, limiting the generalizability of our results to all ECT patients because the more cognitively impaired, the more severely somatically ill and the catatonic patients were excluded. Second, mood disorders were classified according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* by at least 2 clinically experienced psychiatrists but not confirmed using a standardized diagnostic instrument, which might have led to less accurate ascertainment of the diagnosis. Third, two thirds of the patients used concomitant psychotropic medication during the ECT course, as was decided on clinical grounds (e.g., to avoid withdrawal symptoms, to reduce psychosis or postictal delirium, or for sedation). Because this concomitant use was only registered for the overall type of medication without controlling for the clinical indication, analysis of the effects of specific types of (antipsychotic) medications and dosage was not possible. Fourth, the MMSE was used to evaluate global cognitive functioning before and after ECT and that we did not examined retrograde amnesia, which is a cognitive dysfunction of more concern in ECT.[17] Finally, the automatic FSL process to estimate the volumes of CSF, gray and white matter, and WMH also had several limitations, which are described elsewhere in more detail;[25] in short, imperfections in the registration and segmentation process may have led to some measurement and systematic error in establishing the separate volumes.

In conclusion, this prospective, observational study confirmed that psychotic depressed patients and those who were previously treated with ECT responded better to ECT. Unexpectedly, having a bipolar depression predicted better cognitive function after ECT, whereas the use of antipsychotics during ECT and the presence of more persistent depressive symptoms following ECT were associated with a poorer cognitive outcome.

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References

(1) Mann JJ. The medical management of depression. N Engl J Med 2005;353:1819-34.
(2) Abrams R. Electroconvulsive Therapy. Fourth edition. New York, NY: Oxford University Press; 2002.
(3) UK ECT Review Group. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. Lancet 2003;361:799-808.
(4) American Psychiatric Association. The Practice of Electroconvulsive Therapy. Second Edition. Washington DC: American Psychiatric Association; 2001.
(5) Swartz CM. Electroconvulsive and neuromodulation therapies. New York, NY: Cambridge University Press; 2009.
(6) Petrides G, Fink M, Husain MM et al. ECT remission rates in psychotic versus nonpsychotic depressed patients: A report from CORE. Journal of ECT S2- Convuls Ther 2001;17:244-53.
(7) Loo CK, Mahon M, Katalinic N, Lyndon B, Hadzi-Pavlovic D. Predictors of response to ultrabrief right unilateral electroconvulsive therapy. J Affect Disord 2011;130:192-7.
(8) Wesson ML, Wilkinson AM, Anderson DN, Cracken CM. Does age predict the long-term outcome of depression treated with ECT? (a prospective study of the long-term outcome of ECT-treated depression with respect to age). Int J Geriatr Psychiatry 1997;12:45-51.
(9) O'Connor MK, Knapp R, Husain M et al. The influence of age on the response of major depression to electroconvulsive therapy: A C.O.R.E. report. Am J Geriatr Psychiatry 2001;9:382-90.
(10) Feske U, Mulsant BH, Pilkonis PA et al. Clinical outcome of ECT in patients with major depression and comorbid borderline personality disorder. Am J Psychiatry 2004;161:2073-80.
(11) Medda P, Perugi G, Zanello S, Ciuffa M, Cassano GB. Response to ECT in bipolar I, bipolar II and unipolar depression. J Affect Disord 2009;118:55-9.
(12) Perugi G, Medda P, Zanello S, Toni C, Cassano GB. Episode length and mixed features as predictors of ECT nonresponse in patients with medication-resistant major depression. Brain Stimul 2012;5:18-24.
(13) Sackeim HA, Dillingham EM, Prudic J et al. Effect of concomitant pharmacotherapy on electroconvulsive therapy outcomes: short-term efficacy and adverse effects. Arch Gen Psychiatry 2009;66:729-37.
(14) McCall WV, Reboussin DM, Weiner RD, Sackeim HA. Titrated moderately suprathreshold vs fixed high-dose right unilateral electroconvulsive therapy: acute antidepressant and cognitive effects. Arch Gen Psychiatry 2000;57:438-44.
(15) Steffens DC, Conway CR, Dombeck CB, Wagner HR, Tupler LA, Weiner RD. Severity of subcortical gray matter hyperintensity predicts ECT response in geriatric depression. J ECT 2001;17:45-9.
(16) Oudega ML, van Exel E., Wattjes MP et al. White matter hyperintensities, medial temporal lobe atrophy, cortical atrophy, and response to electroconvulsive therapy in severely depressed elderly patients. J Clin Psychiatry 2011;72:104-12.
(17) Sobin C, Sackeim HA, Prudic J, Devanand DP, Moody BJ, McElhiney MC. Predictors of retrograde amnesia following ECT. Am J Psychiatry 1995;152:995-1001.
(18) Semkovska M, McLoughlin DM. Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. Biol Psychiatry 2010;68:568-77.
(19) Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.
(20) Hausner L, Damian M, Sartorius A, Frolich L. Efficacy and cognitive side effects of electroconvulsive therapy (ECT) in depressed elderly inpatients with coexisting mild cognitive impairment or dementia. J Clin Psychiatry 2011;72:91-7.
(21) Sackeim HA, Prudic J, Fuller R, Keilp J, Lavori PW, Olfson M. The cognitive effects of electroconvulsive therapy in community settings. Neuropsychopharmacology 2007;32:244-54.
(22) Tielkes CE, Comijs HC, Verwijk E, Stek ML. The effects of ECT on cognitive functioning in the elderly: a review. Int J Geriatr Psychiatry 2008;23:789-95.
(23) Sackeim HA, Prudic J, Nobler MS et al. Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. Brain Stimul 2008;1:71-83.

(24) Lekwauwa RE, McQuoid DR, Steffens DC. Hippocampal Volume as a Predictor of Short-Term ECT Outcomes in Older Patients with Depression. Am J Geriatr Psychiatry 2005;13:910-3.
(25) Van Waarde JA, Van Oudheusden LJB, Tonino BAR, Van der Wee NJA, Verwey B, Van der Mast RC, Giltay EJ. MRI characteristics predicting seizure threshold in patients undergoing electroconvulsive therapy: a prospective study. Brain Stimul 2013; DOI 10.1016/j.brs.2012.12.003
(26) Van Waarde JA, Van Oudheusden LJB, Verwey B, Giltay EJ, Van der Mast RC. Clinical predictors of seizure threshold in electroconvulsive therapy: a prospective study. Eur Arch Psychiatry Clin Neurosci 2013;263:167-175.
(27) Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382-9.
(28) Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc 1968;16:622-6.
(29) Sanders JB, Bremmer MA, Comijs HC, Deeg DJ, Lampe IK, Beekman AT. Cognitive functioning and the natural course of depressive symptoms in late life. Am J Geriatr Psychiatry 2011;19:664-72.
(30) Dierckx B, Heijnen WT, Van den Broek WW, Birkenhäger TK. Efficacy of electroconvulsive therapy in bipolar versus unipolar major depression: a meta-analysis. Bipolar Disord 2012;14:146-50.
(31) Loo CK, Sainsbury K, Sheehan P, Lyndon B. A comparison of RUL ultrabrief pulse (0.3 ms) ECT and standard RUL ECT. Int J Neuropsychopharmacol 2008;11:883-90.
(32) Hickie I, Scott E, Mitchell P, Wilhelm K, Austin MP, Bennett B. Subcortical hyperintensities on magnetic resonance imaging: clinical correlates and prognostic significance in patients with severe depression. Biol Psychiatry 1995;37:151-60.
(33) Sneed JR, Culang-Reinlieb ME, Brickman AM et al. MRI signal hyperintensities and failure to remit following antidepressant treatment. J Affect Disord 2011;135:315-20.
(34) Cardoner N, Pujol J, Vallejo J et al. Enlargement of brain cerebrospinal fluid spaces as a predictor of poor clinical outcome in melancholia. J Clin Psychiatry 2003;64:691-7.
(35) Burt DB, Zembar MJ, Niederehe G. Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. Psychol Bull 1995;117:285-305.
(36) Brodaty H, Berle D, Hickie I, Mason C. "Side effects" of ECT are mainly depressive phenomena and are independent of age. J Affect Disord 2001;66:237-45.
(37) Holmes MK, Erickson K, Luckenbaugh DA et al. A comparison of cognitive functioning in medicated and unmedicated subjects with bipolar depression. Bipolar Disord 2008;10:806-15.
(38) Campbell N, Boustani M, Limbil T et al. The cognitive impact of anticholinergics: a clinical review. Clin Interv Aging 2009;4:225-33.
(39) Pisani F, Oteri G, Costa C, Di RG, Di PR. Effects of psychotropic drugs on seizure threshold. Drug Saf 2002;25:91-110.
(40) Sackeim HA, Devanand DP, Prudic J. Stimulus intensity, seizure threshold, and seizure duration: impact on the efficacy and safety of electroconvulsive therapy. Psychiatr Clin North Am 1991;14:803-43.
(41) Braga RJ, Petrides G. The combined use of electroconvulsive therapy and antipsychotics in patients with schizophrenia. J ECT 2005;21:75-83.
(42) Haskett RF, Loo C. Adjunctive psychotropic medications during electroconvulsive therapy in the treatment of depression, mania, and schizophrenia. J ECT 2010;26:196-201.