White Matter Hyperintensities, Medial Temporal Lobe Atrophy, Cortical Atrophy, and Response to Electroconvulsive Therapy in Severely Depressed Elderly Patients

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Objective: Electroconvulsive therapy (ECT) is a valuable treatment option in severely depressed elderly patients. Structural abnormalities in the brain, such as white matter hyperintensities, medial temporal lobe atrophy (MTA), or global cortical atrophy, may influence therapeutic response. The respective value of these factors in response prediction is unclear.

Method: In a naturalistic clinical cohort of 81 elderly patients diagnosed with *DSM-IV* major depressive disorder, magnetic resonance imaging (MRI) was recorded and rated before ECT treatment. The study was conducted at the clinic for Geriatric Psychiatry of the VU University Medical Center/Stichting Buitenamstel Geestgronden, Amsterdam, The Netherlands, over a 5-year period (2001–2006). Severity of depressive symptoms was measured by using the Montgomery-Asberg Depression Rating Scale (MADRS). Response to ECT was defined as a decrease of at least 50 percent on the MADRS, and remission was defined as a score below 10 points on the MADRS.

Results: Patients with moderate or severe MTA had a lower mean percentage decrease in MADRS scores after ECT (37.9% in those with MTA, compared to 66.2% in those without MTA, $P = .008$). Patients without MTA had a 3 times greater chance of remitting from their depression compared to patients with moderate or severe MTA, ie, the hazard ratio for remission was 3.22 (95% CI, 1.30 to 7.69, $P = .01$). In contrast, no differences in change in MADRS scores were found for white matter hyperintensities or global cortical atrophy.

Conclusions: Medial temporal lobe atrophy—not white matter hyperintensities or global cortical atrophy—contributes to poor response to ECT in severely depressed elderly patients. These findings suggest that assessment of MTA in severely depressed elderly patients may be useful in the prediction of potential ECT response.

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Electroconvulsive therapy (ECT) is a valuable treatment option for severe depression in the elderly.[1] The efficacy and safety of ECT have been studied extensively in depressed elderly patients. The results show short-term remission rates of around 70% in patients aged 60 years and over.[2] Despite this high success rate, a number of depressed elderly patients do not respond to ECT. As structural brain abnormalities are more common in late-life depression, it has been suggested that white matter hyperintensities could contribute to poor therapeutic response.[3]

White matter hyperintensities caused by an atherosclerotic process in small vessels of the brain[4] are found more often in depressed elderly patients than in younger depressed patients on magnetic resonance imaging (MRI). These white matter hyperintensities have been associated with subtle cognitive deficits, apathy, and depressive symptoms.[5,6] The *subcortical ischemic depression* hypothesis states that vascular lesions in mood-regulating neural circuits contribute to the development of and may influence the course of late-life depression.[7] In line with this theory, 2 studies found less favorable responses in patients with vascular lesions treated with antidepressant medication.[8,9] In contrast, another MRI study found no difference in response to medication between patients with and without MRI-confirmed vascular brain changes.[10] Two small clinical studies with, respectively, 20 and 29 patients found no significant association between white matter hyperintensities and response to ECT.[8,11] A third study with 41 depressed elderly patients found that presence of white matter hyperintensities was associated with a poor response to ECT.[3]

It has been established that the medial temporal lobe plays an important role in memory functioning and affect regulation, which are both disturbed in depressed patients.[12] One observational study showed an association between medial temporal lobe atrophy (MTA) and time to remission with pharmacotherapy in depressed elderly patients.[13] The association between MTA and response to ECT has not been assessed adequately,[14] nor have there been any studies in large clinical cohorts on white matter hyperintensities and the effect of ECT in late-life depression.

Modifying effects of structural brain abnormalities on the outcome of ECT may be important in discussing the odds of recovery with patients and relatives. We designed a naturalistic cohort study to assess whether white matter

hyperintensities, MTA, or global cortical atrophy affects the short-term response to ECT in severely depressed elderly patients. On the basis of the subcortical ischemic depression hypothesis, we expected patients with white matter hyperintensities to have a poorer response to ECT. Moreover, based on data from 1 observational pharmacotherapeutic study,[13] we also expected patients with MTA to have a poorer response to ECT.

METHOD

Study Design

This naturalistic study of ECT in depressed elderly was conducted at the clinic for Geriatric Psychiatry of the VU University Medical Center/Stichting Buitenamstel Geestgronden, Amsterdam, The Netherlands. Inclusion criteria consisted of being 55 years of age and over, being referred for ECT, and a diagnosis of unipolar depression according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*), criteria. Patients with a clinical diagnosis of dementia were excluded. Over a 5-year period (2001–2006), 97 patients, diagnosed with *DSM-IV* unipolar depression were referred for ECT. Sixteen patients were excluded for the current analysis: 3 were diagnosed with dementia and unipolar depression, and MRI data were unavailable for 13 patients. A total of 81 patients provided written informed consent to participate. Patients were recruited from referrals for ECT in the catchment area (n = 30, 37%) and tertiary referrals from throughout The Netherlands (n = 51, 63%). A diagnosis of depression according to *DSM-IV* criteria was confirmed by 2 experienced geriatric psychiatrists (M.L.S., P.E.), who also examined all patients with respect to possible dementia, an exclusion criterion for this study. The Institutional Review Board of the VU University Medical Center approved the study.

Administration of ECT

Patients received a course of twice-weekly ECT, according to European standards.[15] A course started preferably with right unilateral stimuli in order to diminish the effect of ECT on cognition. All treatments were administered using the Thymatron System IV (Somatics, LLC, Lake Bluff, Illinois; maximum energy 200%, 1008 mCoulombs) using an age dosing protocol. Age determined the energy supplied, eg, a 75-year-old patient would receive right unilateral ECT at a dosage of 75%, corresponding with 378 mCoulombs. When treated bilaterally (bitemporal only), half of this dosage was considered adequate.[16] A motor seizure of less than 20 seconds was considered inadequate and the dose was accordingly raised.

Due to acute life-threatening conditions, 2 patients were bilaterally treated from the start of the ECT course. During the course, 18 of the 79 patients who started with unilateral ECT were switched to bilateral ECT. Switching to bilateral ECT was applied when the clinical condition worsened or after 6 unilateral treatments without effect. Clinical evaluation was carried out weekly, and worsening was determined by debilitating psychotic features, increased suicidal thoughts, dehydration or weight loss. ECT treatment was stopped if patients remitted or showed no further improvement in clinical condition during the last 2 weeks of ECT treatments. The number of ECT treatments was decided by the treating psychiatrist on clinical grounds. Psychotropic medications, ie, benzodiazepines and antidepressants, were tapered off within 2 weeks before starting ECT. Antipsychotic medications were allowed when clinically indicated.

Clinical Evaluations

The Montgomery-Asberg Depression Rating Scale (MADRS)[17] was completed by the same research nurse for all patients before the first ECT, every 1 to 2 weeks during ECT, and 1 week after completion of ECT. The trained research nurse was blinded to MRI-rating scale scores.

Patients were defined as initial responders if the MADRS score decreased by at least 50% from pretreatment during the course of ECT.[18] Patients were defined as remitters if the MADRS score decreased below 10 points after completion of ECT.[13] Mini-Mental State Examination (MMSE) scores were completed for all patients within 5 days before starting ECT and 1 week after the last ECT session.

Pharmacotherapy resistance was defined as not responding to 2 different types of antidepressive medication, (ie, selective serotonin reuptake inhibitors and tricyclic antidepressants or monoamine oxidase inhibitors) before ECT. The index episode was defined as the period in months from the start of the depressive episode until the first ECT session.

Magnetic Resonance Imaging

All patients underwent MRI scanning following a standard protocol, during which 0.5-T or 1.5-T scanners were used. Series included axial T2-weighted images, axial fluid-attenuated inversion recovery (FLAIR) images, and coronal 3D T1 sequence images. T1 images could not be obtained for 5 patients, T2 images could not be obtained for 3 patients, and FLAIR images were missing for 1 patient.

Visual Rating

We used validated visual rating scales, with good interobserver reliability, to determine white matter hyperintensities, MTA, and cortical atrophy.[19–23]

We applied the visual rating scales of Fazekas[19] and the Age-Related White Matter Changes (ARWMC) scale[20] to the FLAIR images. The Fazekas scale rates the white matter hyperintensities from 0 (no structural abnormalities) to 3 (severe structural abnormalities). For the analysis, the Fazekas scores were ranked in 3 groups; 0 = no structural abnormalities, 1 = moderate structural abnormalities, and ≥ 2 = severe structural abnormalities. The ARWMC scale was used to score the white matter hyperintensities in 10 different brain regions, the score per region ranging from 0 to 3. The scores of all regions were summed and ranked in

tertiles. Both the Fazekas scale and the ARWMC scale have been validated and compared in large studies.[19–22]

The MTA was rated with a validated visual rating scale[23] on the coronal 3-dimensional T1 images. The MTA scale ranges from 0 to 4, and it was applied to the left and right medial temporal lobe. The score of the left and right lobe were summed and divided by 2. Three groups were identified; 0 = no structural abnormalities, 1 = moderate structural abnormalities and ≥ 2 = severe structural abnormalities. The MTA scale has been validated in an interobserver study of 100 magnetic resonance images.[24]

Cortical atrophy was rated with the Global Cortical Atrophy (GCA) rating scale (range 0 to 3) on the FLAIR images.[25] For the analysis, 3 groups were identified; 0 = no structural abnormalities, 1 = moderate structural abnormalities, and ≥ 2 = severe structural abnormalities.[26]

All ratings in this study were performed by a neuroradiologist (M.P.W.) who was blind to clinical information.

Statistical Methods

Demographic and clinical characteristics, including MRI results and effect of ECT, are reported as means with standard deviations. Since MRI and MMSE results were skewed, these results are presented as medians with interquartile ranges.

Linear regression analyses assessed the association between structural abnormalities in the brain, as defined by the rating scales, and the decrease in MADRS scores after ECT, defined in terms of percentages. All analyses were adjusted for age, sex, and initial MADRS scores. Cox regression models were used to test for differences in time to remission and initial response between patients dichotomized for structural abnormalities in the brain. An additional Cox regression analysis was performed that was adjusted for age, sex, and initial MMSE score.

Finally, we refrained from Bonferroni corrections, since there was only a small chance (1 of 20) that type I errors due to multiple comparisons would occur, and the chance of making type II errors would be increased with Bonferroni corrections.[27] The data were analyzed using SPSS version 15.0 (SPSS Inc, Chicago, Illinois).

RESULTS

Characteristics

Eighty-one patients consented and participated. In the study group (Table 1), 39 patients (48.1%) achieved remission, as defined by a MADRS score below 10 points, after ECT. Sixty patients (74.1%) had a response, defined by a decrease in MADRS score of at least 50% from the initial score, to ECT during treatment. Remitters and nonremitters had a mean age, respectively, of 74.0 and 73.3 years ($P = .7$) at study entry. The duration of treatment was similar for remitters and nonremitters (47.5 vs 50.0 days, respectively; $P = .7$), as were index episode and pharmacotherapy resistance (8.9 vs 11.5 months, respectively; $P = .5$, and 16 vs 11 patients, $P = .16$). There were no significant differences in initial median MMSE scores (28 vs 27 points, respectively; $P = .9$), sex (64.1% male vs 59.5% female patients, respectively; $P = .7$), or mean education levels (11.7 vs 11.9 years of education, respectively; $P = .7$) between remitters and nonremitters. However, the MMSE scores after the ECT course differed significantly between groups, 29 vs 27 points, respectively; ($P = .05$). Finally, we determined other known risk factors for remission rate. The percentage of subjects with pharmacotherapy resistance before ECT was not significantly higher in those who came from tertiary referral than from those who came from within the catchment area (39% vs 27%, respectively; $P = .3$, χ^2). The percentage of subjects who achieved remission within the catchment area of our clinic was not significantly higher compared to those who came from tertiary referral (60% vs 41%, respectively; $P = .09$, χ^2).

Table 1. Demographic and Clinical Characteristics of Depressed Elderly Patients Treated With Electroconvulsive Therapy (ECT) (n = 81)

Characteristic	Elderly Patients With Depression (n = 81)
Demographic characteristics	
Age, mean ± SD, y	74.0 ± 7.8
Female, n (%)	50 (61.7)
Years of education, mean ± SD	11.8 ± 2.7
Clinical characteristics	
Pharmacotherapy resistance before ECT, n (%)[a]	27 (33.3)
Index episode, mean ± SD, mo[b]	10.2 ± 12.0
Late-onset depression, n (%)	48 (59.3)
Psychotic depression, n (%)	34 (42.0)
Magnetic resonance imaging	
Medial temporal lobe atrophy score (median, IQR)	1.0 ± 1.5
Age-Related White Matter hyperintensities score (median, IQR)	5.0 ± 6.0
Fazekas score (median, IQR)	1.0 ± 1.0
Global Cortical Atrophy score (median, IQR)	1.0 ± 1.0
Effect of ECT	
No. of ECT treatments, mean (range)	12.8 (2–39)
MADRS score before ECT, mean ± SD	33.6 ± 9.6
MADRS score after ECT, mean ± SD	12.2 ± 9.6
Absolute decrease in MADRS score, mean points ± SD	−21.4 ± 13.3
Relative decrease in MADRS score, mean % ± SD	−60.8% ± 33.5
Remission after ECT, n (%)[c]	39 (48.1)
Initial response to ECT, n (%)[d]	60 (74.1)
MMSE score before ECT (median, IQR)	27 ± 5.0
MMSE score after ECT (median, IQR)	28 ± 4.0

[a]Pharmacotherapy resistance is defined as not responding to 2 different types of antidepressive medication before ECT.
[b]Index episode is defined as the period in months from the start of the depressive episode until the first ECT session.
[c]Remission after ECT is defined as a MADRS score lower than 10 points after ECT.
[d]Initial response to ECT is defined as 50% improvement or more in MADRS scores from baseline during a course of ECT.
Abbreviations: iqr = interquartile range, MADRS = Montgomery-Asberg Depression Rating Scale, MMSE = Mini-Mental State Examination.

Outcome of ECT and MRI Characteristics

We assessed the association between white matter hyperintensities, MTA, general cortical atrophy, and response to ECT in depression by using a linear regression model. Table 2 shows the mean percentage decrease in MADRS scores for the 3 strata of increasing structural brain abnormalities.

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Table 2. Percentage Decrease in MADRS Score After Electroconvulsive Therapy (ECT), Dependent on Medial Temporal Atrophy, White Matter Hyperintensities, and Global Cortical Atrophy[a,b]

Variable	Score of Structural Brain Abnormalities[c]			*P* Value for Trend
	0	1	≥2	
Medial Temporal Lobe Atrophy scale				
No. of patients[d] (% of total)	55 (67.9)	15 (18.5)	6 (7.4)	
No. of ECT sessions, mean (95% CI)	12.2 (11.4 to 12.9)	13.5 (12.2 to 14.9)	18.5 (13.7 to 23.4)	.06
Percentage decrease in MADRS score, mean (95% CI)	−66.2 (−69.7 to −62.6)	−53.4 (−57.0 to −49.7)	−37.9 (−47.2 to −28.6)	.008
Age-Related White Matter Changes scale				
No. of patients[d] (% of total)	59 (72.8)	12 (14.8)	7 (8.6)	
No. of ECT sessions, mean (95% CI)	13.2 (12.4 to 13.9)	12.6 (11.0 to 14.2)	10.8 (7.6 to 14.0)	.6
Percentage decrease in MADRS score, mean (95% CI)	−59.9 (−62.9 to −56.8)	−63.6 (−67.9 to −59.2)	−62.6 (−69.5 to −55.8)	.9
Fazekas scale				
No. of patients[d] (% of total)	8 (9.9)	46 (56.8)	24 (29.6)	
No. of ECT sessions, mean (95% CI)	12.0 (9.1 to 14.9)	13.3 (12.4 to 14.1)	12.4 (11.3 to 13.4)	1.0
Percentage decrease in MADRS score, mean (95% CI)	−71.6 (−80.0 to −63.1)	−60.8 (−57.5 to −61.2)	−57.3 (−61.5 to −53.0)	.4
Global Cortical Atrophy scale				
No. of patients[d] (% of total)	29 (35.8)	39 (48.1)	9 (11.1)	
No. of ECT sessions, mean (95% CI)	14.2 (13.2 to 15.2)	12.0 (11.3 to 12.8)	9.7 (7.0 to 12.3)	.2
Percentage decrease in MADRS score, mean (95% CI)	−65.6 (−71.2 to −59.9)	−60.0 (−63.3 to −56.8)	−52.6 (−60.6 to −44.6)	.1

[a]Numbers of patients do not add up to 81, because of missing T1, T2, or FLAIR images (see Method section).
[b]Linear regression analysis adjusted for age, gender, and MADRS score before ECT.
[c]0 = no structural abnormalities, 1 = moderate structural abnormalities, and ≥2 = severe structural abnormalities.
[d]Number of patients per stratum.
Abbreviations: FLAIR = fluid-attenuated inversion recovery, MADRS = Montgomery-Asberg Depression Rating Scale.

A significant association was observed for decrease in MADRS scores and increasing strata of MTA (66.2% in those without MTA compared to 37.9% in those with severe MTA, *P* for trend = .008). Results remained significant when we additionally adjusted for length of index episode (period in months from start of the depressive episode until the first ECT session), therapy resistance (defined as not responding to 2 different types of antidepressants before ECT), seizure duration (defined as percentage of motor seizures lasting more than 20 seconds), and energy delivered (defined as maximum energy delivered in mCoulombs); *P* for trend, respectively, .014, .009, .04, and .023, data not shown.

We found no significant association between increased MTA and percentage change in MMSE results after ECT treatment (*P* = .32). Patients without MTA received a mean of 12.2 ECT treatments, and those with severe MTA received a mean of 18.5 ECT treatments (*P* for trend = .06).

When using the ARWMC rating scale, a total of 12 patients (14.8%) in our cohort were rated with moderate white matter hyperintensities and 7 patients (8.6%) with severe white matter hyperintensities. When rated with the Fazekas scale, 46 patients (56.8%) showed moderate white matter hyperintensities, and 24 patients (29.6%) showed severe white matter hyperintensities. There was no association between the mean decrease in MADRS scores and white matter hyperintensities. Furthermore, there was no association between the mean decrease in MADRS scores, MMSE scores, and global cortical atrophy.

In a minority of patients, lacunar infarcts (n = 19) or large-vessel infarcts (n = 6) were observed.

When the linear regression analysis for MTA and the percentage decrease in the MADRS score were adjusted for lacunar infarcts and large-vessel infarcts, the decrease in MADRS score over strata of MTA remained significant (*P* for trend = .014; data not shown).

Finally, we addressed the problem of missing data. When highest scores of MTA for these missing values were imputed, the results remained similar (data not shown).

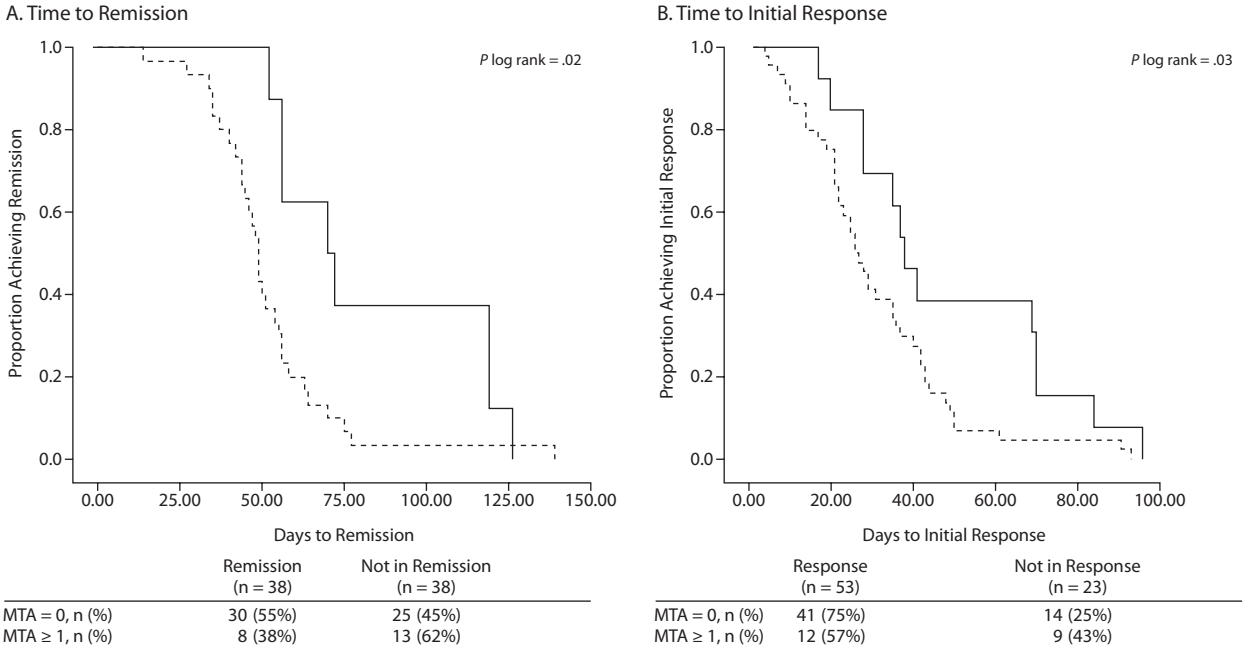
Time to Remission During ECT and MRI Characteristics

A total of 30 of 55 patients (54.5%) without MTA remitted, and 8 of 21 patients (38.1%) with moderate or severe MTA remitted. A total of 44 of 55 patients (80.0%) without MTA and 13 of 21 patients (61.9%) with moderate or severe MTA were initial responders to ECT. Figure 1 shows time to remission and time to initial response for patients with moderate or severe MTA compared to patients without MTA. The graphs show a clear difference between the 2 groups, patients with moderate or severe MTA had a longer time to remission (log rank test *P* = .02) and a longer time to initial response (log rank test *P* = .03). Table 3 shows that patients without MTA had a 3 times greater chance of remitting compared to patients with moderate or severe MTA, ie, the hazard ratio for remission was 3.22 (95% CI, 1.30 to 7.69, *P* = .01). This association remained after adjustment for age, sex, length of index episode, and therapy resistance, ie, the hazard ratio for remission was 5.0 (95% CI, 1.63 to 14.3, *P* = .005) and 2.44 (95% CI, 1.09 to 5.26, *P* = .03) for initial response.

In order to evaluate the effect of the initial MMSE score on the association between MTA and time to remission, we adjusted the Cox regression analysis for age, sex, and initial MMSE score.

All observed associations between remission and MTA remained similar, the hazard ratio for remission was 2.38 (95% CI, 0.96 to 5.88, *P* = .06). Finally, we restricted our analysis to subjects who received a clinically normal range of ECT treatments, since the variation in the number of treatments was high. Table 1 shows that the number of treatments ranged between 2 and 39. The relative risk for remission, when we restricted our analysis to those subjects

Figure 1. Kaplan-Meier Curves Showing Time to Remission or Initial Response After Electroconvulsive Therapy (ECT) in Patients With or Without Moderate or Severe Medial Temporal Lobe Atrophy (MTA)[a]



	Remission (n = 38)	Not in Remission (n = 38)
MTA = 0, n (%)	30 (55%)	25 (45%)
MTA ≥ 1, n (%)	8 (38%)	13 (62%)

	Response (n = 53)	Not in Response (n = 23)
MTA = 0, n (%)	41 (75%)	14 (25%)
MTA ≥ 1, n (%)	12 (57%)	9 (43%)

[a]Solid lines represent patients with moderate or severe MTA, and dotted lines represent patients without MTA.

Table 3. Hazard Ratio of Remission After Electroconvulsive Therapy (ECT), in Depressed Patients With Structural Brain Abnormalities, ie, Medial Temporal Atrophy, White Matter Hyperintensities, and Global Cortical Atrophy, Compared to Those Without Brain Abnormalities[a,b,c]

	Score of Structural Brain Abnormalities[d]		
Variable	>1	0	*P* Value
Medial Temporal Lobe Atrophy scale			
No. of patients in remission/total in group, n/n (%)	8/21 (38.1)	30/55 (54.5)	
Hazard ratio of remission, (95% CI)	1[e]	3.22 (1.30 to 7.69)	.01
Age-Related White Matter Changes scale			
No. of patients in remission/total in group, n/n (%)	9/19 (47.4)	29/59 (49.2)	
Hazard ratio of remission, (95% CI)	1[e]	1.16 (0.50 to 2.70)	.7
Fazekas scale			
No. of patients in remission/total in group, n/n (%)	11/24 (45.8)	27/54 (50.0)	
Hazard ratio of remission, (95% CI)	1[e]	1.72 (0.78 to 3.85)	.2
Global Cortical Atrophy scale			
No. of patients in remission/total in group, n/n (%)	20/48 (41.7)	18/29 (62.1)	
Hazard ratio of remission, (95% CI)	1[e]	0.85 (0.32 to 2.17)	.7

[a]Numbers of patients do not add up to 81, because of missing T1, T2, or FLAIR images (see Method section).
[b]Cox regression analysis adjusted for age and gender.
[c]Remission after ECT is defined as a MADRS score lower than 10 points after ECT.
[d]0 = no structural abnormalities, > 1 = moderate to severe structural abnormalities.
[e]Reference category.
Abbreviations: FLAIR = fluid-attenuated inversion recovery, MADRS = Montgomery-Asberg Depression Rating Scale.

who received 3 or more treatments, with a maximum of 30 treatments, in depressed patients without MTA compared to those with moderate or severe MTA, was 7.04 (95% CI, 2.16 to 22.7, respectively; $P = .001$).

Outcome of ECT and MTA in Subgroups of Depression

In clinical practice, it is important to distinguish late- from early-onset depression and nonpsychotic from psychotic depression. We used a linear regression model to study the response to ECT and the association with MTA in these subgroups. Adjustment was made for age, sex, and initial MADRS score. We restricted the analysis to patients diagnosed with late-onset depression (n = 44, 54.3%), early-onset depression (n = 30, 37.0%), psychotic depression (n = 33, 40.7%), or nonpsychotic depression (n = 43, 53.1%), Table 4. Moderate or severe MTA in nonpsychotic patients, patients with late-onset depression, and patients with early-onset depression were associated with a significantly lower percentage decrease in the MADRS score compared to patients in these subgroups without MTA (all P values ≤ .05). In patients diagnosed with psychotic depression the decrease in MADRS score in both groups was similar (71.4% in patients with moderate or severe MTA and 62.8% in those without MTA, $P = 1.0$). However, the number of ECT treatments in patients diagnosed with psychotic depression with moderate or severe MTA was significantly higher compared to patients diagnosed with psychotic depression without MTA (17.2 vs 12.4, $P = .04$). Finally, we also tested for interaction, ie, if the associations

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Table 4. Relative Decrease in MADRS Score After Electroconvulsive Therapy (ECT), Stratified for Subgroups of Depression, According to Dichotomized Total Medial Temporal Lobe Atrophy[a,b]

Depression Subgroup	Score of Medial Temporal Lobe Atrophy[c] 0	Score of Medial Temporal Lobe Atrophy[c] >1	*P* Value for Trend
Late-onset depression[d]			
No. of patients[e]/total in group, n/n (%)	30/53 (56.6)	14/21 (66.7)	
No. of ECT treatments, mean (95% CI)	12.5 (11.3 to 13.6)	14.3 (12.4 to 16.2)	.2
Decrease in MADRS score, mean (95% CI)	−67.1 (−72.5 to −61.8)	−53.7 (−59.5 to −48.0)	.05
Early-onset depression[f]			
No. of patients[e]/total in group, n/n (%)	23/53 (43.4)	7/21 (33.3)	
No. of ECT treatments, mean (95% CI)	11.7 (10.1 to 13.3)	14.1 (12.1 to 16.0)	.4
Decrease in MADRS score, mean (95% CI)	−69.5 (−76.3 to −62.7)	−44.6 (−54.8 to −34.3)	.02
Nonpsychotic depression			
No. of patients[e]/total in group, n/n (%)	31/55 (56.4%)	12/21 (57.1%)	
No. of ECT treatments, mean (95% CI)	11.9 (10.9 to 13.0)	12.9 (11.8 to 13.9)	.4
Decrease in MADRS score, mean (95% CI)	−67.6 (−71.8 to −63.4)	−35.4 (−41.4 to −29.5)	.004
Psychotic depression			
No. of patients[e]/total in group, n/n (%)	24/55 (43.6%)	9/21 (42.9%)	
No. of ECT treatments, mean (95% CI)	12.4 (10.4 to 14.4)	17.2 (14.0 to 20.4)	.04
Decrease in MADRS score, mean (95% CI)	−62.8 (−69.8 to −55.8)	−71.4 (−76.5 to −66.2)	1.0

[a]Numbers of patients do not add up to 81, because of missing T1, T2, or FLAIR images (see Method section).
[b]Linear regression analysis adjusted for age, gender and MADRS score before ECT.
[c]0 = no medial temporal lobe atrophy, > 1 = moderate or severe medial temporal lobe atrophy.
[d]Late-onset = age at onset depression after 55 years of age.
[e]Number of patients per stratum.
[f]Early-onset = age at onset depression before 55 years of age.
Abbreviations: FLAIR = fluid-attenuated inversion recovery, MADRS = Montgomery-Asberg Depression Rating Scale.

between MTA and percentage decrease in MADRS score differed between subgroups of depression. Interaction was found for psychotic and nonpsychotic depression ($P = .02$). No interaction was found for late- and early-onset depression ($P = .44$). Finally, we studied if a slower response on ECT could be associated with cognitive impairment. Our analysis showed that the median MMSE score before ECT in subjects with psychotic depression was 26 points, and after ECT this score was 27 points, whereas the median MMSE score in nonpsychotic depressed patients stayed at 28 points before and after ECT ($P = .4$ for change in MMSE scores between psychotic depressed patients and nonpsychotic depressed patients). These findings suggest that cognitive functioning after ECT had not significantly changed as measured with the MMSE.

DISCUSSION

In this naturalistic cohort study of 81 patients with unipolar depression, we assessed whether white matter hyperintensities, MTA, or global cortical atrophy was associated with response to ECT in severely depressed elderly patients. The short-term remission rates after ECT were significantly lower in depressed elderly patients with moderate or severe MTA compared to those without MTA. No consistent associations were found between remission or response to ECT and white matter hyperintensities or global cortical atrophy.

Our remission rates were slightly lower compared to previous studies, which showed remission rates of 67% in depressed elderly patients receiving ECT,[2] a rate probably due to the high number of tertiary referrals. The percentage of patients with pharmacotherapy resistance before ECT tended to be higher (although not significantly) in those who came from tertiary referrals than in those from within the catchment area (39% vs 27%, respectively; $P = .3$, χ^2). Furthermore, tertiary-referred patients tended to achieve less remission compared to those from our catchment area (41% vs 60%, respectively; $P = .09$, χ^2). Previous studies showed similar results in this respect.[28,29]

White Matter Hyperintensities and Global Cortical Atrophy

Contrary to our expectation, we found no association between white matter hyperintensities and short-term response to ECT, although 2 rating scales were used (ARWMC and Fazekas). Furthermore, we found no significant association between global cortical atrophy and short-term ECT response. This finding indicates that white matter hyperintensities and global cortical atrophy do not play a major role in predicting efficacy of short-term ECT response in severely depressed elderly patients.

Our findings are in line with 2 other studies on white matter hyperintensities and response to ECT[8,11] (Table 5). However, one study of Steffens et al[3] did show a significant association between white matter hyperintensities and ECT response. An explanation for this discrepancy is that outcome measures were different; the Clinical Global Impressions-Severity of Illness score[30] was used to assess symptom severity. There is an ongoing debate on the validity of this scale, since it has been suggested that this scale could induce inconsistent rating behavior.[31] Moreover, the scale exhibits poor distribution properties and a restricted significance of change ratings,[31] suggesting that the findings from Steffens et al[3] might have been biased.

Medial Temporal Lobe Atrophy

Our results confirmed the hypothesis that patients with MTA have a poor response to ECT compared to patients without MTA. Moreover, in those patients with MTA who recovered, the speed of recovery was significantly slower compared to patients without MTA.

The medial temporal lobe plays an important role in memory functioning and affect regulation, both of which are disturbed in depressive populations. Previous studies have shown an association between MTA and time to remission with pharmacotherapy in elderly populations.[13] Other

Table 5. Summary of Clinical Studies Investigating White Matter Hyperintensities, Medial Temporal Lobe Atrophy, Global Cortical Atrophy, and Response to Electroconvulsive Therapy (ECT)

Author	Journal, Year	Patients	Diagnosis	Age, Mean ± SD (or range), y	MRI	Result
Hickie et al[8]	*Biological Psychiatry*, 1995	n = 20	Unipolar depression	64.6 ± 14.8	WMH	No significant association between presence of WMH and response to ECT
Simpson et al[11]	*Psychological Medicine*, 1998	n = 11	Unipolar depression	74.0 ± 5.8	WMH	No significant association between presence of WMH and response to ECT
Steffens et al[3]	*Journal of ECT*, 2001	n = 41	Unipolar depression	71.2 (58.2–91.1)	WMH	Presence of WMH significantly associated with poor response to ECT
Lekwauwa et al[14]	*American Journal of Geriatric Psychiatry*, 2005	n = 25	Unipolar depression	74.0 ± 7.7	MTA	No significant association between total MTA volume and response to ECT
Oudega et al	*Journal of Clinical Psychiatry*, 2010	n = 81	Unipolar depression	74.0 ± 7.8	MTA, WMH, GCA	Significant association between MTA and poor response to ECT treatment; no significant association for WMH and GCA

Abbreviations: GCA = global cortical atrophy, MRI = magnetic resonance imaging, MTA = medial temporal lobe atrophy, WMH = white matter hyperintensities.

studies have shown that patients with MTA have a higher risk of depression and that MTA is associated with a longer course of depression.[32,33] These findings and the results of our study strongly suggest that MTA contributes to a poor response to ECT in severely depressed elderly patients.

This conclusion is appropriate in the present study for nonpsychotic depressed patients, for both early- or late-onset origin. However, the presence or absence of MTA had no effect on the response to ECT in psychotic depressed patients. This result may be explained by a longer duration of treatment, since these patients were more severely ill (Table 4). Moreover, psychotic features may predict better response to ECT.[34]

Interpretation of Findings

An explanation of our results is speculative. Brodaty et al[35] found in prospective research with a follow-up of 5 years that more than 35% of depressed elderly patients treated with ECT also suffered from dementia at the end of the study. Surprisingly, the elderly depressed patients who were diagnosed with dementia at follow-up performed similarly to other elderly depressed patients on the pre-ECT neuropsychological testing and were clinically indistinguishable from patients who did not develop dementia.[35] In our study, we found comparable results, since patients with increased MTA scores and those without MTA had similar MMSE scores before and after ECT. We therefore hypothesize that depressed patients with moderate or severe MTA who do not respond to ECT could have an increased risk of dementia later on. Assuming this to be the case, the depressive episode in patients with MTA could be viewed as a first symptom of dementia. In psychotic depression, the slower response on ECT could be associated with dementia as a comorbid condition.

The mechanism of action of ECT in late-life depression is unknown. A possible mechanism could be the neurotrophic effect of ECT. Electroconvulsive therapy in rodents increases brain-derived neurotrophic factor (BDNF) gene expression.[36,37] Brain-derived neurotrophic factor induces neuronal sprouting in the medial temporal lobe and cerebral cortex and consequently improves synaptic connectivity and the function of neural circuits, which are involved in mood regulation.[38,39] A clinical pilot study in depressed patients receiving ECT showed a significant increase of plasma BDNF in 87% of the patients.[40] Unfortunately, no MRI recordings were performed in this study. We speculate that patients in whom BDNF did not increase had MTA and that, therefore, BDNF did not have a positive effect on the neuronal sprouting in the brain. Other studies on serum BDNF in patients with mild cognitive impairment suggest that reduced BDNF levels contribute to the pathophysiology of mild cognitive impairment.[41] In addition, reduced BDNF has been shown to contribute to depression in subjects diagnosed with Alzheimer disease.[42] These findings support the idea that patients with MTA are unable to increase BDNF levels on stimulation with ECT, are therefore less likely to respond to ECT, and are at increased risk of dementia. Further follow-up of our sample will hopefully enable us to test this hypothesis.

Strengths and Weaknesses

The current study has several strengths. To our knowledge this is the first relatively large naturalistic study in 81 patients of MRI and ECT results that reflects clinical practice. We used validated MRI rating scales to standardize the interpretation of structural abnormalities in the brain. The neuroradiologist was technically blind to clinical information. Finally, we used 2 rating scales to determine white matter hyperintensities. When rated with the ARMWC scale, 23% of the patients in our study had moderate or severe white matter hyperintensities. However, 86% of the patients in our study had moderate or severe white matter hyperintensities when rated with the Fazekas scale. Irrespective of the scale used, severity of white matter hyperintensities was not associated with response to ECT.

This study also has limitations. First, we used a nonstandardized depression diagnosis. The use of a standardized interview to diagnose depression would have improved the study design. Another concern is the missing magnetic

resonance imaging data. Due to incomplete T1, T2, or FLAIR images of patients, the numbers of patients differed slightly in results for the ARWMC, MTA, Fazekas, and GCA scales. However, when highest scores of pathology for these missing values were imputed, all results remained similar. Finally, 1 out of 7 psychiatrists administering ECT could have had access to MRI results during treatment, so not all psychiatrists in the ECT service were technically blinded.

Clinical Implications

Our study clearly indicates that MTA in severely depressed elderly patients is associated with a poor response to ECT. Other structural brain abnormalities, such as white matter hyperintensities or global cortical atrophy, are not associated with either a worsened or improved response to ECT. If confirmed by future studies, assessment of MTA can assist clinicians in informing depressed patients and relatives about the short-term prognosis of ECT.

Finally, further research is needed to follow up on the patients in this study and to assess whether patients with MTA and depressive symptoms will develop dementia later in life.

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