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Transient cognitive impairment and white matter hyperintensities in severely depressed older patients treated with electroconvulsive therapy --Manuscript Draft--

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Abstract:	<p>Background. Although electroconvulsive therapy (ECT) is a safe and effective treatment for patients with severe late life depression (LLD), transient cognitive impairment can be a reason to discontinue the treatment. The aim of the current study was to evaluate the association between structural brain characteristics and global cognitive functioning during and after ECT.</p> <p>Methods. 80 patients with LLD from the prospective naturalistic follow-up Mood Disorders in Elderly treated with Electro-Convulsive Therapy (MODECT) study were examined. Magnetic Resonance Imaging (MRI)-scans were acquired before ECT. Structural brain characteristics (white and grey matter) were evaluated with visual</p>

	<p>rating scales. Cognitive functioning before, during and after ECT was measured using the Mini-Mental State Examination (MMSE). A linear mixed-model analysis was performed to analyze the association between structural brain alterations and cognitive functioning over time.</p> <p>Results. Patients with moderate to severe white matter hyperintensities (WMH) showed significantly lower MMSE-scores ($F(1,75.54) = 5.42$, $p = 0.02$) before, during and post-ECT, however their trajectory of cognitive functioning is similar to patients without severe WMH as no interaction effect was observed between time x WMH ($F(4,65.85) = 1.9$, $p = 0.25$). Transient cognitive impairment was not associated with medial temporal lobe or global cortical atrophy.</p> <p>Conclusion. Overall, all patients show a significant drop in cognitive functioning during ECT, which resolves above baseline levels post-ECT and remains stable until at least six months post ECT, independently of severity of WMH, GCA or MTA. Clinicians should not be reluctant to start or continue ECT in patients with severe structural brain alterations.</p>
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Amsterdam, November 10th, 2020

Prof. dr. C. Reynolds III
Editor-in-chief
American Journal of Geriatric Psychiatry

Dear prof. dr. C. Reynolds III,

Please, find enclosed our manuscript entitled: "Transient cognitive impairment and white matter hyperintensities in severely depressed older patients treated with electroconvulsive therapy" for publication in the American Journal of Geriatric Psychiatry. We would appreciate your editorial response on its quality. We think the current manuscript fits the scope of the journal since we describe relevant age-related structural brain alterations that might be associated with cognitive functioning in a group of older patients with severe late-life depression (LLD), treated with electroconvulsive therapy (ECT). With this article we hope to inform both psychiatrists and other mental health professionals on the benefits of ECT and to show that clinicians should not be reluctant to start or continue ECT in older patients with severe structural brain alterations.

In short, we aimed to evaluate the association between structural brain characteristics and global cognitive functioning before, during and after ECT in a naturalistic cohort of patients with severe LLD. ECT is highly effective for patients with severe LLD, as reflected by high remission rates (50-70 %). However, the emergence of cognitive decline during ECT can be a reason to discontinue the treatment. As patients with LLD often show severe age-related structural brain alterations such as white matter hyperintensities (WMH), medial temporal lobe atrophy (MTA) and global cortical atrophy (GCA), these patients may predispose increased transient cognitive impairment. The results indicate that patients with severe WMH show worse cognitive functioning before, during and after ECT, however their trajectory of transient cognitive impairment is similar of those without severe WMH. Transient cognitive impairment was not associated with MTA, or GCA. The results indicate that clinicians should not discontinue the ECT course; disturbances in cognition during ECT will resolve when ECT is continued, moreover it remains stable until at least six months after treatment completion, independently from severance of WMH, MTA, or GCA.

The protocol of the MODECT study was approved by the Ethical Review Board of the VU Medical Center and by the ethical review board of the Catholic University of Leuven and was conducted according to the Declaration of Helsinki (clinicaltrials.gov; NCT02667353). Written informed consent was obtained from all patients. All authors have contributed substantially to the conception and design of the study, or to the analysis and interpretation of the data, they also participated in drafting the manuscript or revising it, and have approved the final version to be published. Our work represents original material. The manuscript is not published, nor under consideration for publication elsewhere. All authors declare no potential conflict of interest (Wagenmakers, Vansteelandt, van Exel, Postma, Schouws, Obbels, Rhebergen, Bouckaert, Stek, Barkhof, Beekman, Veltman, Sienaert, Dols and Oudega). I am looking forward to your response.

Yours sincerely, on behalf of all authors,

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Highlights paper Wagenmakers et al transient cognitive impairment and ECT

- 1) What is the primary question addressed by this study?** In this study the association between severe structural brain alterations and transient cognitive impairment was examined in a cohort of patients with severe late life depression (LLD) treated with electroconvulsive therapy (ECT).
- 2) What is the main finding of this study?** The results show that ECT can induce a significant drop in cognitive functioning during the ECT, which recovers above baseline levels and remains stable at least six months after ECT completion. Patients with severe white matter hyperintensities (WMH) show worse cognitive functioning before, during and after ECT compared to patients without severe WMH, however their trajectory is similar as their cognitive decline during ECT is not more extreme.
- 3) What is the meaning of the finding?** With these results, the aim is to better inform patients, caregivers and clinicians on the occurrence of transient cognitive impairment and to stress that clinicians should not be reluctant to start or continue ECT in patients that show cognitive disturbances as it will resolve, independent from severity of structural brain alterations.

Transient cognitive impairment and white matter hyperintensities in severely depressed older patients treated with electroconvulsive therapy

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Abstract

Background. Although electroconvulsive therapy (ECT) is a safe and effective treatment for patients with severe late life depression (LDD), transient cognitive impairment can be a reason to discontinue the treatment. The aim of the current study was to evaluate the association between structural brain characteristics and global cognitive functioning during and after ECT.

Methods. 80 patients with LLD from the prospective naturalistic follow-up Mood Disorders in Elderly treated with Electro-Convulsive Therapy (MODECT) study were examined. Magnetic Resonance Imaging (MRI)-scans were acquired before ECT. Structural brain characteristics (white and grey matter) were evaluated with visual rating scales. Cognitive functioning before, during and after ECT was measured using the Mini-Mental State Examination (MMSE). A linear mixed-model analysis was performed to analyze the association between structural brain alterations and cognitive functioning over time.

Results. Patients with moderate to severe white matter hyperintensities (WMH) showed significantly lower MMSE-scores ($F(1,75.54) = 5.42$, $p = 0.02$) before, during and post-ECT, however their trajectory of cognitive functioning is similar to patients without severe WMH as no interaction effect was observed between time x WMH ($F(4,65.85) = 1.9$, $p = 0.25$). Transient cognitive impairment was not associated with medial temporal lobe or global cortical atrophy.

Conclusion. Overall, all patients show a significant drop in cognitive functioning during ECT, which resolves above baseline levels post-ECT and remains stable until at least six months post ECT, independently of severity of WMH, GCA or MTA. Clinicians should not be reluctant to start or continue ECT in patients with severe structural brain alterations.

Key Words: *Electroconvulsive Therapy; Transient Cognitive Impairment; Structural MRI; White Matter Hyperintensities; severe depression; Late Life Depression.*

Objective

Electroconvulsive therapy (ECT) is a safe and effective treatment with high remission rates for patients with severe late life depression (LLD) (1-4). Older age is associated with better outcome, with remission rates up to 90% for patients above the age of 65 (5-9). Despite the evinced efficacy of ECT, there is an ongoing concern about the side-effects of ECT on cognitive functioning.

During the course of ECT, almost all patients suffer from post-ECT confusion and disorientation, which disappears within several hours (9-12). Some of the patients also experience retrograde and anterograde amnesia, a decline in verbal memory or diminished executive functioning. A subset of patients show transient cognitive impairment, which is a longer period of significant decline in cognitive functioning during the ECT course, lasting from days to weeks (10, 12-14), that recovers as the depressive symptoms remit (14-16). Previously, Obbels et al (2019) demonstrated that cognitive functioning could improve during the ECT course together with a reduction of the depressive symptoms, even in patients with low cognitive functioning at baseline (17). However, transient cognitive impairment during ECT can be a reason for patients and their relatives to discontinue the treatment. For good clinical guidance it is important to investigate the occurrence of transient cognitive impairment and its risk factors more carefully to better inform patients and limit early discontinuation of ECT.

Patients with LLD often show structural brain alterations, such as white matter hyperintensities (WMH), medial temporal lobe atrophy (MTA) and global cortical atrophy (GCA) (18). These structural brain characteristics are part of (abnormal) aging and may predispose increased vulnerability to transient cognitive impairment during ECT. For example, Fiegiel et al (1990) showed that basal ganglia lesions and WMH occurred more frequently in 87 LLD patients who developed ECT-induced transient cognitive impairment (19). Lekwauwa et al (2016) showed in a group of 15 patients with LLD receiving ECT, that MTA was associated with poorer memory outcomes after ECT, but not during ECT (20). In a study by Oudega et al (2014) structural brain characteristics and cognitive functioning during

and after ECT in LLD patients were studied extensively. The authors found that LLD patients with severe WMH, who receive bilateral ECT, were at increased risk of cognitive impairment during an ECT course, however these side-effects recovered after treatment completion(14).

Taken together, these results indicate that ECT-related transient cognitive impairment occurs in a specific subset of patients who are more vulnerable due to WMH, MTA or GCA.

However, studies on the trajectory of cognitive functioning during and after an ECT course in relation to structural brain characteristics are sparse.

The aim of the current study was to evaluate the association between severity of structural brain alterations (WMH, GCA and MTA) and global cognitive functioning assessed by Mini Mental State Examination (MMSE) scores during and after ECT. To overcome limitations of a short follow-up, the trajectory of global cognitive functioning was studied before, during, one week after, four weeks after and six months after ECT completion. It was hypothesized that presence of WMH in patients with severe LLD is associated with an increased risk of transient cognitive impairment (14). Also, we expected that GCA and MTA would be a risk factor to develop transient cognitive impairment (19,20). Altogether we expected that patients with abnormal structural brain characteristics (severe WMH, GCA and MTA) would be more vulnerable to show a significant cognitive decline during ECT. However, as this decline is expected to be transient, no significant difference in cognitive functioning was expected in the period after ECT completion between patients with and without severe structural brain alterations.

Methods

Study design

This naturalistic prospective study was part of the Mood Disorders in Elderly treated with Electroconvulsive Therapy (MODECT) study, investigating clinical and structural brain characteristics and response to ECT (21). In the MODECT study, patients aged 55 years and older were included with a diagnosis of a severe unipolar depression according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*(22). Exclusion criteria were a diagnosis of bipolar disorder, a schizoaffective disorder, comorbid major DSM-IV psychiatric illness or neurological illness (including stroke, dementia, and Parkinson's disease). Diagnoses were established by experienced psychiatrists and confirmed via the Mini International Neuropsychiatric Interview Plus 5.0.0. (M.I.N.I.-plus (MINI))(23). Over a 3-year period (2011 till 2013) a total of 110 patients were included in the study. Patients were enlisted through two tertiary psychiatric hospitals located in Amsterdam (GGZ inGeest, the Netherlands; N = 67) and Leuven (Psychiatric Center, KU Leuven, Belgium; N = 43).

For the current study, we included only patients for whom a MRI-scan was available (n=80). A final sample of 80 patients was included in the current study. Excluded patients (n=30) were not different with regard to age, sex, education-level, cognitive functioning at baseline or depression severity at baseline (details not shown).

Clinical characteristics and assessments

Demographics

Demographic and clinical variables including age, gender, level of education, marital status, age at onset of first depression and information on post-ECT treatment were obtained by an interview and double-checked by chart review. Early onset depression (EOD) was defined as having a first depressive episode before the cut-off age of 55 years (Dols et al., 2017). The diagnosis of depression with or without psychotic symptoms was based on DSM-IV-TR criteria and confirmed using the MINI (23).

Cognition

Cognitive functioning was examined using the Mini-Mental State Examination (MMSE) (24). The MMSE consists of 11 categories aimed to assess the patient's cognition regarding attention, orientation, memory, registration, calculation, language and visual-spatial skills. The MMSE was administered multiple times during and after the ECT-course by a research nurse well-trained on the protocol. For the current study baseline MMSE, the lowest MMSE-score of each participant during ECT, and MMSE-scores one week, four weeks and six months after treatment completion were used. The lowest MMSE-score during ECT was used as this is clinically the worst status concerning cognition, while the exact timing of this worst rating varies between patients.

Depression severity

To monitor the severity of the depressive symptoms of the patients, the Montgomery–Åsberg Depression Rating Scale (MADRS) (25) was administered, before, during and after completing ECT. To be classified as a responder to ECT, a MADRS score decline of at least 50% was required. To be classified as remission after ECT, a MADRS score lower than 10 was required for at least two successive weekly clinical evaluations (25). The MADRS was administered by a research nurse well-trained on the study protocol.

Magnetic Resonance Imaging

Before the start of the ECT course, patients received Magnetic Resonance Imaging (MRI) to evaluate structural brain alterations. A whole-brain 3T MRI-system (*General Electric Signa HDxt*, Milwaukee, WI, USA, in Amsterdam; *Philips Intera*, Best, The Netherlands, in Leuven) was used following a standard protocol (21). Series included structural three-dimensional T1-weighted images and axial Fluid Attenuated Inversion Recovery (FLAIR) images.

Visual rating structural brain characteristics

To evaluate structural brain characteristics, validated rating scales were used to assess the generated MRI scans. All the assessments using the visual rating scales were performed by neuro-radiologists who were blind to the clinical information of the patients.

WMH. For WMH, the Age-Related White Matter Changes (ARWMC) scale (26) was applied using the axial FLAIR images to assess the presence of WMH in 10 different regions of the brain. Regional scores with a maximum score of 3 were summed, with a maximum overall WMH score of 30. Hereafter, the patient was allocated to either having no to mild (score = 0-9) or moderate to severe structural WMH (score = 10-30).

MTA. For the MTA, the validated Scheltens scale (27, 28) was applied using coronal three-dimensional T1-weighted images. With this scale atrophy levels in both left and right medial temporal lobe were assessed, with scores ranging from 0-4. Scores were averaged to obtain a mean MTA score. Subsequently, scores were dichotomized into either no MTA (score = 0-1) or moderate to severe MTA (score = 2-4).

GCA. GCA was measured using the Pasquier rating scale and the axial FLAIR images (29, 30). Atrophy levels of both right and left hemisphere were assessed, with for each hemisphere a score ranging from 0-3. An average score was used to allocate patients into a none to mild GCA group (score = 0-1) or a moderate to severe GCA group (score = 2-3).

ECT procedure

Patients received ECT twice a week according to the Dutch guidelines for ECT (31). ECT was conducted using the *Thymatron System IV* (Somatics, LLC, Lake Bluff, IL, USA; maximum energy 200%, 1,008 C) using a titration protocol (21). Anesthesia was achieved with intravenous administration of etomidate (0.2 mg/kg) and succinylcholine (1 mg/kg). Patients started on a course with right unilateral ECT (d'Elia placement), some patients started with bilateral ECT based on clinical indication (32). At the first treatment, the subject's seizure threshold (ST) was established by empirical titration. Subsequent treatments were given at 6 times the ST for unilateral ECT and 1.5 times the ST for bilateral ECT. Patients were treated until remission, defined as a MADRS score of less than 10 on two consecutive ratings with a week interval, or until patients showed no further improvement in clinical condition during the last 2 weeks of ECT sessions after a minimum of six unilateral and six bilateral sessions. Switching to bilateral ECT was applied when after six unilateral

treatments, the clinical condition worsened (i.e., an increase in total MADRS scores, presence of debilitating psychotic features, increased suicidality, dehydration or weight loss, or when after six unilateral treatments there was no clinical improvement according to the judgment of the treating psychiatrist) (32). Psychotropic medication was discontinued at least one week prior to ECT, or if deemed impossible, kept stable from six weeks before ECT and during the ECT course.

Ethical Issues

The protocol of the MODECT study was approved by the Ethical Review Board of the VU Medical Center and by the ethical review board of the Catholic University of Leuven and was conducted according to the Declaration of Helsinki (clinicaltrials.gov; NCT02667353). Written informed consent was obtained from all patients.

Statistical analysis

Demographic and clinical characteristics of patients are reported as means with standard deviations (SD), medians with inter-quartile range (IQR) or absolute numbers with percentages for the total group.

To analyze the association between the severity of structural brain alterations (absent versus moderate/severe for respectively WMH, MTA, and GCA, and MMSE-scores over time (baseline, lowest during ECT, one week after, four weeks after, and six months after ECT) a linear mixed-model analysis was performed with the MMSE-scores as dependent variable over time. With the use of a linear mixed-model it was examined whether patients with moderate to severe brain alterations had more cognitive impairment during ECT (lowest MMSE-score) and whether this improved after treatment completion (one week, four weeks and six months after ECT) by examining the interactions between time and structural brain characteristics (WMH, MTA, and GCA). Furthermore, the model included gender, MADRS (time-varying covariate), and time as independent variables. The influence of ECT method was analyzed by adding the interaction term of ECT method (unilateral versus bilateral stimulation) x structural brain characteristics in the model.

Multicollinearity of the predictors was checked by looking at the bivariate correlation coefficients between independent variables (> 0.80) and using the Variance Inflation Factor (VIF) < 5 (33). Selection of the correct variance-covariance structure (unstructured, compound symmetry or heterogeneous compound symmetry) was based on likelihood ratio tests and information criteria. Thereafter, the actual linear mixed-model with the adequate variance-covariance matrix was estimated using the restricted maximum likelihood method. If a main effect was considered significant, pairwise comparisons were analyzed. Pairwise comparisons were corrected for multiple comparison with a Bonferroni correction.

Data were analyzed using the Statistical Package of the Social Sciences (SPSS, version 26, SPSS Inc., Chicaco, IL). In all analyses a $p < 0.05$ was considered as statistically significant.

Results

Demographics and clinical characteristics

Patients included in this study ($n = 80$) had a mean age of 72.7 years (standard deviation (SD) = 8.5) and a female predominance ($n = 54$, 67.5%) (Table 1). Of all patients, 16.3 % showed moderate to severe GCA, 33.8 % moderate to severe WMH and 27.5 % moderate to severe MTA. Presence of WMH was significantly associated with GCA, $\chi^2 = 8.74$ ($df = 1$), $p < 0.01$, 33.9 % of the patients with WMH also suffered from moderate to severe GCA, Patients with respectively WMH (78.7 years $\pm$ 7.5) and GCA (81.9 years $\pm$ 7.0) were significantly older than patients without WMH (69.6 years $\pm$ 7.3) or without GCA (71.0 years $\pm$ 7.7) ($p < 0.001$).

Transient cognitive impairment

On average, patients had their lowest MMSE-score in the third week of the ECT-course (Figure 1a, T1). Based on the linear mixed-model that was performed, a significant main effect of time ($F(4, 74.60) = 17.12$, $p < 0.001$) was found (Figure 1a). Pairwise comparison (Table 2) showed that baseline MMSE-scores were significantly higher compared to the mean lowest MMSE-score during ECT (mean difference = 2.00 (SE = 0.55), $p < 0.01$), indicating a significant drop in cognitive functioning. These mean lowest MMSE-scores were also significantly lower compared to one week after ECT (mean difference = -3.45 (SE = 0.56), $p < 0.001$), four weeks after ECT (mean difference = -4.59 (SE = 0.64), $p < 0.001$), and six months after ECT (mean difference = -4.54 (SE = 0.64), $p < 0.010$), thus revealing a significant improvement in cognitive functioning post-ECT. Baseline MMSE was significantly lower compared to both four weeks after ECT (mean difference = -2.59 (SE = 0.72), $p < 0.01$), and six months after ECT (mean difference = -2.54 (SE = 0.79), $p = 0.02$), indicating a significant improvement of cognitive functioning after ECT compared to baseline. Lastly, a significant improvement was observed between one week after ECT (mean difference = -1.14 (SE = 0.37), $p = 0.03$) and four weeks after ECT, which remained stable until six months after ECT (mean difference = 0.05 (SE = 0.35), $p = 1.00$).

Transient cognitive impairment and structural brain characteristics

Concerning the association between structural brain characteristics and MMSE-scores over time, a significant association of WMH and overall cognition observed ($F(1,74.54) = 5.42$, $p = 0.02$), but not for the interaction of WMH x time ($F(4,65.85) = 1.9$, $p = 0.25$) (Figure 1b). This indicated that WMH adversely affects cognitive functioning independent of treatment, these patients having a trajectory of transient cognitive impairment being similar to those without WMH. No significant association of gender ($F(1,72.22) = 2.20$, $p = 0.14$) and depression over time ($F(1,217.25) = 0.70$, $p = 0.40$) with cognitive functioning was observed. Adding the interaction of WMH and ECT method (unilateral versus bilateral stimulation) to the model, did not show a significant association.

Looking at the associations between respectively GCA ($F(1,72.66) = 1.85$, $p = 0.18$) and MTA ($F(1,73.59) = 1.57$, $p = 0.21$) and MMSE-scores over time, no significance was observed, neither for the interaction effects of GCA x time ($F(4,67.24) = 1.97$, $p = 0.11$) or for MTA x time ($F(4,64.08) = 0.94$, $p = 0.45$). Data not shown in a figure or table.

Conclusion and discussion

The aim of the present study was to examine the association between structural brain characteristics and transient cognitive impairment in a naturalistic cohort of patients with severe LLD. The results indicate that patients with severe WMH show worse cognitive functioning before, during and post-ECT. However, their trajectory of cognitive functioning is similar to patients without severe WMH. No significant association between GCA, or MTA and cognitive functioning was observed. All patients showed a significant drop in cognitive functioning during ECT, which improved above baseline levels post-ECT and remained stable until at least six months after ECT completion, independently of severance of WMH, GCA or MTA.

Previously it was observed in the same sample that although patients show baseline cognitive impairment, cognition improves during the ECT course until six months after ECT completion (17, 34). However, the effect of individual differences in structural brain characteristics was not studied (34, 35). Although our results demonstrate that patients with severe WMH show worse cognitive functioning, they equally rehabilitate their cognitive dysfunctions during ECT as patients without severe WMH. In line with our findings, a recent systematic review also showed no predictive value of WMH on cognitive side-effects post-ECT(36).

In the current cohort patients with moderate to severe WMH ($M_{age} = 79.8$) were significantly older compared to those without WMH ($M_{age} = 69.9$, $p < 0.001$), which is in line with previous studies showing an association between age and WMH (37-39). Although Oudega et al. (2014) used age as a confounder in their analyses, we did not. With increasing age, atrophy and WMH in the brain are more prevalent. As WMH is an indicator of aging of the brain, we did not want to correct for age to prevent overcorrection. We evaluated the association between age and MMSE-scores over time without WMH in the statistical model, and found no significant association between age and MMSE before, during and after ECT. Results also showed that patients with WMH more often had high blood pressure and a history of cerebrovascular incidents. Again, we did not correct for these possible covariates as these

medical conditions are related to WMH. Part of the patients in the current study had severe GCA (16 %), and more often this was present in patients who also suffered from severe WMH (34 %). Recent literature shows that WMH promotes cortical atrophy, which in turn could drive cognitive decline (40, 41). However, in the current study we could not confirm that GCA can explain transient cognitive impairment.

Results from the current study differ in several aspects from those of the naturalistic cohort study of Oudega et al (2014). In the current study it was not confirmed that patients with WMH are more vulnerable for transient cognitive impairment. Second, no specific effect was found for the ECT method. Oudega et al (2014) showed that patients with severe WMH, who received bilateral ECT, were at increased risk of transient cognitive impairment. An explanation for the difference with current study may be the use of a different administration protocol. The applied energy dosage in the Oudega et al (2014) study was based on an age dosing protocol, whereas the current study was based on a titration protocol (42). Also, patients received more treatment sessions in the previous study, and the current study had a wider variation of applied dosages. Lastly, the remission rates were 66.4% in the current cohort (21) compared to 48.1% in the study of Oudega et al (2014). Altogether, the current administration protocol, with less treatment sessions, a wider variation of applied dosages and improved remission rates might have influenced the results.

Strengths and weaknesses

To our knowledge this is the second study evaluating the association between structural brain characteristics and cognitive functioning before, during and after ECT. One of the key strengths of this study is its design, with a large sample of severely depressed older patients admitted to receive ECT in a naturalistic way. Another strength is the long follow-up period of six months, which demonstrates that the improvement of cognition is not limited to a short period of time. At the same time, this follow-up period led to a drop out of part of the patients. At baseline N = 80 patients were included, with N = 55 patients left at six months because of drop-out. A selection bias was observed, such that patients that remitted after ECT were more often present at the follow-up phase of the study (data not shown). No difference in

baseline cognitive functioning or directly post-ECT was observed between patients that were examined at follow-up and those that dropped out. Another limitation is the prescribed medication during ECT. No significant difference was observed in whether medication (antidepressant, lithium and/or antipsychotic) was prescribed or between patients with and without severe WMH. Also, no significant difference in prescribed medication and MMSE-scores before, during and after ETC was observed. However, literature shows a specific anticholinergic effect on cognition (43). The type of medication was not registered at site two, therefore we were unable to correct for possible anticholinergic effects.

A potential limitation of this study is the use of visual rating scales to evaluate structural brain alterations. However, these scales are widely used in clinical practice, moreover quantitative techniques such as voxel-based morphometry (VBM) and Freesurfer are suitable for assessments of regional volume changes, but not white matter lesions (44-46). Lastly, although the MMSE is one of the most widely used cognitive tests, it has been criticized because of learning effects and because it only reflects global cognitive impairment (17, 47). As an alternative there is a need for easy-to-use bedside neuropsychological tests appropriate to detect subtle cognitive changes during and after ECT more accurately (35, 48).

Future studies

As demonstrated in the results, severe WMH was mostly present in patients that are older, have a higher blood pressure, and more often have a history of cerebrovascular accidents. These patients show worse cognitive functioning in general, independent of the effect of ECT. At the same time, WMH is not predictive of ECT outcome (Kessel et al., 2020), although age is an important predictor for ECT response (5-8, 36). As the presence of WMH is typical for the ageing brain it would be interesting to study the ageing brain of patients treated with ECT. Emerging studies indicate that chronological age and biological age (49) may be distinct processes (50) and it would be interesting to study this difference in patients receiving ECT.

Conclusion and clinical implications

In conclusion, ECT can induce a significant drop in cognitive functioning during the ECT period, which recovers above baseline levels and remains stable at least six months after ECT completion. Patients with severe WMH show worse cognitive functioning before, during and after ECT compared to patients without severe WMH, however their trajectory is similar. No association between other structural brain alterations and cognitive functioning during and after ECT was found (e.g. MTA and GCA). The findings are of clinical importance as clinicians might be reluctant to start and continue ECT in patients with severe WMH, that already show poor cognitive functioning and additionally develop a drop in their cognition during ECT. It is important to inform patients and their relatives on the occurrence of transient cognitive impairment (48), and clinicians should not be reluctant to start and should not discontinue the ECT course as the results show that disturbances in cognition will resolve when ECT is continued (47). More importantly, cognition remains stable until at least six months after treatment completion, independent from structural brain characteristics.

Author contributions

All authors made a substantial contribution to the manuscript. Dr. Oudega and dr. Dols designed and oversaw the conduct of the study. Drs. Wagenmakers performed the literature search, performed statistical analyses and wrote the first draft of the manuscript. Dr. Vansteelandt contributed substantially to the performances of the statistical analyses. All authors contributed to critical revisions of the draft and have approved the final version before publication.

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Previous presentation

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Figure legends

Table 1. Demographic and clinical characteristics of patients with late life depression, treated with electroconvulsive therapy in total sample size and patients without and moderate to severe white matter hyperintensities

Notes. Abbreviations: SD: standard deviation, IQR: interquartile range, MADRS: Montgomery Åsberg Depression Rating Scale, ECT: electro-convulsive therapy. WMH = white matter hyperintensities, MTA = Medial temporal lobe atrophy, GCA = global cortical atrophy. Education: low no education, primary school), middle: high school, vocational training, high: college, university). Late onset depression = ≥ 55 years. Remission = MADRS-score < 10 points, Response = $\geq 50\%$ improvement in MADRS-score. Medication during ECT: tricyclic antidepressant, Lithium or antipsychotic

Figure 1. Trajectory of MMSE-scores over the course of ECT in late life depression for a) the overall group (N = 80) and b) patients with (N = 27) and without severe white matter hyperintensities (N = 53)

Notes. T0 = before ECT N = 72, T1 = lowest MMSE-score during ECT N = 80, T2 = one week after ECT N = 77, T3 = four weeks after ECT N = 57, T4 = six months after ECT N = 55, with standard error bars. Linear mixed model analysis showed a) significant overall effect of time ($F(4,74.60) = 17.12, p < 0.001$) and WMH ($F(1,74.54) = 5.42, p = 0.02$), but b) not for the interaction time x WMH ($F(4,65.85) = 1.39, p = 0.25$) Abbreviations: MMSE-score Mini Mental State Examination score, ECT = electroconvulsive therapy, WMH = white matter hyperintensities

Table 2. Pairwise comparison MMSE-scores over the course of ECT in late life depression for the overall group (N = 80)

Notes. T0 = before ECT, T1 = lowest MMSE-score during ECT, T2 = one week after ECT, T3 = four weeks after ECT, T4 = six months after ECT Significant overall main effect of time ($F(4,74.60) = 17.12, p < 0.001$). Table shows pairwise comparison between time-points.

* $p < 0.05$

** $p < 0.01$

NS = non-significant

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Figure 1. Trajectory of MMSE-scores over the course of ECT in late life depression for a) the overall group (N = 80) and b) patients with (N = 27) and without severe white matter hyperintensities (N = 53)

Notes. T0 = before ECT N = 72, T1 = lowest MMSE-score during ECT N = 80, T2 = one week after ECT N = 77, T3 = four weeks after ECT N = 57, T4 = six months after ECT N = 55, with standard error bars. Linear mixed model analysis showed a) significant overall effect of time ($F(4,74.60) = 17.12, p < 0.001$) and WMH ($F(1,74.54) = 5.42, p = 0.02$), but b) not for the interaction time x WMH ($F(4,65.85) = 1.39, p = 0.25$) Abbreviations: MMSE-score Mini Mental State Examination score, ECT = electroconvulsive therapy, WMH = white matter hyperintensities

Table 1. Demographic and clinical characteristics of patients with late life depression, treated with electroconvulsive therapy in total sample size and patients without and moderate to severe white matter hyperintensities

Demographics	All patients (N = 80)	WMH absent (N = 53)	WMH present (N = 27)	Statistics χ^2/t (df)/MW	p-value
Age (mean, SD)	72.7 $\pm$ 8.5	69.6 $\pm$ 7.3	78.7 $\pm$ 7.5	-5.22 (78)	p < 0.01
Female (N, %)	54 (67.5)	32 (60.4)	22 (81.5)	3.63 (1)	0.057
Educational level (N, %)	66 (82.5)	45 (84.9)	21 (77.8)	1.09 (3)	0.78
Low	9 (11.3)	6 (11.3)	3 (11.1)		
Middle	50 (62.5)	35 (66.0)	15 (55.6)		
High	7 (8.8)	4 (7.5)	3 (11.1)		
Structural MRI characteristics (N, %)					
Moderate to severe MTA	22 (27.5)	16 (30.2)	6 (22.2)	0.57 (1)	0.45
Moderate to severe GCA	13 (16.3)	4 (7.5)	9 (33.9)	8.74 (1)	p < 0.01
ECT characteristics					
Number of ECT treatments (median, IQR)	11.0 (7.0)	10.0 (7.0)	12.0 (6.0)	MW	0.87
Patients treated unilateral (N, %)	53 (66.3)	34 (64.2)	19 (70.4)	0.31 (1)	0.59
Patients treated bilateral or switched to bilateral (N, %)	27 (33.8)	19 (35.8)	8 (29.6)		
Clinical characteristics					
Late onset depression (N, %)	43 (53.8)	28 (52.8)	15 (55.6)	0.53 (1)	0.82
Psychotic depression (N, %)	41 (51.3)	24 (45.3)	17 (63.0)	2.24 (1)	0.135
MADRS-score before ECT (mean, SD)	N = 79 33.9 (9.5)	N = 52 31.7 (12.5)	N = 27 32.6 (11.6)	-0.33 (78)	0.74
MADRS-score directly after ECT (mean, SD)	N = 79 9.8 (9.7)	N = 52 9.8 (10.6)	N = 27 9.6 (7.8)	0.09 (77)	0.93
MADRS-score 4 weeks after ECT (mean, SD)	N = 58 12.02 (8.9)	N = 39 11.6 (8.0)	N = 19 12.8 (10.8)	-0.46 (56)	0.65
MADRS-score 6 months after ECT (mean, SD)	N = 65 10.9 (10.1)	N = 46 10.8 (10.6)	N = 19 11.1 (9.2)	-0.11 (63)	0.91
Remission after ECT (N, %)	N = 79 54 (68.4)	N = 52 36 (69.2 %)	N = 27 18 (66.7 %)	0.05 (1)	0.82
Response to ECT (N, %)	N = 76 62 (81.6)	N = 50 41 (82.0 %)	N = 26 21 (80.8 %)	0.02 (1)	0.90
Medication during ECT (N, %)	32 (40)	21 (39.6)	11 (40.7)	0.01 (1)	0.92

Notes. Abbreviations: SD: standard deviation, IQR: interquartile range, MADRS: Montgomery Åsberg Depression Rating Scale, ECT: electro-convulsive therapy. WMH = white matter hyperintensities, MTA = Medial temporal lobe atrophy, GCA = global cortical atrophy. Education: low no education, primary school), middle: high school, vocational training, high: college, university). Late onset depression = $\geq$ 55 years. Remission = MADRS-score < 10 points, Response = $\geq$ 50% improvement in MADRS-score. Medication during ECT: tricyclic antidepressant, Lithium or antipsychotic

Table 2. Pairwise comparison MMSE-scores over the course of ECT in late life depression for the overall group (N = 80)

	Lowest N = 80 Mean diff (SE), df	1 week post N = 77 Mean diff (SE), df	4 weeks post N = 57 Mean diff (SE), df	6 months post N = 55 Mean diff (SE), df
Baseline N = 72	2.00 (0.55), 79.32**	-1.44 (0.79) 130.36, NS	-2.59 (0.72) 120.18**	-2.54 (0.79) 109.20*
Lowest N = 80		-3.45 (0.56) 98.24**	-4.59 (0.64) 92.15**	-4.54 (0.64) 92.15**
1 week post N = 77			-1.14 (0.37) 66.12*	-1.10 (0.45) 69.18, NS
4 weeks post N = 57				0.045 (0.35) 48.90, NS

Notes. T0 = before ECT, T1 = lowest MMSE-score during ECT, T2 = one week after ECT, T3 = four weeks after ECT, T4 = six months after ECT Significant overall main effect of time (F (4,74.60) = 17.12, $p < 0.001$. Table shows pairwise comparison between time-points.

* $p < 0.05$

** $p < 0.01$

NS = non-significant