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

Margot J. Wagenmakers, MSc[1,2#], Kristof Vansteelandt, PhD[3], Eric van Exel, MD, PhD[1,2,4], Rein Postma, BSc[1], Sigfried N.T.M. Schouws, PhD[1,2,4],Jasmien Obbels, MSc[3,5], Didi Rhebergen, MD, PhD[1,4], Filip Bouckaert, MD, PhD[3], Max L. Stek, MD, PhD[1,2,4], Frederik Barkhof, MD, PhD[6,7,8], Aartjan T.F. Beekman, MD, PhD[1,2,4], Dick J. Veltman, MD, PhD[2,4], Pascal Sienaert, MD, PhD[3], Annemieke Dols, MD PhD[1,2,4], Mardien L. Oudega, MD, PhD[1,2,4]

Affiliations

[1]GGZ inGeest Specialized Mental Health Care, Amsterdam, The Netherlands;

[2]Amsterdam UMC, Vrije Universiteit, Psychiatry, Amsterdam Neuroscience, The Netherlands;

[3]Academic Center for ECT and Neuromodulation (AcCENT), University Psychiatric Center KU Leuven (Catholic University of Leuven), Leuven, Belgium;

[4]Amsterdam UMC, Vrije Universiteit, Psychiatry, Amsterdam Public Health (research institute), The Netherlands;

[5]University Psychiatric Center, KU Leuven-University of Leuven, Kortenberg, Belgium;

[6]Institute of Healthcare Engineering, University College London, London, UK;

[7]Institute of Neurology, University College London, London, UK;

[8]Radiology & Nuclear Medicine, VU University Medical Center, Amsterdam, Netherlands;

[9]KU Leuven, Leuven Brain Institute, Department of Neurosciences, Neuropsychiatry & Geriatric Psychiatry, University Psychiatric Center KU Leuven

[#]Corresponding author:

Margot Josephina Wagenmakers, MSc |GGZ inGeest, department of Research and Innovation, Oldenaller 1, 1081 HJ Amsterdam, The Netherlands, E-Mail: m.wagenmakers@ggzingeest.nl, telephone: +31 20 788 4666

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 before, 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.

Transient cognitive impairment and ECT

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 a., 2017). The diagnosis of depression with or without psychotic symptoms was based on DSM-IV-TR criteria and confirmed using the MINI (23).

5

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 total score for the MMSE ranges from 0 to 30; scores > 24 indicate no cognitive impairment. 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.

6

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

7

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. For demographic data, group differences in continuous variables were determined by independent samples t-test. If a variable did not met the assumptions, a Mann-Whitney U test was used as alternative. Group differences in categorical variables were calculated using χ^2-tests.

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.

Transient cognitive impairment and ECT

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, χ^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 ± 7.5) and GCA (81.9 years ± 7.0) were significantly

older than patients without WMH (69.6 years ± 7.3) or without GCA (71.0 years ± 7.7) (Table

1).

Transient cognitive impairment

On average, patients had their lowest MMSE-score in the third week of the ECT-course

(Figure 1a, T1). The individual trajectory of each participant's MMSE-scores over the course

of ECT is demonstrated in a spaghetti plot (Figure 2), showing a drop in cognitive functioning

during the ECT course. 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

Transient cognitive impairment and ECT

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.

Transient cognitive impairment and ECT

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). Of clinical interest is the level of clinical dysfunction represented by the absolute MMSE-scores, with scores > 24 being indicative of no cognitive impairment (ref). The results show that both patients with and without severe WMH show significant cognitive decline during ECT, with a mean absolute MMSE-score below the clinical cut-off, however both patient groups rehabilitate above that cut-off.

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

Transient cognitive impairment and ECT

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 and because of multicollinearity reseasons. 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 charge 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

Transient cognitive impairment and ECT

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.. 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 ECT 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). Additionally, the MMSE could be not sensitive enough for ECT-induced cognitive changes. 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

Transient cognitive impairment and ECT

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 and to incorporate this in an up-to-date treatment plan (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.

Transient cognitive impairment and ECT

Previous presentation

This paper has been present at the RedPECT (Research in Psychiatry and ECT) meeting in Leuven at 12th of March 2020.

Transient cognitive impairment and ECT

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 = ≥ 50% improvement in MADRS-score. Medication during ECT: tricyclic antidepressant, Lithium or antipsychotics. Group differences in continuous variables were determined by independent samples t-test. If a variable did not met the assumptions, a Mann-Whitney U test was used as alternative. Group differences in categorical variables were calculated using χ^2-tests.

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. P-values represent pairwise comparisons Abbreviations: MMSE-score Mini Mental State Examination score, ECT = electroconvulsive therapy, WMH = white matter hyperintensities

Figure 2. Trajectory of MMSE-scores over the course of ECT in late-life depression for each participant (N = 80)

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. Abbreviations: MMSE-score Mini Mental State Examination score, ECT = electroconvulsive therapy. This plot shows the individual trajectories for each participant over the course of ECT in late-life depression.

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. Means (M) and standard-deviation (SD) are used to present the average mean MMSE-score at each time-point. Linear mixed model showed a significant overall main effect of time ($F_{(4, 74.60)}$ = 17.12, $p < 0.001$. Table shows pairwise comparison between each time-points with the mean difference (degree of freedom (df)) and values in brackets indicating the 95% confidence intervals (CI), p-values were Bonferroni corrected.
* $p < 0.05$
** p < 0.01

References

1.   Socci C, Medda P, Toni C, et al: Electroconvulsive therapy and age: Age-related clinical features and effectiveness in treatment resistant major depressive episode. J Affect Disord 2018; 227:627-632

2.   Tew JD, Jr., Mulsant BH, Haskett RF, et al: Acute efficacy of ECT in the treatment of major depression in the old-old. Am J Psychiatry 1999; 156:1865-1870

3.   Spaans HP, Sienaert P, Bouckaert F, et al: Speed of remission in elderly patients with depression: electroconvulsive therapy v. medication. Br J Psychiatry 2015; 206:67-71

4.   Salzman C, Wong E,Wright BC: Drug and ECT treatment of depression in the elderly, 1996-2001: a literature review. Biol Psychiatry 2002; 52:265-284

5.   van Diermen L, van den Ameele S, Kamperman AM, et al: Prediction of Electroconvulsive Therapy Response and Remission in Major Depression: Meta-analysis - CORRIGENDUM. Br J Psychiatry 2018; 212:322

6.   Haq AU, Sitzmann AF, Goldman ML, et al: Response of Depression to Electroconvulsive Therapy: A Meta-Analysis of Clinical Predictors. J Clin Psychiat 2015; 76:1374-1384

7.   Rhebergen D, Huisman A, Bouckaert F, et al: Older age is associated with rapid remission of depression after electroconvulsive therapy: a latent class growth analysis. Am J Geriatr Psychiatry 2015; 23:274-282

8.   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; 9:382-390

9.   Sackeim HA, Prudic J, Fuller R, et al: The cognitive effects of electroconvulsive therapy in community settings. Neuropsychopharmacology 2007; 32:244-254

10.   Tielkes CE, Comijs HC, Verwijk E, et al: The effects of ECT on cognitive functioning in the elderly: a review. Int J Geriatr Psychiatry 2008; 23:789-795

11.   Ingram A, Saling MM,Schweitzer I: Cognitive side effects of brief pulse electroconvulsive therapy: a review. J ECT 2008; 24:3-9

Transient cognitive impairment and ECT

12.   Semkovska M,McLoughlin DM: Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. Biol Psychiatry 2010; 68:568-577

13.   Rubin EH, Kinscherf DA, Figiel GS, et al: The nature and time course of cognitive side effects during electroconvulsive therapy in the elderly. J Geriatr Psychiatry Neurol 1993; 6:78-83

14.   Oudega ML, van Exel E, Wattjes MP, et al: White matter hyperintensities and cognitive impairment during electroconvulsive therapy in severely depressed elderly patients. Am J Geriatr Psychiatry 2014; 22:157-166

15.   Kumar S, Mulsant BH, Liu AY, et al: Systematic Review of Cognitive Effects of Electroconvulsive Therapy in Late-Life Depression. Am J Geriat Psychiat 2016; 24:547-565

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; 72:104-112

17.   Obbels J, Vansteelandt K, Verwijk E, et al: MMSE Changes During and After ECT in Late-Life Depression: A Prospective Study. Am J Geriatr Psychiatry 2019;

18.   Naismith SL, Norrie LM, Mowszowski L, et al: The neurobiology of depression in later-life: clinical, neuropsychological, neuroimaging and pathophysiological features. Prog Neurobiol 2012; 98:99-143

19.   Figiel GS, Coffey CE, Djang WT, et al: Brain magnetic resonance imaging findings in ECT-induced delirium. J Neuropsychiatry Clin Neurosci 1990; 2:53-58

20.   Lekwauwa RM, D.,Steffens DC: Hippocampal volume is associated with physician-reported acute cognitive deficits after electroconvulsive therapy. J Geriatr Psychiatry Neurol 2006; 19:5

21.   Dols A, Bouckaert F, Sienaert P, et al: Early- and Late-Onset Depression in Late Life: A Prospective Study on Clinical and Structural Brain Characteristics and Response to Electroconvulsive Therapy. Am J Geriatr Psychiatry 2017; 25:178-189

Transient cognitive impairment and ECT

22.   Association AP: Diagnostic and statistical manual of mental disorders, Washington DC, American Psychiatric Press, 2000

23.   Sheehan DV, Lecrubier Y, Sheehan KH, et al: The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998; 59 Suppl 20:22-33;quiz 34-57

24.   Folstein MF, Folstein SE,McHugh PR: "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. . J Psychiatric Res. 1975; 12:9

25.   Montgomery SA,Asberg M: A new depression scale designed to be sensitive to change. Br J Psychiatry 1979; 134:382-389

26.   Wahlund LO, Barkhof F, Fazekas F, et al: A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 2001; 32:1318-1322

27.   Scheltens P, Launer LJ, Barkhof F, et al: Visual assessment of medial temporal lobe atrophy on magnetic resonance imaging: interobserver reliability. J Neurol 1995; 242:557-560

28.   Scheltens P, Leys D, Barkhof F, et al: Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry 1992; 55:967-972

29.   Pasquier F, Leys D, Weerts JG, et al: Inter- and intraobserver reproducibility of cerebral atrophy assessment on MRI scans with hemispheric infarcts. Eur Neurol 1996; 36:268-272

30.   Scheltens P, Pasquier F, Weerts JG, et al: Qualitative assessment of cerebral atrophy on MRI: inter- and intra-observer reproducibility in dementia and normal aging. Eur Neurol 1997; 37:95-99

31.   Van den Broek WW, Birkenhager TK, De Boer D, et al: Richtlijn Elektroconvulsietherapie. Ned Ver voor Psychiatr. 2010; 36

32.   Kellner CH, Knapp R, Husain MM, et al: Bifrontal, bitemporal and right unilateral electrode placement in ECT: randomised trial. Br J Psychiatry 2010; 196:226-234

33.   Ringle CM, Wende S,Becker J-M: SmartPLS 3, http://www.smartpls.com, 2015

34.   Obbels J, Verwijk E, Vansteelandt K, et al: Long-term neurocognitive functioning after electroconvulsive therapy in patients with late life depression. Journal of Ect 2018; 34:207-207

35.   Verwijk E, Comijs HC, Kok RM, et al: Short- and long-term neurocognitive functioning after electroconvulsive therapy in depressed elderly: a prospective naturalistic study. Int Psychogeriatr 2014; 26:315-324

36.   Kessel v, M.A., Vlugt J, Spaans HP, et al: Psychotic depressive subtype and white mater hyperintensities do not predict cognitive side effects in ECT: A systematic review of pretreatment predictors. Journal of Affective Disorders 2020; 272:

37.   Habes M, Erus G, Toledo JB, et al: White matter hyperintensities and imaging patterns of brain ageing in the general population. Brain 2016; 139:1164-1179

38.   Hase Y, Horsburgh K, Ihara M, et al: White matter degeneration in vascular and other ageing-related dementias. J Neurochem 2018; 144:617-633

39.   Maniega SM, Valdes Hernandez MC, Clayden JD, et al: White matter hyperintensities and normal-appearing white matter integrity in the aging brain. Neurobiol Aging 2015; 36:909-918

40.   Vipin A, Foo HJL, Lim JKW, et al: Regional White Matter Hyperintensity Influences Grey Matter Atrophy in Mild Cognitive Impairment. J Alzheimers Dis 2018; 66:533-549

41.   Rizvi B, Narkhede A, Last BS, et al: The effect of white matter hyperintensities on cognition is mediated by cortical atrophy. Neurobiol Aging 2018; 64:25-32

42.   O'Neill-Kerr A, Yassin A, Rogers S, et al: Switching From Age-Based Stimulus Dosing to Dose Titration Protocols in Electroconvulsive Therapy: Empirical Evidence for Better Patient Outcomes With Lower Peak and Cumulative Energy Doses. J ECT 2017; 33:181-184

43.   Salahudeen MS, Duffull SB,Nishtala PS: Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review. BMC Geriatr 2015; 15:31

Transient cognitive impairment and ECT

44. Oltedal L, Kessler U, Ersland L, et al: Effects of ECT in treatment of depression: study protocol for a prospective neuroradiological study of acute and longitudinal effects on brain structure and function. BMC Psychiatry 2015; 15:94

45. Repple J, Meinert S, Bollettini I, et al: Influence of electroconvulsive therapy on white matter structure in a diffusion tensor imaging study. Psychol Med 2019; 1-8

46. Oudega ML, van Exel E, Stek ML, et al: The structure of the geriatric depressed brain and response to electroconvulsive therapy. Psychiatry Res 2014; 222:1-9

47. Bouckaert F, Emsell L, Vansteelandt K, et al: Electroconvulsive therapy response in late-life depression unaffected by age-related brain changes. J Affect Disord 2019; 251:114-120

48. Verwijk E, Obbels J, Spaans HP, et al: [Doctor, will I get my memory back? Electroconvulsive therapy and cognitive side-effects in daily practice]. Tijdschr Psychiatr 2017; 59:632-637

49. Cole JH, Franke K: Predicting Age Using Neuroimaging: Innovative Brain Ageing Biomarkers. Trends in Neurosciences 2017; 40:681-690

50. Jylhava J, Pedersen NL, Hagg S: Biological Age Predictors. EBioMedicine 2017; 21:29-36

Transient cognitive impairment and ECT