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Neurocognitive functioning after electroconvulsive therapy in late-life depression: a four-year prospective study

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Abstract

Objective: Despite the proven efficacy and safety of ECT, there is still concern about the possible cognitive side-effects of ECT in older patients. In this study we aimed to characterize the long-term cognitive effects of ECT in patients with late-life depression (LLD) from before the start until four years after the index ECT course.

Methods: 41 patients aged 55 years and older with a unipolar depression, referred for ECT were included. The neuropsychological test battery was assessed prior to ECT, 6 months, 1 year, 2 years, 3 years and 4 years after the last ECT session.

Results: We did not find any statistically significant cognitive changes from before the start to four years after ending the ECT-course. Although we could not detect cognitive changes at group level, we found clinically important differences on an individual level.

Conclusion: Cognitive performance in patients with LLD run a stable course from before the start of ECT until four years after the index course. At an individual level, however, both cognitive decline and improvement can be witnessed. Older patients can tolerate ECT and most of them will not experience long-term cognitive side-effects.

Key words: ECT, depression, cognition, old age.

Significant outcomes:

- ° A course of ECT in patients with late-life depression does not cause significant cognitive changes from before the start of ECT until four years after the index course.
- ° Cognitive decline and improvement were present at an individual level, although at a group level no significant cognitive changes were detected. At an individual level, an impact of normal aging cannot be ruled out.

Limitations:

- ° Missing of data due to patients drop-out must be taken into consideration when interpreting our results.
- ° Autobiographical memory was not assessed.

° The possible impact of practice effects was not assessed.

Conflict of interest:

The authors have no financial conflicts or other conflict of interest to disclose.

Data availability statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

1. Introduction

Depressive disorder is the most common mental disorder in people over 60, affecting 7% of the older population (1). Although, in older persons, depression accounts for 5.7% of years lived with disability (1) and is associated with an increased risk of death (2), it is still undertreated (3). Electroconvulsive therapy (ECT) is a safe, effective, and tolerable antidepressant for patients with late-life depression (LLD) (4), and it is used frequently in old age (5-7). An older age, even in the presence of somatic comorbidity and/or age-related brain changes, predicts a better therapeutic outcome (8-11). However, despite its proven efficacy and safety, there is still concern about the possible cognitive side-effects of ECT in older patients who may be more vulnerable to these effects than younger patients (12,13). The possible negative impact of ECT on cognition is one of the major reasons why patients

are afraid of ECT (14), why there is a long-standing stigma associated with ECT and why clinicians are reluctant to prescribe it in geriatric patients.

The recent PRIDE-study (15), however, demonstrated only minor acute cognitive side-effects in 240 LLD-patients, aged 60 or higher. These data confirm the conclusions of 3 earlier reviews: cognitive effects of ECT in LLD are limited and transient (16-18). The studies included in these reviews, however, suffer important methodological limitations. Global cognitive screening instruments are used, in small sample sizes, lacking homogeneity in diagnoses. High attrition rates are reported and results are described on a group level (18,19). It remains unclear which factors are associated with the severity and persistence of cognitive side-effects (18,19). There are, for example, conflicting results on the impact of the number of ECT-sessions, depression severity and age (20-24).

Moreover, there is a lack of long-term follow-up studies. Only 5 studies investigated the impact of ECT on cognition in older patients one-year or longer after ending an ECT-course (25-29). These studies showed that neuropsychological performance did not change (26,28,29) or showed a small improvement (25,27) during the long-term follow-up. None of these studies used a comprehensive neuropsychological test battery. Only global cognitive-screening-instruments, like the Mini Mental State Examination (30) and the Mattis Dementia Rating Scale (31) were used and follow-up was limited to a maximum of two years after ending the ECT treatment. To our knowledge, only Stoudemire et al. (25) investigated cognitive side-effects during a longer follow-up period. In that study, 74 patients (mean age of 72 years (SD=7)) were followed during four years. Cognitive function, as measured with the Mattis Dementia Rating Scale, either did not change, or improved (25).

Our study is the first to use an extensive neuropsychological test battery in patients with LLD, up to four years after finishing an ECT course, assessing cognitive function before ECT, after six months, 1 year, 2 years, 3 years, and 4 years. We also aimed to investigate whether we could find different individual courses in cognitive performance from baseline until four-years of follow-up.

2. Methods

2.1 Participants

This naturalistic four-year longitudinal study was part of the Mood Disorders in Elderly treated with ECT study (MODECT) investigating the clinical and structural brain characteristics and response to ECT (32) and builds further on an earlier study of our group on cognitive effects of ECT after six months (23). Our study was conducted at the University Psychiatric Center (KU Leuven), a tertiary psychiatric hospital in Belgium. Inclusion criteria for patients were an age of 55 years and older, a diagnosis of a unipolar depression according to DSM-IV-TR criteria (33) and a referral for an ECT treatment. Exclusion criteria were a DSM-IV psychiatric illness of bipolar disorder or schizoaffective disorder and a (history of) neurological illness (including stroke, dementia and Parkinson's disease). Forty-one patients met the inclusion/exclusion criteria and provided their written informed consent. The protocol was reviewed and approved by the local ethics review board (Ethical Review Board of the Leuven University Hospitals).

2.2 ECT procedure

ECT was administered twice a week with a constant-current brief-pulse (0.5-1 ms) device (Thymatron System IV, Somatics, IL, USA). Etomidate (0.2mg/kg) and succinylcholine (1mg/kg) was used for anaesthetic induction. At the first session, after establishing the subject's seizure threshold (ST), right unilateral ECT (RUL) (d'Elia placement) was administered at 6 times ST. Patients were treated until remission -defined as a Montgomery-Åsberg Depression Rating scale (MADRS) (34) score of less than 10 at two consecutive ratings with a week interval-, or until patients showed no further improvement during the last 2 weeks of ECT. Switching to bitemporal ECT (1.5xST) was applied when, after six RUL treatments, there was insufficient clinical improvement. Psychotropic medication was stopped at least one week prior to ECT, or if deemed impossible, kept stable from six weeks prior to and during the ECT course.

2.3 Assessments

2.3.1 Clinical assessment

The 30-item Geriatric Depression Scale (GDS) (35) was used to assess the depressive symptom severity one week prior to ECT, six months, one year, two years, three years and

four years after the last ECT. Diagnosis of depression were defined by the DSM-IV criteria (33) and confirmed by the Mini International Neuropsychiatric Interview (MINI) (36). Demographic variables and medication use were obtained by interview.

2.3.2 Neuropsychological assessment

An extensive neuropsychological test battery, assessed by a trained neuropsychologist, was used to determine cognitive functioning. The neuropsychological test covered the domain of attention, executive functioning and memory (see Table 1 for a description of the test battery). The test battery was assessed in the week before the start of the treatment course, 6 months, 1 year, 2 years, 3 years and 4 years after the last acute ECT session.

We compared the neuropsychological test performance at baseline of our sample with test performance from a matched representative normal population without a history of depression. The data of the matched normal population were obtained from studies and test manuals describing normative data (38,39,43-45). We tested whether the z-scores of our sample of patients with a depression were significantly below zero indicating significant cognitive impairment compared to the healthy control group. Results (see supplementary material for further details) indicate that depressed patients in our sample at baseline (before the start of ECT) performed significantly worse compared to the healthy control group on all the neuropsychological tests (with exception of the Meander Luria). For example, using z-scores, our sample scored at baseline on average 0.97 standard deviations below the mean of the healthy normative group on the Fluency Test-Animals (0.97 is significantly below zero; $t(36) = -7.40$, $p < 0.0001$).

2.4 Statistical analysis

To examine whether age, global cognitive functioning (MMSE) and depression-severity (GDS) at baseline could predict dropout, a logistic regression model with these predictors and dropout as criterion (1=drop-out, 0=still in the study at 4 year follow-up time point) was performed.

To investigate the change of the scores on the cognitive tests over the different discrete time points (baseline, and respectively 6 months, one year, two years, three years and four years

post-ECT) Linear Mixed Models (LMMs) (46) were estimated for each cognitive variable with repeated measurements (level 1) being nested within patients (level 2). Firstly, we estimated LMMs without covariates. Secondly, we examined the effect of age as time-invariant predictors in the model. In addition, we examined the effect of depression at the time of assessment, and number of ECT sessions since the previous assessment by including these variables as time-varying predictors in the model. Model selection and selection of the adequate variance-covariance structure was based on likelihood ratio tests and information criteria (46). When the overall F-test for time revealed significant differences between time points, pair-wise post-hoc comparisons between time points were performed using Tukey-Kraemer adjustments for multiple testing. LMMs can properly account for the correlation between repeated measurements on the same subject, use all available data, and inference is valid under the assumption of Missingness At Random (MAR) (46,47).

3. Results

3.1 Clinical and demographic characteristics

Figure 1 shows a flow chart of the patient selection. Clinical and demographic characteristics of the patients who were included are shown in Table 2. Patients had a mean age of 73.17 (sd=7.43, min=59, max=86). The sample consisted of 12 men (29 %) and 29 women (71 %). The mean GDS score decreased significantly from 23.19 (SE=0.77, min=12.5, max=29) at baseline to 9.4 (SE=1.77, min=0, max=26.5) at the four-year follow-up measurement ($F(1,19.6)=53.62, p<0.0001$). In 31 (76 %) patients, RUL ECT was used. 10 (24 %) patients were treated with bilateral ECT or switched from unilateral to bilateral ECT during their treatment course. During the follow-up period of 4 years, 15 (37,5%) patients started a second ECT-course, after which 10 (66%) patients had maintenance ECT. Two patients had a third ECT-course. We refer to the article of Dols and colleagues (32) to obtain a more detailed description of the demographics and clinical characteristics of the Belgian sample. Patients who completed the neuropsychological assessment at four years, did not differ from patients that dropped out in terms of age, baseline GDS-score and baseline MMSE-score ($X^2(3) = 3.44, p=0.33$).

3.2 Neuropsychological assessment

3.2.1 Evolution of cognitive variables from before ECT to four years after ECT without covariates

Performance on all the neuropsychological tests did not change during the four years of follow-up (Table 3) with the exception of the Meander Figure Test. Raw scores on the Meander Figure Test were, compared to baseline, significant lower at two ($t(118)=-2.99$, $p = 0.04$) and three years ($t(119)=-3.28$, $p = 0.02$) after finishing the ECT course.

3.2.2 Evolution of cognitive variables from before to four years after ECT in relation to demographic and clinical variables

After adjustment for the covariates, we could not find any statistically significant changes from before the start to four years after ending the ECT-course on any of the cognitive variables. We did not find any association between the cognitive evolution over time and the number of ECT sessions since the previous assessment. However, we found a main effect of age on five neuropsychological tests. At every time point, older patients performed worse than younger patients on the VAT A ($F(1,36)=4.96$, $p=0.03$), RAVLT total score ($F(1,41)=8.06$, $p=0.007$), RAVLT 7A ($F(1,42)=10.59$, $p=0.002$), TMT A ($F(1,41)=7.39$, $p=0.001$) and Category Fluency Test-Animals ($F(1,49)=4.06$, $p=0.049$). We did not found effects of the GDS-scores except for a negative association between GDS-scores and the performance on the Meander Figure Test two years after ending the ECT-course (time x GDS interaction: $F(5,87.3)=2.57$, $p=0.03$; slope for GDS after two years different from zero: $t(87.2)=-3.83$, $p= 0.0002$), and a negative association between GDS-scores and performance on the RAVLT 7A at all assessment (main effect: $F(1,49)=4.06$, $p=0.049$).

3.2.3 Individual differences in cognitive performance

Although we could not detect significant cognitive changes at a group level, we found individual differences among our patients at an individual level using the reliable change index. Table 4 shows that neuropsychological performance in some patients significantly deteriorated, whereas in others, it improved or remained stable. For example, Figure 2 shows individual differences in cognitive scores on the Visual Association Test.

4. Discussion

Cognitive performance, assessed with an extensive cognitive battery, in patients with LLD, runs a stable course from before the start of ECT until four years after the index course. These findings corroborate Stoudemire's results (25), failing to detect a significant change in cognitive function during 4 years after an index course of ECT, as measured with a global screening instrument (Mattis Dementia Rating Scale). Likewise, previous studies with a follow-up period of six to 24 months also suggested that older adults can tolerate ECT remarkably well (18,21).

We could not find an association between neuropsychological performance over time and the total number of ECT sessions. This strengthens the idea of other authors (48) that a higher number of ECT-sessions during maintenance ECT does not cause additional deleterious effects on cognitive function.

Our finding that a higher age, at every point in time, predicted a decreased learning capacity and delayed recall and a lower processing speed is consistent with normal aging (49,50). It is, most probably, not related to ECT.

Although we could not detect cognitive changes at a group level, we found that cognitive function in a small number of patients improved or declined during the four-year follow-up period. For example, as shown in Table 4, on the VAT A, one patient (7%) performed significantly worse, 11 patients (73%) remained stable and 3 (20%) patients performed significantly better. Several authors, although investigating individual differences during a shorter follow-up period (until 6 months post-ECT), have reported similar findings (23,51-53). At present, we know little about why some patients' cognitive function will improve and others' will decline after ECT. In our study, the number of patients experiencing a significant change in their cognitive functions was too small to analyze possible predictors.

Hypothetically, it has been argued that individuals differ in the way they cognitively evolve during their aging process (54). Consequently, a wide individual variation in paths of cognitive change is just part of normal aging. Wilson et al. (54) found in a large group of

healthy non-demented participants of 65 or older that, over a period of six years, cognitive function of some participants declined sharply, some declined gradually, and some stayed unchanged or improved. This is also in line with the study of Schouws et al. (55) who found that older patients with a bipolar disorder did not have greater cognitive decline over a five-year follow-up period as compared to a healthy control group. Our group of older patients with a unipolar depression seems to have a similar cognitive course during the four-year follow-up period.

One could argue that an improvement in cognitive performance mirrors an improvement of depression after ECT. We did not, however, find such an association, nor did several others (15,21,56). Nevertheless, interpreting cognitive performance after ECT, the impact of the depressive status cannot be overlooked. During acute phases of LLD, deficits have been observed across a wide range of cognitive domains (57-59). Moreover, longitudinal studies in older patients, as in adults, conclude that cognitive deficits could persist during remission (60,61). Our results confirm these findings. Our patients performed worse on almost every cognitive test at baseline and at four years follow-up, compared to healthy controls. Our findings are in line with the “scar hypothesis” (62,63), stating that recurrent depressive episodes are associated with more cognitive problems during aging.

The patients who showed cognitive decline did so on various neuropsychological tests. No pattern emerged from the data, and the number of ‘cognitive decliners’ was too small to perform statistical analyses. It is possible that the few patients who showed some form of cognitive decline during follow-up suffered from a (subclinical) neurodegenerative disorder, although patients with a (suspected) neurodegenerative disorder were excluded at baseline. It is also not impossible that some patients developed a neurodegenerative disorder during the follow-up period. An older age is, off course, associated with a higher prevalence of dementia in a normal population (64). Moreover, depression in later life is, likewise, associated with an increased risk of dementia (65,66). ECT, however, as shown in two large population-based studies (67,68) and in our study, is not associated with an increased risk of dementia. These findings support the use of ECT in older patients with affective disorders.

Our study is not without limitations. Firstly, we have missing data due to patients drop-out. At 4 years follow-up, only 18 patients were assessed, limiting the generalizability of our results. Missing of data must be taken into consideration when interpreting our results. Moreover, the small sample size did not allow for the comparison of different clinical and demographic characteristics between the groups of cognitive stable participants, decliners and improvers.

Secondly, we did not include an assessment of autobiographical memory. Although studies that have investigated the impact of ECT on autobiographical memory shortly after ending ECT conclude that autobiographical memory impairment seems to persist longer than other cognitive side-effects (69), studies investigating the long-term impact are lacking.

Thirdly, the lack a control arm with a group of older patients with a unipolar depression not treated with ECT precludes ruling out that the individual differences in cognitive performance are associated with other interventions than ECT during the four-year follow-up period.

A final limitation is the possible impact of practice effects. It has been shown that a performance on a cognitive test benefits from a previous experience with the test (54,70). Therefore, it is possible that the observed levels of cognitive decline after multiple testing are an underestimation of the actual levels of decline during the four-year follow-up period.

To our knowledge, this is the first study that investigated the long-term cognitive effects up to four years after ECT, using an extensive cognitive test-battery, in a larger group of patients with LLD. It is reassuring to notice that in this age-group, cognitive performance did not change from baseline to four years after ECT. At an individual level, however, both cognitive decline and improvement can be witnessed. These individual differences could be part of normal cognitive aging. Older patients can tolerate ECT and most of them will not experience long-term cognitive side-effects.

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Table 1. Overview of the neuropsychological test battery

Test	Domain
Trail Making Test A and B (TMT A & B) (37)	Processing speed and divided attention
Clock drawing (subtask “10 past 11”) (38)	Executive functioning
Meander Figure Test (39)	Executive functioning
Letter Fluency Test -“D” (40)	Fonemic fluency
Rey Auditory Verbal Learning Test (RAVLT) (41)	Verbal memory
Visual Association Test (VAT A) (42)	Visual memory
Category Fluency Test	Semantic memory

-Animals (40)

Table 2. Demographic and clinical characteristics (N = 41)

Mean age, yr (SD, min-max)	73.17 (7.43, 59-86)
Gender, male, n (%)	12 (29.27)
GDS, mean (SD, min-max)	
Baseline	23.20 (4.42, 12.50-29)
Six months post-ECT	14.17 (8.89, 1-29.5)
1 year post-ECT	9.61 (6.27, 1-20.50)

2 years post-ECT	14.78 (8.39, 2-27)
3 years post-ECT	8.76 (6.97, 1-24)
4 years post-ECT	9.12 (7.17, 0-26.5)
Total number of ECT treatments, mean (SD, min-max)	
Six months post-ECT	15.35 (9.06, 4-40)
1 year post-ECT	18.86 (14.12, 4-54)
2 years post-ECT	23.30 (20.33, 4-85)
3 years post-ECT	25.65 (23.86, 4-86)
4 years post-ECT	28.35 (27.44, 4-107)
Electrode position, n (%)	
Unilateral	31 (75.61)
Bilateral or switch from unilateral to bilateral	10 (24.39)
Number of previous depressive episodes, mean (IQR)	3.85 (2)
Onset depression, n (%)	
Early onset (<55 years)	18 (43.9)
Late onset (≥ 55 years)	23 (56.1)

Notes: SD: standard deviation; GDS: Geriatric Depression Scale.

Table 3. Neuropsychological performances from baseline until four-years after ending ECT

	Baseline	6 months post-ECT	1 year post- ECT	2 years post- ECT	3 years post- ECT	4 years post-ECT	F-test	p- value
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)		
TMT A	4.46 (0.08) ^a	4.37 (0.08) ^a	4.28 (0.09) ^a	4.38 (0.09) ^a	4.25 (0.09) ^a	4.30 (0.10) ^a	F(5,104)=1.87	0.11
TMT B	5.38 (0.10) ^a	5.38 (0.11) ^a	5.18 (0.10) ^a	5.29 (0.12) ^a	5.11 (0.14) ^a	5.14 (0.16) ^a	F(5,48.4)=1.53	0.20
Clock	2.66 (0.23) ^a	2.55 (0.31) ^a	2.30 (0.20) ^a	2.26 (0.26) ^a	2.45 (0.21) ^a	2.42 (0.32) ^a	F(5,59.8)=0.55	0.74

Drawing								
Meander Figure	3.42 (0.22) ^a	3.32 (0.24) ^{a,b}	2.96 (0.26) ^{a,b}	2.61 (0.27) ^b	2.43 (0.30) ^b	2.72 (0.30) ^{a,b}	F(5,113)=3.61	0.004
Letter Fluency- “D”	6.59 (0.61) ^a	7.38 (0.65) ^a	8.33 (0.70) ^a	7.17 (0.74) ^a	8.65 (0.82) ^a	7.57 (0.84) ^a	F(5,116)=1.64	0.15
RAVLT								
Total Score	25.96 (2.14) ^a	28.55 (1.77) ^a	27.82 (1.87) ^a	26.91 (1.73) ^a	24.89 (1.71) ^a	25.27 (1.81) ^a	F(5,18.6)=1.29	0.31
Delayed recall	4.50 (0.69) ^a	4.63 (0.55) ^a	4.81 (0.49) ^a	4.52 (0.59) ^a	4.06 (0.55) ^a	4.52 (0.62) ^a	F(5,66.5)=0.36	0.88
VAT A	9.20 (0.58) ^a	10.23 (0.42) ^a	10.32(0.43) ^a	10.03 (0.57) ^a	10.85 (0.33) ^a	10.21 (0.56) ^a	F(5,61.5)=1.77	0.13
Category Fluency Test- Animals	12.84 (0.73) ^a	13.80 (0.78) ^a	14.67 (0.83) ^a	13.44 (0.87) ^a	14.72 (0.93) ^a	14.31 (0.99) ^a	F(5,119)=1.37	0.24

Notes: TMT: Trail Making Test; RAVLT: Rey Auditory Verbal Learning Test; VAT: Visual Association Test; SE: Standard Error; Means that do not share the same superscript are significantly different using Tukey–Kramer adjustment for multiple comparisons.

Table 4. Frequency of subjects who decrease, remain stable or increase from baseline to four-years post-ECT on cognitive tasks according to the Reliable Change Index.

Decrease	Stable	Increase
Frequency (Percent)	Frequency (Percent)	Frequency (Percent)

TMT A	0	13 (92.68)	1 (7.14)
Clock Drawing	2 (13.33)	13 (86.67)	0
Meander Figure	5 (33.33)	9 (60)	1 (6.67)
RAVLT (total score)	0	13 (81.25)	3 (18.75)
VAT A	1 (6.67)	11 (73.33)	3 (20)
Category Fluency	1 (7.14)	12 (85.71)	1 (7.14)
Test-Animals			

Note: TMT B is not included in the table due to the very small sample of subjects with a TMT B (frequency: 2) score at four-year follow-up.

Figure 1. Flow chart of patient selection

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Figure 2. Individual differences in cognitive performances on the Visual Association Test (VAT) (from baseline until four-years after ECT).

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