Journal of Affective Disorders 349 (2024) 321–331

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Pre-treatment predictors of cognitive side-effects after treatment with electroconvulsive therapy in patients with depression: A multicenter study☆

Dore Loef[a,b,c,*], Philip van Eijndhoven[d], Eva van den Munckhof[d], Adriaan Hoogendoorn[a,b,c], Ruby Manten[e], Harm-Pieter Spaans[f], Indira Tendolkar[d,g], Bart Rutten[h], Jasper Nuninga[i], Metten Somers[i], Edwin van Dellen[i,j], Eric van Exel[a,b,c], Sigfried Schouws[a,b,c], Annemiek Dols[a,b,i,1], Esmée Verwijk[f,k,l,1]

[a] Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Psychiatry, Boelelaan 1117, Amsterdam, the Netherlands
[b] Amsterdam Neuroscience, Mood, Anxiety, Psychosis, Sleep & Stress Program, Amsterdam, the Netherlands
[c] GGZ inGeest Mental Health Care, Amsterdam, the Netherlands
[d] Department of Psychiatry, Radboud umc, Nijmegen, the Netherlands
[e] GGZ Noord-Holland-Noord Mental Health Care, Alkmaar, the Netherlands
[f] Parnassia Psychiatric Institute, The Hague, the Netherlands
[g] Donders Institute for Brain, Cognition and Behavior, Department of Psychiatry, Nijmegen, the Netherlands
[h] Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, the Netherlands
[i] Department of Psychiatry, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[j] Department of Neurology, Universitair Ziekenhuis Brussel Center for Neurosciences, Vrije Universiteit Brussel Brussels, Belgium
[k] University of Amsterdam, Department of Psychology, Amsterdam, the Netherlands
[l] Amsterdam UMC, AMC, Department of Medical Psychology, Amsterdam, the Netherlands

ARTICLE INFO

Keywords:
Cognitive side-effects
Electroconvulsive therapy
Depression
Predictors
Age

ABSTRACT

Background: Electroconvulsive therapy (ECT) is a highly effective treatment for major depressive episodes (MDE). However, ECT-induced cognitive side-effects remain a concern. Identification of pre-treatment predictors that contribute to these side-effects remain unclear. We examined cognitive performance and individual cognitive profiles over time (up to six months) following ECT and investigated possible pre-treatment clinical and demographic predictors of cognitive decline shortly after ECT.

Methods: 634 patients with MDE from five sites were included with recruitment periods between 2001 and 2020. Linear mixed models were used to examine how cognitive performance, assessed with an extensive neuropsychological test battery, evolved over time following ECT. Next, possible pre-treatment predictors of cognitive side-effects directly after ECT were examined using linear regression.

Results: Directly after ECT, only verbal fluency (animal and letter; $p < 0.0001$; Cohen's *d*: −0.25 and −0.29 respectively) and verbal recall ($p < 0.0001$; Cohen's *d*: −0.26) significantly declined. However, during three and six months of follow-up, cognitive performance across all domains significantly improved, even outperforming baseline levels. No other pre-treatment factor than a younger age predicted a larger deterioration in cognitive performance shortly after ECT.

Limitations: There was a substantial amount of missing data especially at 6 months follow-up.

Conclusions: Our findings show that verbal fluency and memory retention are temporarily affected immediately after ECT. Younger patients may be more susceptible to experiencing these acute cognitive side-effects, which seems to be mostly due to a more intact cognitive functioning prior to ECT. These findings could contribute to decision-making regarding treatment selection, psychoeducation, and guidance during an ECT course.

☆ The work in this manuscript is presented at the International Brain Stimulation Conference February 2023.

* Corresponding author at: Amsterdam UMC, Oldenaller 1, office H2.01, 1081 HJ Amsterdam, the Netherlands.
E-mail address: d.loef@ggzingeest.nl (D. Loef).

[1] Shared supervision.

https://doi.org/10.1016/j.jad.2024.01.049
Received 28 August 2023; Received in revised form 29 December 2023; Accepted 3 January 2024
Available online 7 January 2024

1. Introduction

Electroconvulsive therapy (ECT) is a highly effective treatment for major depressive episodes (MDE) in the context of major depressive disorder or bipolar disorder, even when psychopharmacological treatments have failed (Weiner and Reti, 2017). Despite the efficacy of ECT, only 1.2 % of patients with chronic depression received ECT in Dutch practice, resulting in a severe gap between patients who could benefit from ECT and patients actually receiving ECT (Scheepens et al., 2019). This undertreatment with ECT is mainly due to the risk of (transient) cognitive side-effects, which remains an important issue despite modern ECT techniques (Andrade et al., 2016; Porter et al., 2020). A substantial proportion of patients experience anxiety of undergoing ECT, which is often linked to the fear of memory impairment and frequently leads to refusal or discontinuation of a much-needed treatment (Obbels et al., 2017). Underuse of ECT may lead to a prolonged disease course and psychiatric malfunctioning which is associated with reduced quality of life (Johnston et al., 2019; Nuevo et al., 2010). Furthermore, cognitive impairments are already a common symptom of MDE itself (Hammar and Ardal, 2009). Reliable information on the cognitive side-effects of ECT will increase the likelihood of ECT being considered as a viable treatment option.

ECT-related cognitive side-effects have been described in several neuropsychological domains: anterograde and retrograde memory, attention, and executive functioning (Semkovska et al., 2011; Verwijk et al., 2012). ECT-induced cognitive side-effects are mainly transient. In the long term, it has been demonstrated that repeated ECT sessions do not lead to cumulative cognitive impairments (Kirov et al., 2016; Semkovska et al., 2011). Furthermore, numerous studies have shown an improvement in cognitive functioning compared to baseline, several weeks to months after a successful ECT course (Bodnar et al., 2016; Dybedal et al., 2014; Obbels et al., 2018; Verwijk et al., 2014; Weiner and Reti, 2017), which partially could be due to a learning effect (Obbels et al., 2019). However, evidence regarding changes in cognitive functioning following ECT is mainly based on the average outcome at a group level. Yet, interindividual differences exist with a subgroup of patients experiencing cognitive deficits six months post-ECT (Dybedal et al., 2014; Obbels et al., 2018). Therefore, it would be valuable to identify those patients who might be at risk for developing cognitive side-effects in response to ECT treatment and to follow up cognitive functioning over time.

Currently, it is not possible to determine a priori who is vulnerable to develop cognitive side-effects following ECT (van Kessel et al., 2020). A recent systematic review found 16 studies with over 80 % of sample sizes <100 (n range = 11 to 347) identifying a total of 16 possible pre-treatment predictors (van Kessel et al., 2020). Psychotic features and white matter hyperintensities did not predict ECT-induced cognitive side-effects, while evidence regarding the other 14 factors remained inconclusive due to conflicting results. Furthermore, 37.5 % of the studies included in this systemic review were solely based on the Mini Mental State Examination (MMSE) as cognitive outcome (Folstein et al., 1975), which may lack sensitivity to identify ECT-induced cognitive changes (Landry et al., 2021). The other 14 factors included age, sex, baseline cognitive functioning, educational level, bipolar depression and depression severity (van Kessel et al., 2020). Studies with a larger sample size are needed to identify pre-treatment predictors for ECT-induced cognitive side-effects. Also, an extended cognitive assessment battery is needed to assess domain-specific ECT-induced cognitive deficits in memory and executive functioning (van Kessel et al., 2020).

Here, we performed a unique multicenter study with a large sample size after combining data from research cohorts and clinical cohorts in which an extended neuropsychological battery was administered before, directly after, three months after, and/or six months after the ECT course. We aimed to I) examine the evolution of multi-domain cognitive performance over time following ECT, II) investigate individual cognitive profiles over time following ECT, and III) identify individual pre-treatment clinical and demographic predictors for cognitive side-effects shortly after ECT.

2. Methods

2.1. Study population

Well-characterized observational research and clinical cohorts were selected from the Dutch ECT Cohort (DEC) based on having extensive neuropsychological data available. Cohorts from five different sites were included and after excluding 29 patients due to missing information on cognitive outcomes, the resulting study sample consisted of 634 participants in total. Details about each cohort including the exclusion criteria are provided in Supplementary Table 1. In short, all cohorts recruited individuals that were diagnosed with MDE in the context of major depressive disorder or bipolar disorder by a psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria. Generally, ECT was administered twice weekly in accordance with Dutch guidelines (Van den Broek et al., 2010).

2.2. Ethical considerations

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving patients were approved by the local ethics committees of each recruiting center. For this specific study combining different cohorts, the Medical Ethics Review Committee of VU University Medical Center confirmed that the Medical Research Involving Humans Subjects Act (WMO) does not apply to the present study, as the participants were not subjected to actions and no rules or behavior were imposed on them (METC number 2021.0029). The present study used data from the Dutch ECT Cohort (DEC), which is a database partly filled with data collected from patients who are no longer under treatment and for which explicit informed consent was not obtained from all patients at the time. Given the size of DEC (n > 2000), it would cost a disproportionate amount of effort to obtain consent from these subjects, which is, among other things, due to outdated contact information and a part of patients that have passed away. Taking into account that patients have been given the opportunity to object to the use of the Data, the grounds for exception ex art. art. 24 Dutch GDPR Implementation Act juncto art. 458 WGBO (Dutch Medical Treatment Contracts Act) are invoked. Therefore, the Database will consist partly of data for which informed consent has not been obtained (but which is subject to the exceptions listed above) and partly of data for which informed consent has been obtained. Importantly, the present study does not contravene the Institutional Review Board.

2.3. Neuropsychological assessment

Neuropsychological functioning was assessed by a neuropsychologist or a supervised trained test assistant. Among the different cohorts, patients were assessed at different time points: before ECT (T0), one week after ECT (T1), at 3 months follow-up (T2), and/or at 6 months follow-up (T3) (Supplementary Table 1). The examined neuropsychological domains were attention, memory, processing speed, and executive functioning. Table 1 shows an overview of the used neuropsychological test battery per site.

For each test, norm scores expressed as T-scores were calculated if available based on demographic characteristics such as age, sex and level of education (Schmand et al., 2012). A higher T-score indicates a better cognitive performance. Standardized *Z*-scores were calculated for those tests without norm scores or in order to compare different test versions with each other (words memory learning test and Digit Span Task). In line with the method of Muslimović et al. (2009), we replaced a missing value by the worst value observed within that specific cohort,

Table 1
Overview of the neuropsychological test battery with the corresponding cognitive functions used per cohort.

	Measuring cognitive function	Parnassia clinical cohort	Parnassia research cohort	GGZ inGeest first research cohort	GGZ inGeest MODECT	Radboudumc research cohort	UMC Utrecht research cohort	Maastricht UMC research cohort
Words memory learning test	Verbal memory and learning with subtests: immediate recall, delayed recall and recognition	8-Words memory learning subtest of the ADS6 (Lindeboom and Jonker, 1989) and D-RAVLT (Saan and Deelman, 1986)	Not available	10-Words memory learning test	8-Words memory learning subtest of the ADS6 (Lindeboom and Jonker, 1989)	D-RAVLT (Saan and Deelman, 1986)	D-RAVLT (Saan and Deelman, 1986)	D-RAVLT (Saan and Deelman, 1986)
Verbal fluency test (Dutch version)								
Letter fluency (Mulder et al., 2006)	Executive functioning	Letters "D", "A", "T"	Letters "D", "A", "T"	Letter "D"	Letter "D"	Letters "N", "A"	Letters "N", "A"	Not available
Categorical fluency (Luteijn and Van der Ploeg, 1983)	Semantic memory	Animals and professions	Animals and professions	Animals	Animals	Animals and professions	Animals and professions	Animals and professions
Trail making test (TMT) A + B (Reitan and Wolfson, 1985)	TMT A: visual attention, TMT B: task switching to measure executive functioning	TMT A + B	Not available	TMT A + B	TMT A + B	TMT A + B	TMT A + B	Not available
Stroop-color word interference test (duration in seconds) (Delis et al., 2001)	Stroop 1 (word naming) + 2 (color naming): processing speed, Stroop 3 (color naming with incongruent stimuli): verbal inhibition	Stroop 1–3	Not available	Stroop 1–3	Not available	Stroop 1–3	Stroop 1–3	Stroop 1–3
Digit span tasks of the Wechsler Adults Intelligence Scale (WAIS)	Processing speed, working memory and task switching	Digit span task Version IV (Wechsler, 2012)	Not available	Digit span task Version III (Wechsler, 2000)	Not available	Not available	Digit span task Version IV (Wechsler, 2012)	Not available

In order to analyze the results of the letter fluency (LF) altogether, we calculated the expected total LF score on the "D" "A" and "T" for participants with only a score on the "D" and the total score on the "N", "A" and "K" for participants with only a score on the "N" and "A" by means of regression formulas based on a large existing database (de Vent et al., 2016). ADS6 = Amsterdamse Dementie-Screeningtest; D-RAVLT = Dutch version of the Rey Auditory Verbal Learning Test.

when a participant had attempted to perform a test, but was unable to do it (46 values in total over all time points) (Muslimović et al., 2009).

2.4. Clinical characteristics

The following demographical and clinical characteristics were assessed at baseline: age, sex assigned at birth (female/male), level of education (lower = no education to finished low-level secondary education/medium = finished average-level secondary education/high = finished high-level secondary education or university degree), type of depression (unipolar/bipolar), age at first depressive episode, number of previous depressive episodes, duration of current episode (in months), history of cardiovascular disease (yes/no), Diabetes Mellitus type 2 (yes/no), hypertension (yes/no), Body Mass Index (BMI), smoking status (current/former/non-smoker), presence of psychotic features (yes/no), pre-ECT severity of depression, and pre-ECT MMSE scores (Folstein et al., 1975).

Regarding the assessment of depression severity, Montgomery–Åsberg Depression Rating Scale (MADRS; (Montgomery and Asberg, 1979)) scores were available of more patients than Hamilton Depression Rating Scale (HDRS) 17-item scores (Hamilton, 1960). Therefore, HDRS scores were converted to MADRS scores using a validated method (Leucht et al., 2018).

2.5. Statistical analysis

Analyses were performed in Stata version 18.0 and IBM SPSS version 28. Pearson correlations were executed to examine the relation between symptom severity and cognitive performance. To examine the course of the cognitive variables over time following ECT, 18 linear mixed models (LMM) were estimated, one for each cognitive variable. Since the data were structured in three levels – repeated measurements (level 1; T0–T3) nested within patients (level 2) who are nested within study cohorts (level 3) – each LMM had two levels of random effects and time indicators as fixed effects modelling mean development from baseline measurement over time. LMMs for cognitive outcomes without norm scores were adjusted for age and level of education, by including these variables in the model as additional fixed effects. Bonferroni correction for 18 cognitive outcomes ($p = 0.05/18 = 0.0028$) was used to correct for multiple testing. For each outcome, when the null-hypothesis for constant levels over time was rejected at the Bonferroni-corrected significance level, pairwise comparisons between time points were performed to identify time points where predicted outcomes differed significantly. Effect sizes (standardized mean differences) were calculated by dividing differences of expected means between time points by the standard deviation at T0.

Next, to explore individual cognition profiles over time, individuals' Reliable Change Index (RCI) was calculated using the raw scores in the RCI formula of Jacobson and Truax: $(X_2 - X_1)$ / SEdiff, where SEdiff denotes the standard error of the difference score, and X_2 and X_1 is the retest and the initial baseline score of the cognitive variable respectively (Jacobson and Truax, 1991). SEdiff = $\sqrt{(2S^2(1 - r))}$ with S being the standard deviation of the baseline scores and r being the test-retest reliability of the cognitive test. Test-retest reliability coefficients indicated in the manuals of the included tests were used. RCI values larger than ±1.645 (alpha set to 0.10, two-tailed) were defined as reliable

change (i.e. a reliable decrease or increase) in a cognitive measure.

Finally, we developed prognostic prediction models for change in cognitive functioning directly after ECT using pre-treatment clinical and demographic factors. The continuous RCI from T0 to T1 of those cognitive measures that showed a significant decline directly after ECT were selected as outcome measures, as these identify the most evident cognitive deficits that could best be attributed to the effects of ECT. Fourteen baseline characteristics were included as potential predictors based on previous literature (van Kessel et al., 2020), while all analyses were corrected for number of ECT sessions and electrode placement (unilateral/(switched to) bilateral). To deal with missing data on both independent variables and outcome variables (Supplementary Table 2), missing values were imputed using multiple imputation (100 imputations) with chained equations, implicitly implying the assumption of missingness at random. Correcting for study cohorts as random effects was omitted, as this did not improve the model in 99 % of imputations. Multivariable linear regression was executed to develop a prediction model using the backward elimination technique in which the independent variable with the highest *p*-value was repeatedly removed manually from the model if it exceeded a p-value of 0.1. Models were fitted using the combined imputed data sets and model coefficients and their standard errors were estimated using Rubin's rules. Multivariable fractional polynomials were used to consider nonlinear associations between continuous predictors and the outcomes using the mfpmi package (Morris and Royston, 2016). The models' overall predictive performance was evaluated using R^2-statistic (i.e. a measure of the proportion of variance explained by the models). Furthermore, calibration was assessed, which is the models ability to give unbiased estimated of the predicted outcome. First, the mean calibration was calculated, which is the difference between the mean observed outcome and the mean predicted outcome. Second, the calibration slope was calculated, which indicates the average strength of the predictor effects. We used internal validation to check if the developed prediction models were overfitted, applying the bootstrap resampling technique to adjust the apparent R^2-statistic, the mean calibration and the calibration slope for optimism. For each imputed data set, we generated 500 bootstrap samples from the original sample, fitted the model in each bootstrap sample and tested the model on the original sample to estimate optimism in model performance. We used median scores to combine adjusted versions of the R^2-statistic, mean calibration and calibration slopes across imputed data sets. The optimism adjusted calibration slope was also used as a uniform shrinkage factor to adjust the effects of predicted regression coefficients for potential over or underfitting and the intercept of the model with the adjusted coefficients was re-estimated to maintain overall model calibration, thus producing a final model.

Table 2
Baseline demographic, clinical and treatment characteristics.

	All participants N = 634	Parnassia clinical cohort n = 255	Parnassia research cohort n = 79	GGZ inGeest first research cohort n = 64	GGZ inGeest MODECT n = 64	Radboudumc research cohort n = 110	UMC Utrecht research cohort n = 43	Maastricht UMC research cohort n = 19
Demographic characteristics								
Age, mean (SD)	61.3 (15.9)	61.1 (16.5)	62.9 (14.5)	73.8 (8.0)	72.2 (9.0)	52.3 (13.4)	51.1 (14.5)	52.6 (14.4)
Sex, female, n (%)	401 (63.2)	159 (62.4)	53 (67.1)	40 (62.5)	40 (62.5)	68 (61.8)	28 (65.1)	13 (68.4)
Level of education								
Lower, n (%)	228 (37.6)	88 (34.8)	39 (50.0)	24 (44.4)	18 (36.0)	34 (30.9)	18 (41.9)	7 (36.8)
Medium, n (%)	184 (30.3)	87 (34.4)	17 (21.8)	13 (24.1)	12 (24.0)	37 (33.6)	13 (30.2)	5 (26.3)
High, n (%)	195 (32.1)	78 (30.8)	22 (28.2)	17 (31.5)	20 (40.0)	39 (35.5)	12 (27.9)	7 (36.8)
Clinical characteristics								
Bipolar disorder n (%)	85 (13.4)	44 (17.3)	14 (17.7)	0 (0.0)	0 (0.0)	17 (15.5)	3 (7.0)	7 (36.8)
Previous depressive episodes, median (IQR)	2.0 (3), n = 432	0.0 (2), n = 84	2.0 (3), n = 75	2.0 (3). n = 61	2.0 (3), n = 64	2.0 (2), n = 103	2.5 (5), n = 38	2.0 (3), n = 7
Duration of current episode in months, median (IQR)	8.0 (14), n = 425	6.0 (7), n = 101	8.0 (21), n = 78	6.0 (9), n = 62	8.0 (15), n = 63	12.0 (16), n = 106	Not available	11.0 (19), n = 15
Age at onset of first depression, mean (SD)	43.5 (20.1), n = 395	43.5 (21.5), n = 133	Not available	60.3 (18.3), n = 38	54.9 (17.4), n = 64	35.7 (15.1), n = 109	32.5 (16.2), n = 41	38.0 (12.6), n = 10
With psychotic features n (%)	258 (41.1)	113 (44.3)	40 (53.3)	38 (60.3)	31 (48.4)	29 (26.4)	2 (4.9)	5 (26.3)
MMSE before, mean (SD)	26.2 (4.0), n = 413	26.6 (4.0), n = 216	Not available	25.5 (3.9), n = 62	24.4 (5.5), n = 53	27.1 (2.2), n = 65	Not available	26.7 (3.7), n = 17
ECT characteristics								
Number of ECT sessions, mean (SD)	12.7 (7.5), n = 574	11.3 (7.2), n = 254	11.8 (7.3), n = 76	11.9 (7.1), n = 32	12.0 (6.7), n = 64	16.7 (6.1), n = 93	19.2 (9.5), n = 36	6.2 (2.8), n = 19
Patients treated bilateral or switched to bilateral, n (%)	244 (43.2)	71 (27.8)	20 (27.0)	8 (44.4)	31 (48.4)	52 (56.5)	43 (100.0)	19 (100.0)
Depression measures								
MADRS before, mean (SD)	30.7 (8.7), n = 552	30.8 (8.0), n = 200	28.9 (9.5), n = 75	34.3 (9.7), n = 62	32.5 (9.2), n = 58	28.9 (7.5), n = 96	29.9 (10.0), n = 43	32.6 (6.8), n = 18
MADRS after, mean (SD)	12.2 (10.3), n = 521	10.6 (10.4), n = 181	9.5 (10.9), n = 65	10.4 (9.7), n = 62	10.6 (9.6), n = 62	17.6 (9.3), n = 96	15.1 (9.6), n = 38	15.3 (8.4), n = 17
Response after ECT, n (%)	315 (64.4)	110 (70.1)	45 (69.2)	50 (80.6)	42 (73.7)	37 (39.4)	19 (50.0)	12 (75.0)
Remission after ECT, n (%)	264 (50.7)	107 (59.1)	43 (66.2)	38 (61.3)	38 (61.3)	19 (19.8)	13 (34.2)	6 (35.3)

Note: Categorical variables document valid percentages, i.e. excluding missing data. Level of education is divided in lower (i.e. no education to finished low-level secondary education), medium (i.e. finished average-level secondary education), and high (i.e. finished high-level secondary education or university degree). ECT = electroconvulsive therapy; MMSE = Mini-Mental State Examination; MADRS = Montgomery-Asberg Depression Rating Scale.

3. Results

3.1. Study sample

In total, 634 patients of five different sites were included in the analyses. The age ranged from 17 to 92 (M = 61.3, SD = 15.9) and 63.2 % was female (Table 2). Response after ECT, defined as a reduction in MADRS score of ≥50 %, was achieved by 64.4 % of patients. Remission after ECT, defined as a MADRS score below 10, was achieved by 50.7 % of patients.

3.2. Course of cognitive performance following ECT

A significant change in all sub-items of the verbal fluency, words memory learning tests and TMT, and in Stroop 2 and Stroop 3 (given the score on Stroop 2) over the four time points was found ($p < 0.001$) (Table 3; Fig. 1), whereas the Stroop 1 and Digit Span Tasks showed only a nominally significant change between the different time points.

Cognitive performance shortly after ECT (T0 compared to T1) showed a significant decline in the RAVLT delayed recall (given the total score) and the verbal fluency (CF animals and LF). Furthermore, verbal learning measured by the combined words memory learning tests total score and the ability to inhibit cognitive interference (both Stroop 3 and Stroop 3 given the score on Stroop 2), showed a significant improvement from T0 to T1.

Concerning the three months follow-up after ECT (T1–T2), performance on all cognitive measures improved significantly, except for the ability to inhibit cognitive interference (Stroop 3 given the score on Stroop 2). The cognitive outcomes at three months following ECT were even significantly better than the performance before ECT (T0–T2), except for RAVLT delayed recall given the total score and CF animals. Six months following ECT, most cognitive measures showed no further improvement compared to three months follow up (T2–T3). However, some cognitive functions showed a significant decline at six months following ECT compared to three months: the RAVLT delayed recall (given the total score), task switching (TMT B given the score on TMT A), and the ability to inhibit cognitive interference (Stroop 3 given the score on Stroop 2).

Pearson correlations showed only a significant association between pre-ECT depression severity and processing speed (Stroop 1, $p = 0.046$ and Stroop 2, $p = 0.042$) and between depression severity directly after ECT and delayed recall measured by the combined words memory learning tests (p = 0.046), processing speed and the ability to inhibit cognitive interference (all Stroop tasks: 1, $p = 0.023$; 2, $p = 0.039$; 3, $p = 0.004$; 3 given score on Stroop 2, $p = 0.045$).

3.3. Individual variability in cognitive changes over time following ECT

Supplementary Fig. 1 shows the percentages of patients per reliable change category (i.e. declined, stable or improved). For almost all cognitive variables, the performance of the majority of patients remained stable after ECT. However, a subset of patients showed a clinically relevant decline or improvement on cognitive performance. Compared to baseline (T0), the percentage of patients who deteriorated per cognitive measure ranged from 5 % to 17 % directly after ECT (T1), from 2 % to 9 % after 3 months (T2), and from 4 % to 23 % after 6

Table 3
Estimated means (SE) and sample size for different cognitive performances over time following electroconvulsive therapy with test results for equality over time from Linear Mixed Models and pairwise comparisons of time points of the cognitive measures that showed a Bonferroni-corrected significant difference between the different time points.

	T0 (before ECT)	T1 (one week after ECT)	T2 (follow-up after 3 months)	T3 (follow-up after 6 months)	Difference between the different time points	Pairwise comparison of time points					
						T0 – T1	T0 – T2	T0 – T3	T1 – T2	T1 – T3	T2 – T3
RAVLT total score, norm score	35.0 (0.95), n=316	36.4 (1.10), n=236	41.2 (1.17), n=127	40.7 (2.53), n=25	**F(3, 58.2)=18.69, *p*<0.001**	d=0.10	d=0.47****	d=0.43*	d=0.37****	d=0.33	d=-0.04
RAVLT delayed recall, norm score	37.8 (0.97), n=313	34.6 (1.10), n=234	41.0 (1.19), n=127	36.1 (2.32), n=25	**F(3, 61.5)=27.83, *p*<0.001**	**d=-0.26**** **	d=0.33****	d=-0.14	d=0.60****	d=0.13	**d=-0.47***
RAVLT delayed recall given the total score, norm score	48.2 (0.62), n=312	41.5 (0.72), n=234	47.1 (0.96), n=127	41.7 (2.33), n=25	**F(3, 59.4)=23.42, *p*<0.001**	**d=-0.62**** **	d=-0.10	**d=-0.59***	d=0.51****	d=0.03	**d=-0.49***
Combined words memory learning tests total score, Z-score	-0.08 (0.09), n=458	0.08 (0.09), n=344	0.37 (0.10), n=157	0.32 (0.12), n=90	**F(3, 155.4)=25.39, *p*<0.001**	d=0.16**	d=0.45****	d=0.40***	d=0.29****	d=0.24*	d=-0.05
Combined words memory learning tests delayed recall, Z-score	-0.03 (0.06), n=458	-0.11 (0.07), n=342	0.36 (0.08), n=158	0.34 (0.11), n=92	**F(3, 165.0)=29.81, *p*<0.001**	d=-0.08	d=0.42****	d=0.39***	d=0.50****	d=0.48****	d=-0.03
Combined words memory learning tests recognition, Z-score	-0.06 (0.06), n=425	-0.09 (0.06), n=339	0.17 (0.07), n=156	0.37 (0.10), n=78	**F(3, 114.7)=14.60, *p*<0.001**	d=-0.03	d=0.24***	d=0.44****	d=0.27****	d=0.47****	d=0.20
CF animals, norm score	42.9 (3.85), n=525	39.3 (3.86), n=400	44.1 (3.88), n=215	43.8 (3.92), n=139	**F(3, 194.5)=21.88, *p*<0.001**	**d=-0.25**** **	d=0.08	d=0.06	d=0.33****	d=0.31****	d=-0.02
CF professions, norm score	39.6 (6.32), n=245	41.5 (6.35), n=167	46.3 (6.37), n=102	46.1 (6.43), n=76	**F(3, 88.5)=13.62, *p*<0.001**	d=0.09	d=0.33****	d=0.32****	d=0.24****	d=0.23**	d=-0.01
LF, norm score	43.0 (1.95), n=491	39.5 (1.97), n=366	44.9 (2.02), n=209	45.8 (2.04), n=135	**F(3, 208.3)=38.29, *p*<0.001**	**d=-0.29**** **	d=0.16**	d=0.24***	d=0.46****	d=0.53****	d=0.07
TMT A, norm score	35.2 (2.25), n=427	35.5 (2.28), n=316	37.9 (2.36), n=153	39.9 (2.45), n=86	**F(3, 153.1)=7.10, *p*<0.001**	d=0.02	d=0.17**	d=0.30***	d=0.15**	d=0.28**	d=0.13
TMT B, norm score	34.3 (2.91), n=386	35.1 (2.94), n=275	39.8 (2.99), n=142	38.2 (3.03), n=87	**F(3, 130.5)=16.37, *p*<0.001**	d=0.06	d=0.37****	d=0.26**	d=0.31****	d=0.21*	d=-0.11
TMT B given the score on TMT A, norm score	40.1 (1.69), n=385	41.0 (1.75), n=275	44.4 (1.81), n=140	40.8 (1.90), n=87	**F(3, 157.8)=8.89, *p*<0.001**	d=0.08	d=0.34****	d=0.06	d=0.26***	d=-0.02	**d=-0.28***
Stroop 1, norm score	35.2 (2.14), n=364	35.0 (2.14), n=308	36.9 (2.21), n=147	37.9 (2.41), n=49	F(3, 74.4)=4.07, *p*=0.010						
Stroop 2, norm score	35.1 (1.53), n=363	34.8 (1.56), n=306	38.6 (1.62), n=146	41.0 (2.29), n=49	**F(3, 68.0)=14.99, *p*<0.001**	d=-0.02	d=0.30****	d=0.51**	d=0.32****	d=0.52**	d=0.20
Stroop 3, norm score	38.1 (1.92), n=349	40.2 (1.95), n=296	42.0 (1.99), n=144	42.1 (2.26), n=49	**F(3, 53.6)=13.76, *p*<0.001**	d=0.20***	d=0.37****	d=0.37**	d=0.17**	d=0.18	d=0.01
Stroop 3 given the score on Stroop 2, norm score	47.7 (0.65), n=349	50.5 (0.70), n=296	50.4 (0.78), n=144	47.5 (1.17), n=49	**F(3, 98.9)=10.14, *p*<0.001**	d=0.30****	d=0.28****	d=-0.02	d=-0.02	**d=-0.32***	**d=-0.30***
Digit Span Task forward, Z-scores	-0.30 (0.30), n=300	-0.37 (0.30), n=241	-0.18 (0.30), n=109	-0.40 (0.30), n=60	F(3, 11.3)=4.48, *p*=0.027						
Digit Span Task backward, Z-scores	-0.18 (0.17), n=297	-0.16 (0.17), n=240	-0.05 (0.18), n=109	-0.09 (0.18), n=60	F(3, 88.4)=1.36, *p*=0.259						

Differences between the different time points at a Bonferroni-corrected significance level (p = 0.05/18 = 0.0028) are displayed in boldface. Effect sizes (Cohen's *d*; calculated by dividing the estimated mean difference by the standard deviation at T0) of pairwise comparisons of time points are only displayed of the cognitive measures that showed a Bonferroni-corrected significance difference between the different time points: significant differences are displayed in boldface where green indicates a significant increase and red indicates a significant decrease in mean scores. * = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$, **** = $p \leq 0.0001$. CF = category fluency; LF = letter fluency; RAVLT = Rey Auditory Verbal Learning Test; TMT = Trail Making Test.

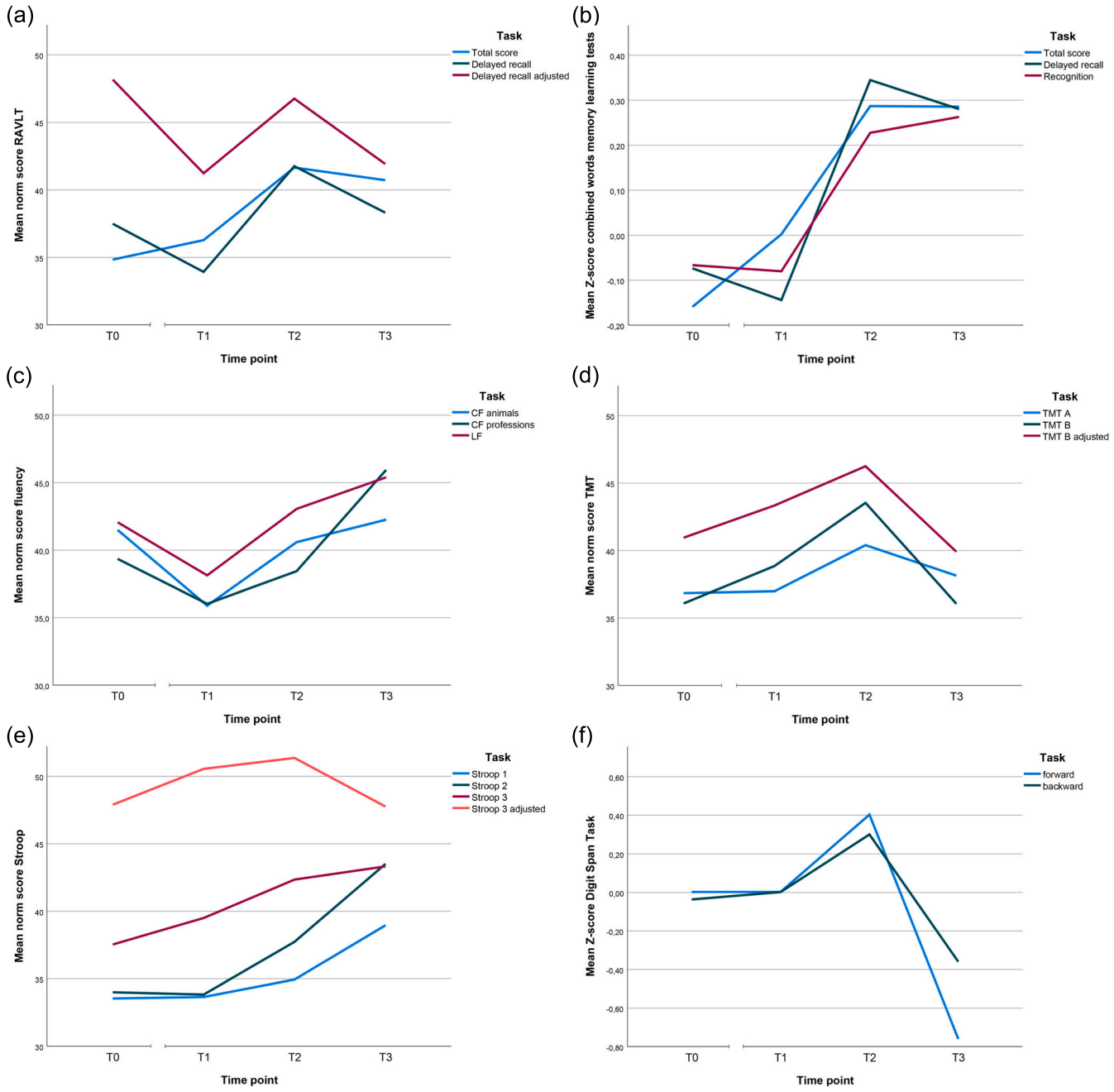

Fig. 1. The observed means of all cognitive measures at each time point (T0 = before ECT, T1 = one week after ECT, T2 = 3 months follow-up, T3 = 6 months follow = up).
(a) the Rey Auditory Verbal Learning Test (RAVLT) subtests (verbal memory and learning), (b) the combined words memory learning tests (verbal memory and learning), (c) the fluency tasks (CF = category fluency; executive functioning, LF = letter fluency; semantic memory), (d) the Trail Making Test (TMT; visual attention and task switching), (e) the Stroop (processing speed and verbal inhibition), and (f) the Digit Span Task (processing speed, working memory, and task switching). The x-axis between T0 and T1 shows a small interruption, as the time between the start of ECT and one week after ECT is variable. The delayed recall adjusted is a separate norm score given the total score, the TMT B adjusted is a separate norm score given the score on TMT A, and the Stroop 3 adjusted is a separate norm score given the score on Stroop 2.

months (T3). Furthermore, compared to baseline, the percentage of patients who improved per cognitive measure ranged from 1 % to 30 % at T1, from 0 % to 47 % at T2, and from 0 % to 60 % at T3.

3.4. Pre-treatment predictors for cognitive side-effects shortly after ECT

The cognitive variables RAVLT delayed recall, CF (animals), and LF showed a statistical significant decline between T0–T1 (Table 3) and were therefore selected for prognostic modelling. Table 4 shows that after backward elimination, age remained in all models of the three cognitive outcomes and sex, although not significant ($p = 0.093$), only remained for RAVLT delayed recall. Continuous factors were modelled as linear in all models. In all models, the strongest predictor in terms of statistical significance was age. Only for the fluency tasks, age significantly predicted cognitive change after ECT (T0–T1): a younger age predicted a higher decrease in verbal fluency after ECT (Fig. 2). The apparent R^2-statistic were low: ranging from 0.044 to 0.077 for the full models with all predictors and from 0.020 to 0.043 for the reduced

Table 4
Estimated regression coefficients β (95 % CI) with *p*-values of the retained predictors of the cognitive outcomes (T0–T1 Reliable Change Indices (RCI) of the RAVLT delayed recall, Category Fluency animals and Letter Fluency) after backward elimination.

	RCI T0–T1 RAVLT delayed recall	RCI T0–T1 Category Fluency animals	RCI T0–T1 Letter Fluency
Model intercept	−1.030	−1.114	−0.795
Age, years	0.008 (−2.28 × 10^{-4} to 0.016), p = 0.057	0.013 (0.006 to 0.020), p < 0.001	0.008 (4.93 × 10^{-4} to 0.015), p = 0.036
Sex (male)	0.216 (−0.036 to 0.469), p = 0.093		
ECT parameters corrected for			
Electrode placement (bilateral)	−0.140 (−0.456 to 0.175), p = 0.383	−0.198 (−0.461 to 0.064), p = 0.139	−0.209 (−0.511 to 0.092), p = 0.173
Total number of sessions	−0.005 (−0.025 to 0.015), p = 0.637	−6.64 × 10^{-4} (−0.018 to 0.017), p = 0.941	0.002, (−0.017 to 0.021), p = 0.844
R^2	0.025	0.043	0.020
Optimism adjusted R^2	0.014	0.035	0.012
Optimism adjusted calibration mean	−0.046	−0.013	−0.033
Optimism adjusted calibration slope	0.874	0.967	0.914
Optimism adjusted intercept	−1.048	−1.135	−0.807

RCI = Reliable Change Index; T0 = before ECT, T1 = one week after ECT; RAVLT = Rey Auditory Verbal Learning Test; ECT = electroconvulsive therapy. Note on calibration: for a prognostic prediction model, the optimism adjusted calibration slope should be applied as a uniform shrinkage factor (i.e. optimism adjusted coefficients of the prediction model can be obtained by multiplying the regression coefficients in the upper part of the table with this factor) and the adjusted intercept should be used.

models. After adjusting for optimism, R^2 values ranged from 0.003 to 0.031 for the full models and 0.012 to 0.035 for the reduced models (Table 4).

Age median split was performed to provide insight into the cognitive performance for the different age groups at baseline and shortly after ECT. Fig. 2 shows that the cognitive performance (norm scores) at baseline (T0) was higher in the younger age group (≤62 years) compared to the older age group, followed by a decrease in the younger age group shortly after ECT (T1), while the cognitive performance of the older group remained relatively stable. The significant relationship between age and deterioration in verbal fluency indeed disappeared when correction for baseline norm scores. Thus, the higher decrease in cognitive performance after ECT in younger patients appears to be mainly due to the better cognitive performance of this group before ECT. In the final models, none of the ECT parameters corrected for (electrode placement and total number of ECT sessions) were significantly associated with the cognitive outcome measures (Table 4). To examine the possible effect of additional ECT parameters, mean dosage (begin and end dose averaged) relative to seizure threshold and pulse width at the first and last ECT were added to the final models, which did not alter the results and were therefore omitted.

4. Discussion

We examined cognitive performance in this unique, multi-cohort study with the largest study sample to date with extended neuropsychological data of patients undergoing ECT for unipolar or bipolar depression. Examining the course over time showed that some cognitive side-effects emerge directly after ECT, but these changes are transient and over the long term (at three months follow-up) cognitive performance exceeds baseline levels. Age was the only characteristic that predicted cognitive decline in verbal fluency from baseline to directly after ECT. A younger age was associated with a higher decrease in cognitive performance, as the cognitive performance before ECT was higher in younger patients, after which they decreased substantially after ECT, while older patients remained relatively stable.

4.1. Course of cognitive performance following ECT

The first aim of the present study was to examine the evolution of multi-domain cognitive performance over time following ECT. Directly after ECT, significant declines in the ability to facilitate information retrieval from memory (verbal fluency — categorical and letter) and the ability to recollect earlier acquired information (delayed recall) were identified, which is in line with the findings of several studies (Bodnar et al., 2016; Hebbrecht et al., 2022; Semkovska and McLoughlin, 2010; Verwijk et al., 2012). Our findings support the trend reported in several reviews that the recall of new verbal information is more disturbed than learning new verbal information (Semkovska and McLoughlin, 2010; Verwijk et al., 2012). As for the long-term effects, a significant improvement was found in all included cognitive domains from directly after ECT to three months follow-up, which is in line with research results indicating that ECT-induced cognitive deterioration is transient (Kirov et al., 2016; Semkovska et al., 2011). Additionally, the level of cognitive functioning after three months following ECT outperformed the level of cognitive functioning pre-ECT, which might be a confirmation for the association between symptom severity in MDE and cognitive performance (McClintock et al., 2010b; McDermott and Ebmeier, 2009). This association could also be an explanation for the significant decline of some cognitive measures from three to six months follow-up, as relapse rates after successful ECT are approximately 50 % at six months follow-up (Jelovac et al., 2013; Prudic et al., 2013). However, some studies, among which several ECT studies, did not find this specific association (Hebbrecht et al., 2020; McClintock et al., 2010a; Obbels et al., 2018; Verwijk et al., 2014). In our sample, Pearson correlations indicate only significant associations between depression severity and delayed recall measured by the combined words memory learning tests, processing speed and the ability to inhibit cognitive interference (all Stroop tasks). Correspondingly, a higher depression severity score is associated with worse performance on these tasks.

4.2. Pre-treatment clinical predictors of ECT-induced short term cognitive side-effects

The second aim was to investigate individual cognitive profiles over time following ECT. In line with previous research (Dybedal et al., 2014; Hebbrecht et al., 2020; Obbels et al., 2018; Ziegelmayer et al., 2017), our study demonstrated that whereas the vast majority of patients remained cognitively stable, there is a subset of patients who may experience cognitive side-effects following ECT and another subset of patients who may show cognitive improvement. Thus, in clinical practice this considerable heterogeneity regarding ECT-induced cognitive deficits should be taken into account and further guidance should be tailored to the specific individual. The third aim was to identify individual pre-treatment clinical and demographic predictors for cognitive side-effects shortly after ECT. Although we included a large number of factors identified by previous research to develop prognostic models, the performance of the models were poor and they failed to accurately predict ECT-induced cognitive side-effects. In accordance with a recent systematic review (van Kessel et al., 2020), the presence of psychotic features did not predict cognitive outcome. Only age was predictive of deterioration in cognitive performance directly after ECT: a younger age predicted a higher decrease in verbal fluency after ECT, as the cognitive performance before ECT was better in younger patients, after which they decreased substantially after ECT, while older patients remained relatively stable. A previous ECT study with a large sample size reported that

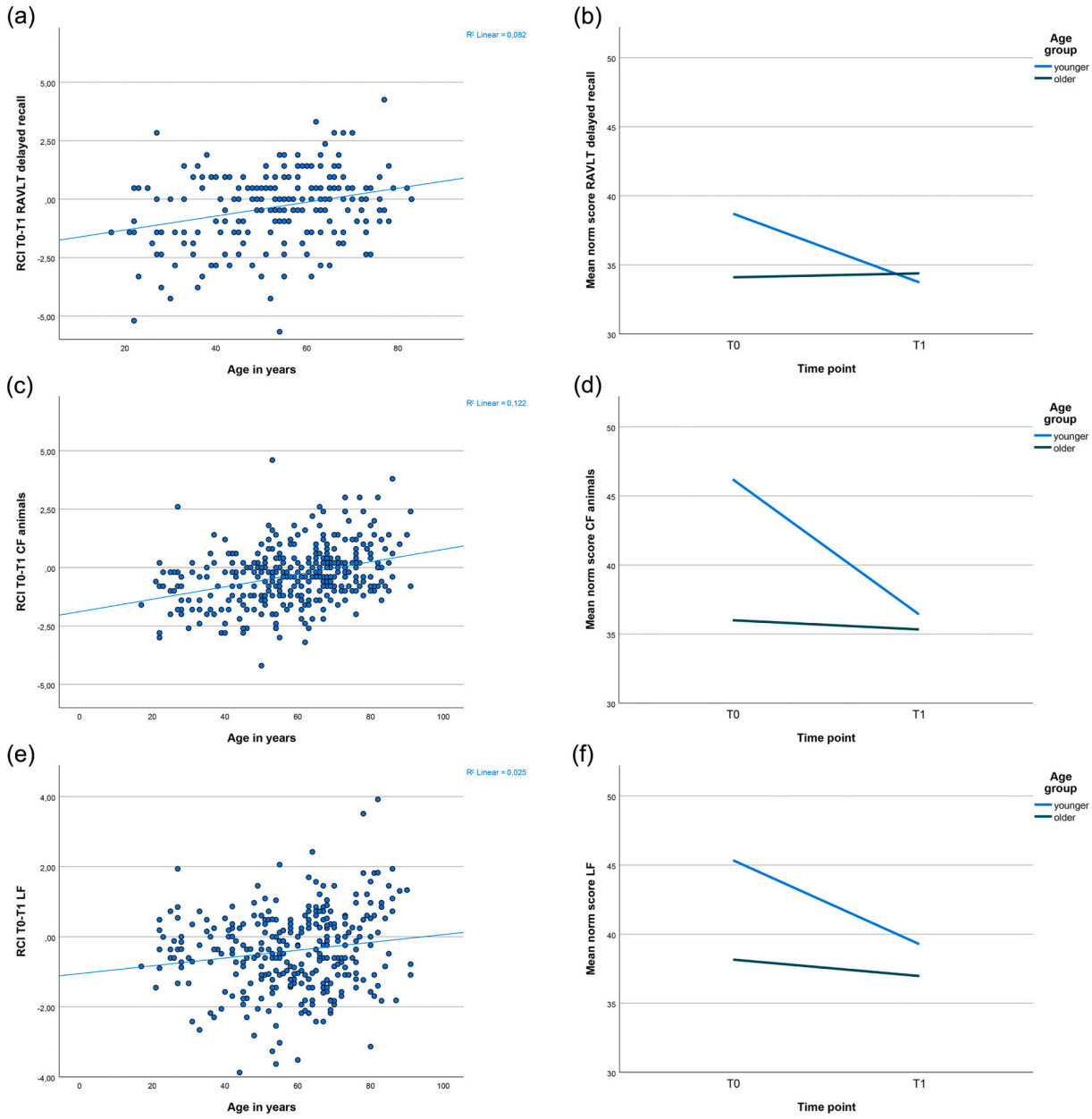

Fig. 2. Relationship between age and reliable change of the cognitive measures and difference between the age groups in both baseline and change in norm scores of the Rey Auditory Verbal Learning Test (RAVLT) delayed recall (a, b), category fluency (CF) animals (c, d), and letter fluency (LF) (e, f).
RCI = Reliable Change Index; T0 = before ECT; T1 = one week after ECT.

advancing age was associated with greater cognitive deficits (Sackeim et al., 2007). This contradiction may be explained by several factors. First, none of the cognitive outcomes used in our prediction analysis are equivalent to those of the study of Sackeim et al. (2007). Second, there are demographic differences between the study cohorts with a mean age of 61.3 in our study versus 56.7 in the study of Sackeim et al. (2007). Third, a part of Sackeim's study sample was treated with sine wave stimulation, which is known to cause more cognitive side-effects (Sackeim et al., 2007), and thus is difficult to compare with the results of modern ECT techniques.

Our finding that the association between age and deterioration in cognitive performance is mainly caused by the better baseline performance of younger MDE patients is in line with research results showing that cognitive impairments are more prevalent in late-life depression (Lockwood et al., 2002; Thomas and O'Brien, 2008). More specifically, compared to both younger MDE patients and healthy older controls, older MDE patients score disproportionately poorly on executive tasks (Lockwood et al., 2002; Thomas and O'Brien, 2008). These results might indicate that the cognitive ability that is affected by ECT is already impaired in older MDE patients with more prominent cognitive symptoms before ECT, resulting in a relatively stable cognitive functioning from before to after ECT. On the other hand, younger MDE patients with generally a more intact cognitive functioning may therefore be more susceptible to experiencing cognitive side-effects.

4.3. Limitations

To the best of our knowledge, this is the largest ECT study to date examining the course of cognitive performance over time following ECT and investigating pre-treatment predictors for cognitive side-effects shortly after ECT, which was crucial for revealing abovementioned findings while being able to control for confounding factors due to the

statistical power. However, our findings should be interpreted considering its limitations. Study cohorts used slightly different test batteries and in none of the cohorts a standardized test of autobiographical memory was included, while retrograde amnesia is a major concern for patients and studies have shown that it persists longer than other cognitive side-effects after ECT (Fraser et al., 2008; Obbels et al., 2017). Also, there was a substantial amount of missing data and especially the sample sizes at six months follow-up were considerably lower, so these results should be interpreted with caution. However, to deal with missing data we applied multiple imputation and we used LMMs which use all available data and can handle missing data adequately (Gueorguieva and Krystal, 2004). While twice-weekly ECT sessions is standard Dutch practice (Van den Broek et al., 2010), for other countries such as the United States a frequency of three times per week is common practice (Lerer et al., 1995; Sackeim, 1989; Thirthalli et al., 2020). As more frequent sessions could results in increased cognitive side-effects (Weiner and American Psychiatric Association, 2001), it is important to be precautious with generalization to countries with a different treatment regime. The less frequent sessions might also be an explanation for the lack of association between ECT parameters and cognitive outcomes (Spaans et al., 2013). Moreover, we did not correct for a possible learning effect due to repeatedly assessment of the same neuropsychological measures. Previous research also identified several pre-treatment anatomical, physiological and genetic factors which we were not able to examine (van Kessel et al., 2020). Furthermore, in future studies a prospective design with a large study sample would be advisable with the inclusion of a (healthy) control group.

4.4. Neurobiological mechanism of ECT-induced cognitive side-effects

A prospective longitudinal study showed that the deterioration in cognitive functioning shortly after ECT is associated with the temporary increase in hippocampal volume following ECT (van Oostrom et al., 2018). The increase in hippocampal volume may result from a broad range of neuroplasticity processes such as neurogenesis or enabling existing neurons to rewire and re-mature (Imoto et al., 2017; Joshi et al., 2016; Olesen et al., 2017). The depolarization threshold of new or immature neurons is lower than that of mature neurons, which could explain the acute cognitive side-effects after ECT, as the discrepancy in excitability might affect functionality within the entire hippocampal formation (Joshi et al., 2016; van Oostrom et al., 2018). Therefore, in line with our findings, cognitive functioning could first become temporarily impaired and subsequently improved, even exceeding pre-ECT levels, when new and immature cells have been integrated (van Oostrom et al., 2018). Speculatively, the disruption of a pre-ECT relatively well-functioning cognitive system in younger patients may lead to a relatively larger impairment in cognition directly after ECT.

5. Conclusions

In conclusion, we provided evidence for the presence of some acute ECT-induced cognitive side-effects in anterograde memory and executive functioning, after which cognitive functioning across all domains improved on the long term, even outperforming baseline levels. Thus, ECT should be seen as a viable treatment option and should not be abolished due to the risk of mostly transient cognitive side-effects. Delayed recall and verbal fluency may be the most sensitive cognitive measures to monitor ECT-induced cognitive side-effects.

In addition, characteristics such as level of education, type and severity of depression, and several cardiovascular risk factors do not predict deterioration in cognitive performance directly after ECT. However, younger patients may be more susceptible to acute cognitive side-effects, which seems to be mostly due to a more intact cognitive functioning prior to ECT. If prospective clinical trials replicate our findings, age could help predict cognitive side-effects directly after ECT. Our findings could contribute to reliable information on cognitive side-effects following ECT, the development of a sensitive neurocognitive screening battery for ECT, decision-making and enhanced ECT applicability, and prevention and treatment of cognitive side effects in the future.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.01.049.

Funding/support

This study (with project number 60-63600-98-903, PI Dols) was supported in part by The Netherlands Organization for Health Research and Development (ZonMW). The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, writing, review, or approval of the manuscript; and decision to submit the manuscript for publication.

CRediT authorship contribution statement

Dore Loef: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Philip van Eijndhoven:** Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. **Eva van den Munckhof:** Data curation, Validation, Writing – review & editing. **Adriaan Hoogendoorn:** Conceptualization, Data curation, Formal analysis, Software, Writing – review & editing. **Ruby Manten:** Data curation, Validation, Writing – review & editing. **Harm-Pieter Spaans:** Data curation, Validation, Writing – review & editing. **Indira Tendolkar:** Conceptualization, Supervision, Validation, Writing – review & editing. **Bart Rutten:** Data curation, Writing – review & editing. **Jasper Nuninga:** Data curation, Validation, Writing – review & editing. **Metten Somers:** Conceptualization, Data curation, Validation, Writing – review & editing. **Edwin van Dellen:** Validation, Writing – review & editing. **Eric van Exel:** Data curation, Validation, Writing – review & editing. **Sigfried Schouws:** Conceptualization, Data curation, Validation, Writing – review & editing, Methodology. **Annemiek Dols:** Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Esmée Verwijk:** Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None.

Data availability

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

Acknowledgements

None.

References

Andrade, C., Arumugham, S.S., Thirthalli, J., 2016. Adverse effects of electroconvulsive therapy. Psychiatr. Clin. North Am. 39 (3), 513–530. https://doi.org/10.1016/j.psc.2016.04.004.

Bodnar, A., Krzywotulski, M., Lewandowska, A., Chlopocka-Wozniak, M., Bartkowska-Sniatkowska, A., Michalak, M., Rybakowski, J.K., 2016. Electroconvulsive therapy and cognitive functions in treatment-resistant depression. World J. Biol. Psychiatry 17 (2), 159–164. https://doi.org/10.3109/15622975.2015.1091501.

Delis, D.C., Kaplan, E., Kramer, J.H., 2001. Delis-Kaplan Executive Function System.

Dybedal, G.S., Tanum, L., Sundet, K., Gaarden, T.L., Bjølseth, T.M., 2014. Cognitive side-effects of electroconvulsive therapy in elderly depressed patients. Clin.

Neuropsychol. 28 (7), 1071–1090. https://doi.org/10.1080/13854046.2014.958536.
Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12 (3), 189–198. https://doi.org/10.1016/0022-3956(75)90026-6.
Fraser, L.M., O'Carroll, R.E., Ebmeier, K.P., 2008. The effect of electroconvulsive therapy on autobiographical memory: a systematic review. J. ECT 24 (1), 10–17. https://doi.org/10.1097/YCT.0b013e3181616c26.
Gueorguieva, R., Krystal, J.H., 2004. Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the archives of general psychiatry. Arch. Gen. Psychiatry 61 (3), 310–317. https://doi.org/10.1001/archpsyc.61.3.310.
Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23 (1), 56–62. https://doi.org/10.1136/jnnp.23.1.56.
Hammar, A., Ardal, G., 2009. Cognitive functioning in major depression—a summary. Front. Hum. Neurosci. 3, 26. https://doi.org/10.3389/neuro.09.026.2009.
Hebbrecht, K., Giltay, E.J., Birkenhäger, T.K., Sabbe, B., Verwijk, E., Obbels, J., Roelant, E., Schrijvers, D., Van Diermen, L., 2020. Cognitive change after electroconvulsive therapy in mood disorders measured with the Montreal Cognitive Assessment. Acta Psychiatr. Scand. 142 (5), 413–422. https://doi.org/10.1111/acps.13231.
Hebbrecht, K., Dejaeger, M., Giltay, E.J., Birkenhäger, T., Sabbe, B., Verwijk, E., Obbels, J., Schrijvers, D., Van Diermen, L., 2022. Cognitive trajectories during and after electroconvulsive therapy in patients with MDE: taking different perspectives. J. Psychiatr. Res. 156, 132–140. https://doi.org/10.1016/j.jpsychires.2022.09.028.
Imoto, Y., Segi-Nishida, E., Suzuki, H., Kobayashi, K., 2017. Rapid and stable changes in maturation-related phenotypes of the adult hippocampal neurons by electroconvulsive treatment. Mol. Brain 10 (1), 8. https://doi.org/10.1186/s13041-017-0288-9.
Jacobson, N.S., Truax, P., 1991. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J. Consult. Clin. Psychol. 59 (1), 12–19. https://doi.org/10.1037//0022-006x.59.1.12.
Jelovac, A., Kolshus, E., McLoughlin, D.M., 2013. Relapse following successful electroconvulsive therapy for major depression: a meta-analysis. Neuropsychopharmacology 38 (12), 2467–2474. https://doi.org/10.1038/npp.2013.149.
Johnston, K.M., Powell, L.C., Anderson, I.M., Szabo, S., Cline, S., 2019. The burden of treatment-resistant depression: a systematic review of the economic and quality of life literature. J. Affect. Disord. 242, 195–210. https://doi.org/10.1016/j.jad.2018.06.045.
Joshi, S.H., Espinoza, R.T., Pirnia, T., Shi, J., Wang, Y., Ayers, B., Leaver, A., Woods, R.P., Narr, K.L., 2016. Structural plasticity of the hippocampus and amygdala induced by electroconvulsive therapy in major depression. Biol. Psychiatry 79 (4), 282–292. https://doi.org/10.1016/j.biopsych.2015.02.029.
van Kessel, M.A., van der Vlugt, J.J.B., Spaans, H.P., Murre, J.M.J., Verwijk, E., 2020. Psychotic depressive subtype and white mater hyperintensities do not predict cognitive side effects in ECT: a systematic review of pretreatment predictors. J. Affect. Disord. 272, 340–347. https://doi.org/10.1016/j.jad.2020.03.181.
Kirov, G.G., Owen, L., Ballard, H., Leighton, A., Hannigan, K., Llewellyn, D., Escott-Price, V., Atkins, M., 2016. Evaluation of cumulative cognitive deficits from electroconvulsive therapy. Br. J. Psychiatry 208 (3), 266–270. https://doi.org/10.1192/bjp.bp.114.158261.
Landry, M., Moreno, A., Patry, S., Potvin, S., Lemasson, M., 2021. Current practices of electroconvulsive therapy in mental disorders: a systematic review and meta-analysis of short and long-term cognitive effects. J. ECT 37 (2), 119–127. https://doi.org/10.1097/yct.0000000000000723.
Lerer, B., Shapira, B., Calev, A., Tubi, N., Drexler, H., Kindler, S., Lidsky, D., Schwartz, J. E., 1995. Antidepressant and cognitive effects of twice- versus three-times-weekly ECT. Am. J. Psychiatry 152 (4), 564–570. https://doi.org/10.1176/ajp.152.4.564.
Leucht, S., Fennema, H., Engel, R.R., Kaspers-Janssen, M., Szegedi, A., 2018. Translating the HAM-D into the MADRS and vice versa with equipercentile linking. J. Affect. Disord. 226, 326–331. https://doi.org/10.1016/j.jad.2017.09.042.
Lindeboom, J., Jonker, C.A., 1989. Handleiding Dementie-Screeningtest [Amsterdam Dementia-Screening Test, Manual]. Swets & Zeitlinger, Lisse.
Lockwood, K.A., Alexopoulos, G.S., van Gorp, W.G., 2002. Executive dysfunction in geriatric depression. Am. J. Psychiatry 159 (7), 1119–1126. https://doi.org/10.1176/appi.ajp.159.7.1119.
Luteijn, F., Van der Ploeg, F., 1983. Handleiding groninger intelligentietest (git). Sweitz & Zeitlinger, Lisse, the Netherlands.
McClintock, S.M., Cullum, M., Husain, M.M., Rush, A.J., Knapp, R.G., Mueller, M., Petrides, G., Sampson, S., Kellner, C.H., 2010a. Evaluation of the effects of severe depression on global cognitive function and memory. CNS Spectr. 15 (5), 304–313. https://doi.org/10.1017/s109285290002753x.
McClintock, S.M., Husain, M.M., Greer, T.L., Cullum, C.M., 2010b. Association between depression severity and neurocognitive function in major depressive disorder: a review and synthesis. Neuropsychology 24 (1), 9–34. https://doi.org/10.1037/a0017336.
McDermott, L.M., Ebmeier, K.P., 2009. A meta-analysis of depression severity and cognitive function. J. Affect. Disord. 119 (1–3), 1–8. https://doi.org/10.1016/j.jad.2009.04.022.
Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389. https://doi.org/10.1192/bjp.134.4.382.
Morris, T., Royston, P., 2016. MFPMI: Stata Module to Build Multivariable Fractional Polynomial Models in Multiply Imputed Data.
Mulder, J., Dekker, P., Dekker, R., 2006. Handleiding Woord-Fluency Test/Figuur-Fluency Test. PITS, Nederland, Leiden, Leiden.
Muslimović, D., Post, B., Speelman, J.D., De Haan, R.J., Schmand, B., 2009. Cognitive decline in Parkinson's disease: a prospective longitudinal study. J. Int. Neuropsychol. Soc. 15 (3), 426–437. https://doi.org/10.1017/s1355617709090614.
Nuevo, R., Leighton, C., Dunn, G., Dowrick, C., Lehtinen, V., Dalgard, O.S., Casey, P., Vázquez-Barquero, J.L., Ayuso-Mateos, J.L., 2010. Impact of severity and type of depression on quality of life in cases identified in the community. Psychol. Med. 40 (12), 2069–2077. https://doi.org/10.1017/s0033291710000164.
Obbels, J., Verwijk, E., Bouckaert, F., Sienaert, P., 2017. ECT-related anxiety: a systematic review. J. ECT 33 (4), 229–236. https://doi.org/10.1097/yct.0000000000000383.
Obbels, J., Verwijk, E., Vansteelandt, K., Dols, A., Bouckaert, F., Schouws, S., Vandenbulcke, M., Emsell, L., Stek, M., Sienaert, P., 2018. Long-term neurocognitive functioning after electroconvulsive therapy in patients with late-life depression. Acta Psychiatr. Scand. 138 (3), 223–231. https://doi.org/10.1111/acps.12942.
Obbels, J., Vansteelandt, K., Verwijk, E., Dols, A., Bouckaert, F., Oudega, M.L., Vandenbulcke, M., Stek, M., Sienaert, P., 2019. MMSE changes during and after ECT in late-life depression: a prospective study. Am. J. Geriatr. Psychiatry 27 (9), 934–944. https://doi.org/10.1016/j.jagp.2019.04.006.
Olesen, M.V., Wörtwein, G., Folke, J., Pakkenberg, B., 2017. Electroconvulsive stimulation results in long-term survival of newly generated hippocampal neurons in rats. Hippocampus 27 (1), 52–60. https://doi.org/10.1002/hipo.22670.
van Oostrom, I., van Eijndhoven, P., Butterbrod, E., van Beek, M.H., Janzing, J., Donders, R., Schene, A., Tendolkar, I., 2018. Decreased cognitive functioning after electroconvulsive therapy is related to increased hippocampal volume: exploring the role of brain plasticity. J. ECT 34 (2), 117–123. https://doi.org/10.1097/yct.0000000000000483.
Porter, R.J., Baune, B.T., Morris, G., Hamilton, A., Bassett, D., Boyce, P., Hopwood, M.J., Mulder, R., Parker, G., Singh, A.B., Outhred, T., Das, P., Malhi, G.S., 2020. Cognitive side-effects of electroconvulsive therapy: what are they, how to monitor them and what to tell patients. BJPsych Open 6 (3), e40. https://doi.org/10.1192/bjo.2020.17.
Prudic, J., Haskett, R.F., McCall, W.V., Isenberg, K., Cooper, T., Rosenquist, P.B., Mulsant, B.H., Sackeim, H.A., 2013. Pharmacological strategies in the prevention of relapse after electroconvulsive therapy. J. ECT 29 (1), 3–12. https://doi.org/10.1097/YCT.0b013e31826ea8c4.
Reitan, R.M., Wolfson, D., 1985. The Halstead-Reitan neuropsychological test battery: theory and clinical interpretation. In: Reitan Neuropsychology, vol. 4.
Saan, R., Deelman, B., 1986. Dutch Version of the Rey Auditory Verbal Learning Test. Department of Neuropsychology, RUG, provisional manual, Groningen.
Sackeim, H.A., 1989. ECT: twice or thrice a week? Convuls. Ther. 5 (4), 362–364.
Sackeim, H.A., Prudic, J., Fuller, R., Keilp, J., Lavori, P.W., Olfson, M., 2007. The cognitive effects of electroconvulsive therapy in community settings. Neuropsychopharmacology 32 (1), 244–254. https://doi.org/10.1038/sj.npp.1301180.
Scheepens, D.S., van Waarde, J.A., Lok, A., Zantvoord, J.B., de Pont, B., Ruhé, H.G., Denys, D., van Wingen, G.A., 2019. Electroconvulsion therapy for persistent depression in the Netherlands; very low application rate. Tijdschr. Psychiatr. 61 (1), 16–21 (Elektroconvulsietherapie bij persisterende depressie in Nederland; zeer lage toepassingsgraad.).
Schmand, B., Houx, P., de Koning, I., Hoogman, M., Muslimovic, D., Rienstra, A., 2012. Normen van psychologische tests voor gebruik in de klinische neuropsychologie [Norms for psychological tests for use in clinical neuropsychology]. In: Published on the Website of the Section Neuropsychology of the Dutch Institute of Psychology (Nederlandse Instituut van Psychologen).
Semkovska, M., McLoughlin, D.M., 2010. Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. Biol. Psychiatry 68 (6), 568–577. https://doi.org/10.1016/j.biopsych.2010.06.009.
Semkovska, M., Keane, D., Babalola, O., McLoughlin, D.M., 2011. Unilateral brief-pulse electroconvulsive therapy and cognition: effects of electrode placement, stimulus dosage and time. J. Psychiatr. Res. 45 (6), 770–780. https://doi.org/10.1016/j.jpsychires.2010.11.001.
Spaans, H.-P., Verwijk, E., Comijs, H.C., Kok, R.M., Sienaert, P., Bouckaert, F., Fannes, K., Vandepoel, K., Scherder, E.J., Stek, M.L., 2013. Efficacy and cognitive side effects after brief pulse and ultrabrief pulse right unilateral electroconvulsive therapy for major depression: a randomized, double-blind, controlled study. J. Clin. Psychiatry 74 (11), 6001.
Thirthalli, J., Naik, S.S., Kunigiri, G., 2020. Frequency and duration of course of ECT sessions: an appraisal of recent evidence. Indian J. Psychol. Med. 42 (3), 207–218. https://doi.org/10.4103/ijpsym.Ijpsym_410_19.
Thomas, A.J., O'Brien, J.T., 2008. Depression and cognition in older adults. Curr. Opin. Psychiatry 21 (1), 8–13. https://doi.org/10.1097/YCO.0b013e3282f2139b.
Van den Broek, W., Birkenhäger, T., De Boer, D., Burggraaf, J., van Gemert, B., Groenland, T., 2010. Richtlijn elektroconvulsietherapie. Ned Ver voor Psychiatr 36, 1–200.
de Vent, N.R., Agelink van Rentergem, J.A., Schmand, B.A., Murre, J.M., Huizenga, H.M., 2016. Advanced neuropsychological diagnostics infrastructure (ANDI): a normative database created from control datasets. Front. Psychol. 7, 1601. https://doi.org/10.3389/fpsyg.2016.01601.
Verwijk, E., Comijs, H.C., Kok, R.M., Spaans, H.P., Stek, M.L., Scherder, E.J., 2012. Neurocognitive effects after brief pulse and ultrabrief pulse unilateral electroconvulsive therapy for major depression: a review. J. Affect. Disord. 140 (3), 233–243. https://doi.org/10.1016/j.jad.2012.02.024.
Verwijk, E., Comijs, H.C., Kok, R.M., Spaans, H.P., Tielkes, C.E., Scherder, E.J., Stek, M. L., 2014. Short- and long-term neurocognitive functioning after electroconvulsive

therapy in depressed elderly: a prospective naturalistic study. Int. Psychogeriatr. 26 (2), 315–324. https://doi.org/10.1017/s1041610213001932.
Wechsler, D., 2000. WAIS III, Nederlandstalige Bewerking: Afname en Scoringshandleiding. Swets Test Publishers, Lisse.
Wechsler, D., 2012. WAIS-IV-NL: Wechsler Adult Intelligence Scale—Nederlandstalige bewerking. Pearson.
Weiner, R.D., American Psychiatric Association, 2001. The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training, and Privileging: A Task Force Report of the American Psychiatric Association. Amer Psychiatric Pub Inc.
Weiner, R.D., Reti, I.M., 2017. Key updates in the clinical application of electroconvulsive therapy. Int. Rev. Psychiatry 29 (2), 54–62. https://doi.org/10.1080/09540261.2017.1309362.
Ziegelmayer, C., Hajak, G., Bauer, A., Held, M., Rupprecht, R., Trapp, W., 2017. Cognitive performance under electroconvulsive therapy (ECT) in ECT-naive treatment-resistant patients with major depressive disorder. J. ECT 33 (2), 104–110. https://doi.org/10.1097/yct.0000000000000385.