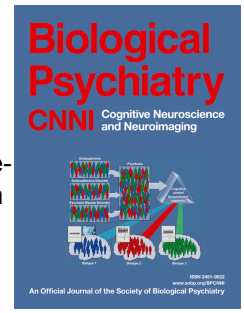

The sensitivity of the Mini-Mental State Examination to detect objective cognitive side-effects induced by electroconvulsive therapy, results from the Dutch ECT Consortium

Dore Loef, M.Sc., Philip F.P. van Eijndhoven, M.D., Ph.D., Sigfried N.T.M. Schouws, Ph.D., Arjen J.C. Slooter, M.D., Ph.D., Nikki Janssen, Ph.D., Rob M. Kok, M.D., Ph.D., Bart P.F. Rutten, M.D., Ph.D., Eric van Exel, M.D., Ph.D., Didi Rhebergen, M.D., Ph.D., Mardien L. Oudega, M.D., Ph.D., Roel J.T. Mocking, M.D., Ph.D., Indira Tendolkar, M.D., Ph.D., Annemiek Dols, M.D., Ph.D., Esmée Verwijk, Ph.D.

PII: S2451-9022(24)00236-2

DOI: https://doi.org/10.1016/j.bpsc.2024.08.002

Reference: BPSC 1277

To appear in: *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*

Received Date: 10 July 2024

Revised Date: 19 July 2024

Accepted Date: 1 August 2024

Please cite this article as: Loef D., van Eijndhoven P.F.P., Schouws S.N.T.M., Slooter A.J.C., Janssen N., Kok R.M., Rutten B.P.F., van Exel E., Rhebergen D., Oudega M.L., Mocking R.J.T., Tendolkar I., Dols A. & Verwijk E., The sensitivity of the Mini-Mental State Examination to detect objective cognitive side-effects induced by electroconvulsive therapy, results from the Dutch ECT Consortium, *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* (2024), doi: https://doi.org/10.1016/j.bpsc.2024.08.002.

The sensitivity of the Mini-Mental State Examination to detect objective cognitive side-effects induced by electroconvulsive therapy, results from the Dutch ECT Consortium

Running title: MMSE is insensitive for cognitive side-effects of ECT

Dore Loef* [a,b,c], M.Sc., Philip F.P. van Eijndhoven [d,e], M.D., Ph.D., Sigfried N.T.M. Schouws [a,b,c], Ph.D., Arjen J.C. Slooter [f,g,h], M.D., Ph.D., Nikki Janssen [d,e,i], Ph.D., Rob M. Kok [j], M.D., Ph.D., Bart P.F. Rutten [k], M.D., Ph.D., Eric van Exel [a,b,c], M.D., Ph.D., Didi Rhebergen [a,l], M.D., Ph.D., Mardien L. Oudega [a,b,c], M.D., Ph.D., Roel J.T. Mocking [b,m], M.D., Ph.D., Indira Tendolkar [d,e,n], M.D., Ph.D., Annemiek Dols# [a,b,f], M.D., Ph.D., Esmée Verwijk# [o,p,q], Ph.D.

a) Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Psychiatry, De 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 University Medical Center, Nijmegen, The Netherlands.
e) Donders Institute for Brain, Cognition and Behavior, Department of Psychiatry, Nijmegen, The Netherlands
f) Department of Psychiatry, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands.
g) Department of Intensive Care Medicine, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands.
h) Department of Neurology, UZ Brussel and Vrije Universiteit Brussel, Brussels, Belgium.
i) Donders Centre for Medical Neuroscience, Department of Medical Psychology, Radboud University Medical Center, Nijmegen, The Netherlands.
j) Department of Old Age Psychiatry, Parnassia Psychiatric Institute, The Hague, The Netherlands.
k) Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, The Netherlands.
l) Department of Research, GGZ Centraal Mental Health Care, Amersfoort, The Netherlands.
m) Amsterdam UMC, University of Amsterdam, Department of Psychiatry, Amsterdam, The Netherlands.
n) Department of Psychiatry and Psychotherapy, University Hospital Essen, Essen, Germany.
o) University of Amsterdam, Department of Psychology, Brain and Cognition, Amsterdam, The Netherlands.
p) Amsterdam UMC, Department of Medical Psychology, Amsterdam, The Netherlands.
q) ECT department, Parnassia Psychiatric Institute, The Hague, The Netherlands.

Shared supervision.

*Corresponding author; Dore Loef | Amsterdam UMC, Oldenaller 1, office H2.01, 1081 HJ Amsterdam | The Netherlands | d.loef@ggzingeest.nl

Keywords: MMSE, electroconvulsive therapy, cognitive side-effects, depression, mood disorders, cognition

Abstract

Background: Monitoring cognitive side-effects following electroconvulsive therapy (ECT) is crucial for balancing side-effects and clinical effectiveness. Unfortunately, evidence-based guidelines on cognitive testing following ECT are lacking. A frequently used test in global ECT practice is the Mini Mental State Examination (MMSE). We examined the change of the MMSE and its performance in identifying a decline in predefined neuropsychological measures sensitive to ECT-induced cognitive changes: verbal recall and verbal fluency.

Methods: The mean MMSE scores pre- and one week post-ECT were compared using a Wilcoxon signed-rank test. The Reliable Change Index was calculated for all cognitive measures to indicate whether an individual's change score from pre- to post-ECT is considered statistically significant. The sensitivity and specificity of the MMSE were calculated.

Results: 426 patients with depression from five sites were included from the Dutch ECT Consortium. The mean MMSE increased significantly from 26.2 (SD=3.9) pre-ECT to 26.8 (SD=3.8) post-ECT (p=0.002). 36 patients (8.5%) showed a significant decline in MMSE score post-ECT. The sensitivity of the MMSE in identifying patients who experienced a significant decline in verbal recall or verbal fluency ranged from 3.6% to 11.1%. The specificity of the MMSE in identifying patients who did not experience a significant decline in verbal recall or verbal fluency ranged from 95.6% to 96.6%.

Conclusions: Given the very low sensitivity of the MMSE, we propose reconsidering the prominence of the MMSE in ECT practice and cognitive monitoring guidelines, advocating for a more comprehensive approach to assess ECT-induced cognitive changes.

Introduction

Electroconvulsive therapy (ECT) is reported to be the most effective treatment for severe major depression, but its cognitive side-effects remain an important concern, despite modern ECT techniques (1). ECT-induced cognitive side-effects have been described particularly in domains of executive functioning and anterograde and retrograde memory (2, 3). These cognitive side-effects are a key element to guide decision-making for both patients and professionals and the main reason for the limited use of this highly effective treatment (4).

Monitoring of side-effects is crucial for balancing side-effects and clinical effectiveness. Therefore, monitoring of side-effects events following treatment should be standard practice in modern healthcare, but this is currently inadequately applied in the field of ECT. Although there is consensus that some type of cognitive monitoring should be undertaken, it is not clear what should be routinely assessed and evidence-based guidelines are lacking (5). For cognitive tests to be efficient, they need to be replicable, concise, and easy to handle within clinical settings (5, 6).

Rasmussen et al. (2016) reviewed 18 books and practice guidelines from several sources, among which the American Psychiatric Association, which revealed that no specific recommendations were given by six sources (5). Overall, no consensus exists in these recommendations on cognitive testing regarding ECT. The neuropsychological screener most frequently mentioned (six times) in the recommendations is the Mini Mental State Examination (MMSE; (7)). The MMSE is a global cognitive screening instrument developed to screen for dementia which assesses orientation, attention, memory and executive functioning (7, 8). The MMSE is a commonly used cognitive test in ECT trials and clinical practice. It was used in 35.7% and 38.5% of the studies reviewed and meta-analyzed by Semkovska & McLoughlin (2010) and Landry et al. (2021), respectively (2, 9).

Although the MMSE is the most widely studied measure concerning cognitive changes after ECT, research results show inconsistencies. Several previous studies showed no significant change in mean total MMSE score from pre- to post-ECT (6, 10), while a study on late-life depression revealed a significant improvement in mean total score post-ECT (11). The meta-analysis of Semkovska & McLoughlin (2010) showed a decline in total MMSE score at zero to three days after the ECT course compared to baseline, followed by an improvement at 4-15 days post-treatment (2). On the other hand, the meta-analysis of Landry et al. (2021) demonstrated no significant change in MMSE total score both within 24 hours after the last ECT and at 1-28 days post-ECT (9). Inconsistencies in these results are likely due to the mainly inadequately powered studies with individual-level data in ECT research.

Furthermore, the MMSE may lack sensitivity to identify subtle ECT-induced cognitive changes in psychiatric patients. For example, another global cognitive screening measure, the Montreal Cognitive Assessment (MoCA; (12)), detected more ECT-induced side-effects in cognitive domains of memory, language, and visuo-executive functioning than the MMSE (6). A valid screening instrument should, however, be capable of detecting a high proportion of cognitive impairments, even if they are mild (8, 9, 13). Additionally, the MMSE has only one version and previous research results demonstrated test-retest effects, as patients that had been tested more frequently had higher MMSE scores (11). Another limitation of using the MMSE in clinical practice is that it is patented and incurs a cost for use. Due to these shortcomings, the use of the MMSE has declined in favor of the MoCA, but it was still used at 42% of the ECT sites in the United States, Europe, Canada, and Asia that participated in a recent survey (14).

Therefore, large studies with individual-level data are needed to examine ECT-induced cognitive side-effects measured by the MMSE and to indicate whether the MMSE lacks sensitivity for monitoring these side-effects in comparison to extended neuropsychological measures. This could contribute to the development of evidence-based guidelines and to the enhanced assessment of cognitive side-effects in ECT-treated patients. We first examined the change in cognitive performance measured by the MMSE in one of the largest ECT cohorts to date: the Dutch ECT Consortium (DEC). In a subset of patients, we additionally investigated the sensitivity of the MMSE in identifying patients who experienced a decline in the extended neuropsychological measures (verbal fluency and verbal recall) that were previously suggested to be the most sensitive cognitive measures to monitor ECT-induced cognitive side-effects (15, 16). We hypothesize that the MMSE lacks sensitivity to properly identify objective ECT-induced cognitive side-effects.

Methods and materials

Study sample

Research and clinical cohorts with available MMSE data were selected from DEC, described in more detail elsewhere (17). In short, patients with a diagnosis of major depressive episode in the context of major depressive disorder or bipolar disorder treated with ECT between 2001 and 2022 were included. Patients were diagnosed by a psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria. Only the cohorts that routinely assessed the MMSE (≥25% of subjects) were selected from DEC to prevent selection bias, resulting in the inclusions of several cohorts from five different sites: Amsterdam UMC, GGZ inGeest, Maastricht UMC, Parnassia, and Radboudumc. ECT was

generally administered twice weekly in accordance with Dutch guidelines (18). Details about each included cohort and the corresponding ECT procedures are provided in Supplementary Table 1. The Medical Ethics Review Committee of VU University Medical Center confirmed that the Medical Research Involving Humans Subjects Act 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). Informed consent was obtained in accordance with applicable national and European law, if applicable, in line with the grounds for exception ex art. 24 Dutch GDPR Implementation Act juncto art. 458 WGBO (Dutch Medical Treatment Contracts Act) are invoked. 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 2013. All procedures involving patients were approved by the local ethics committees of each recruiting center.

Neuropsychological assessment and clinical characteristics

Neuropsychological functioning was assessed by a neuropsychologist or a trained research assistant. Patients were assessed before ECT and one week after the course of ECT. In a subset of patients, extended neuropsychological measures were available in addition to the MMSE. First, the subtest delayed recall of the Dutch version of the Rey Auditory Verbal Learning Test (D-RAVLT) was included to measure verbal memory (19). Second, the Dutch versions of the verbal fluency tests were included: category fluency animals (CF; (20)) mainly to measure semantic memory and letter fluency (LF; (21)) mainly to measure executive functioning (responses to the letter “D” at GGZ inGeest; letters “D”, “A” and “T” at Parnassia; letters “N” and “A” at Radboudumc). In order to analyze the results of the letter fluency altogether, we calculated the expected total 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 formula’s based on a large existing database (22).

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 mood disorder (unipolar/bipolar), age at first depressive episode, number of previous depressive episodes, duration of current episode (in months), and presence of psychotic features (yes/no). Regarding the assessment of depression severity at baseline and one week post-ECT, Montgomery–Åsberg Depression Rating Scale (MADRS; (23)) scores were available of more patients than Hamilton Depression Rating Scale (HDRS) 17-item scores (24). Therefore, HDRS scores were converted to MADRS scores using a validated method (25).

Statistical analyses

Analyses were carried out in IBM SPSS version 28. First, the Wilcoxon signed-rank test was used to compare the mean total MMSE scores before and after ECT. Next, individuals' Reliable Change Index (RCI) were calculated for all cognitive measures using the raw scores. The RCI could provide more insight into the different subsets of patients that may have been affected by ECT, as it indicates whether an individual change score is statistically significantly greater than a difference that could be caused by merely random test or individual measurement error. In the present study, the RCI formula of Jacobson and Truax was used: $(X_2 – X_1)$ / Standard Error of the difference score (SEdiff) with X_2 and X_1 being the retest and the initial baseline score on a cognitive variable (26). The 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. The 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 significant change (i.e. a reliable decrease or increase) in a cognitive measure (26). By means of the RCI, it was indicated whether an individual's change score from pre- to post-ECT is considered statistically significant. In order to describe the group that experiences a decline in the MMSE, differences in clinical and demographic variables between patients who showed a significant decline in the MMSE versus patients who did not show a significant decline in the MMSE were tested using the independent samples T-test (for continuous normally distributed variables), Mann-Whitney U test (for continuous non-normally distributed variables), and Chi-squared test (for categorical variables). McNemar's tests were used to compare the proportion of patients that significantly declined on the MMSE versus the proportion of patients that significantly declined on each of the extended neuropsychological measures (delayed recall, CF, LF). Subsequently, the sensitivity and specificity of the MMSE in comparison to the extended neuropsychological measures was determined, meaning the ability of the MMSE to identify all patients who experienced a significant decline in verbal recall and verbal fluency and the ability of the MMSE to identify all patients who did not experience a significant decline in verbal recall and verbal fluency, respectively. Regarding ECT parameters, the sensitivity and specificity of the MMSE were subsequently calculated separately for patients treated with right unilateral ECT only (RUL) and patients treated with bilateral ECT (BL). ECT parameters such as dosing method and pulse width at the beginning and the end of the ECT course were not incorporated in the analyses, as they were not significantly correlated with the RCI of the cognitive outcomes (MMSE, delayed recall, CF, LF). Receiver operating characteristics (ROC) curves were used to assess the predictive ability of the MMSE difference score from pre- to post-ECT in identifying a significant decline in each of the extended neuropsychological measures. The

area under the curve (AUC) was calculated to quantify the discriminative power of the MMSE difference score. All tests were two-sided with a p-value ≤0.05 denoting statistical significance.

Results

Description of the study population and change in the MMSE

In total, the study sample consisted of 426 patients after exclusion of 327 subjects due to missing MMSE total scores before or after ECT (Supplementary Figure 1). These excluded patients did not significantly differ from the included patients in characteristics such as age, sex, depression outcome measures, number of ECT sessions, and bilateral treatment. The age of the included patients ranged from 21 to 92 (mean=64.0, SD=15.8) and 62.4% (n=266) was female (Table 1). Response (≥50% reduction in MADRS score) and remission (MADRS score <10) after ECT was achieved by 64.4% and 50.2% of patients, respectively. From the 426 patients, 56.1% originating from pre-existing research cohorts and 43.9% from clinical cohorts. The mean MMSE pre-ECT was 26.2 (SD=3.9, median=27.0, IQR=4.0) and the mean MMSE one week post-ECT was 26.8 (SD=3.8, median=28.0, IQR=3.0). The Wilcoxon signed-rank test showed a significant increase from mean pre- to post-ECT MMSE scores ($z=4.24$, $p<0.0001$). The RCI of the MMSE showed that 36 patients (8.5%) significantly declined, 327 patients (76.8%) remained stable, and 63 patients (14.8%) significantly improved from pre- to post-ECT.

Descriptive statistics of MMSE-decliners versus non-decliners

Table 1 shows that the mean age was significantly higher in patients that significantly declined (mean=71.8, SD=15.0) than in patients that did not significantly decline in MMSE total score (mean=63.2, SD=15.7; p=0.002). Furthermore, the mean number of previous depressive episodes was higher in patients that significantly declined (mean=3.7, SD=3.6) than in patients that did not significantly decline (mean=2.1, SD=2.7; p=0.011). Also, patients that significantly declined had fewer ECT sessions (p=0.009). None of the other baseline or ECT characteristics were significantly different between patients who showed a significant decline in the MMSE and patients who did not.

Sensitivity and specificity of the MMSE

A subset of the total study sample (n=236) also had available data on the extended neuropsychological measures: 164 for the delayed recall of the D-RAVLT, 227 for the CF, and 202 for the LF. On a group level, a significant decrease was found in each of the extended neuropsychological measures from before to after ECT (Table 2). The McNemar's

tests showed that the proportion of patients experiencing a significant decline in the MMSE is significantly lower compared to the proportion of patients experiencing a significant decline in each of the extended neuropsychological measures (D-RAVLT: p=0.0003, CF: p<0.0001, LF: p=0.001).

Figure 1 shows the number of patients that declined on the MMSE compared to each of the extended neuropsychological measures. The sensitivity of the MMSE, i.e. the chance that the MMSE identified a significant decline in patients who experienced a significant decline in verbal fluency or verbal recall, ranged from 3.6% to 11.1% (Table 3). The specificity of the MMSE, i.e. the chance that no significant decline was identified by the MMSE in patients who did not experience a significant decline in verbal recall or verbal fluency, ranged from 95.6% to 96.6%. Out of the 236 patients with available data in at least one of the extended measures, 32.2% (n=76) showed a significant decline in ≥1 of the extended measures (delayed recall, CF, LF). This resulted in 5 patients that declined on both the MMSE and the extended measures, 71 patients that declined only on the extended measures, 7 patients that declined only on the MMSE, and 153 patients that declined on neither. This led to a comparable sensitivity and specificity of the MMSE when the extended neuropsychological measures were examined together (Table 3).

Regarding RUL patients only (RAVLT n=84, CF n=115, LF n=113), the sensitivity and specificity of the MMSE ranged from 11.1% to 18.2% and from 94.7% to 95.8%, respectively. For BL patients (RAVLT n=67, CF n=73, LF n=57), the sensitivity measures could not be calculated, as zero patients declined on both the MMSE and on an extended neuropsychological measure, indicating an extremely low sensitivity. The specificity of the MMSE for BL patients ranged from 98.1% to 100%.

The ROC curves are displayed in Figure 2. The AUC was 0.540 for delayed recall, 0.642 for CF, and 0.559 for LF, indicating limited discriminative ability of the MMSE (27).

Discussion

In the present study, we examined the change of the MMSE in patients with a major depressive episode treated with ECT. Moreover, we investigated the sensitivity of the MMSE in identifying declines in predefined neuropsychological measures sensitive to ECT-induced cognitive changes (verbal recall and verbal fluency) immediate after ECT. The mean MMSE total score showed a small but significant improvement from before ECT to one week after ECT. Only 8.9% of patients showed a significant decline in MMSE score from pre- to post-ECT. With a range from 3.6% to 11.1%, the sensitivity of the MMSE in identifying patients who experienced a significant decline in verbal recall or verbal fluency was low.

Our results showed a small but significant improvement in mean total MMSE score from before to one week after ECT, in line with the meta-analysis of Semkovska & McLoughlin (2010) displaying a decline at zero to three days post-ECT followed by an improvement at 4-15 days post-ECT compared to baseline (2). Only 36 patients (8.5%) showed a significant decline in MMSE score, while the vast majority remained stable and some improved. The lack of change may be partly due to the well-known ceiling effect of the MMSE. Previous research also showed that the MMSE is not an adequate cognitive screening instrument in late-life depression (28). In the present study, we intended to provide descriptive statistics of patients who declined versus those who did not decline on the MMSE. In comparison to the group without a significant decline in the MMSE, the group with a significant decline was significantly older, had experienced more previous episodes and received fewer ECT sessions. The significant fewer ECT sessions in the group that declined may be explained by the higher percentage of discontinuations of the ECT course due to clinical reasons or severe side-effects (30.0%), compared to the group that did not decline (11.6%). It is demonstrated that the MMSE lacks sensitivity in measuring ECT-induced cognitive side-effects, thereby diminishing the relevance for investigating potential predictors of MMSE decline. Importantly, both our statistical methods and their application to a small group of 36 patients that declined are not suited to make statements regarding prognostic factors of change in cognitive functioning following ECT (29).

While the MMSE showed a significant improvement in mean total score from before to one week after ECT, all the extended neuropsychological measures showed a significant decrease. The proportion of patients that declined was significantly higher in each of the extended neuropsychological measures compared to the MMSE. Furthermore, the AUC showed the limited discriminative ability of the MMSE in predicting a significant decline in each of the extended neuropsychological measures. Although the MMSE had a high specificity in identifying patients who did not experience a decline in verbal recall or verbal fluency, the sensitivity of identifying patients who did experience a decline was low. For RUL patients, the sensitivity of the MMSE was slightly better, although it still remained low. Almost all patients that showed a significant decline in verbal recall or verbal fluency from before to after ECT were mislabeled as cognitive stable by cognitive monitoring with the MMSE. Thus, if a patient remains stable on the MMSE, one could certainly not conclude that no ECT-induced cognitive side-effects are present. A valid screening instrument should be capable of detecting a high proportion of cognitive impairments (9), consequently one could argue that the use of the MMSE for monitoring ECT-induced cognitive changes is not legitimate. When only the MMSE is administered for cognitive monitoring following ECT, this can lead to a severe underestimation of the presence of cognitive side-effects and a lack of recognition,

guidance, and support for patients. Therefore, we would suggest a shift away from the MMSE as most frequently used test in ECT practice and most common measure in ECT guidelines on cognitive monitoring. Instead, measures on verbal recall and verbal fluency could be used in combination with a measure to assess autobiographical memory, such as the Colombia University Autobiographical Memory Interview-SF (CUAMI-SF) (30). However, the ecological validity of the CUAMI-SF has been criticized and the administration of the instrument is fairly time-consuming (31). If only a global cognitive screening measure is feasible, the MoCA would be preferred over the MMSE, as it is more sensitive and includes a sub-item on verbal fluency and a more reliable recall measure (6). Furthermore, the ElectroConvulsive therapy Cognitive Assessment (ECCA) could be considered, as it is a concise cognitive screening tool that includes an autobiographical memory section (32).

This is one of the largest studies to date with available data on both the MMSE and extended cognitive measures in patients with depression treated with ECT. Nevertheless, it is essential to interpret our findings considering its limitations. Despite the large sample size, there was a substantial amount of missing data for the MMSE in some of the included cohorts (overall 43.4%). Furthermore, verbal recall and verbal fluency were used as the 'gold standard' in the present study, while there are no evidence-based guidelines indicating these measures as such (5). However, contrary to most other cognitive measures, a significant decline is demonstrated on a group level in verbal recall and verbal fluency post-ECT (9, 15, 16), indicating that these may be the most sensitive cognitive measures to monitor ECT-induced cognitive side-effects (16). Moreover, we did not correct for a possible learning effect due to the repeated assessment of the same neuropsychological measures. However, the primary focus was to compare these measures with each other, and consequently, the learning effect was assumed to be reasonably consistent across all assessments. Another limitation of the present study was that the limited availability of the MMSE scores at sub-item level hindered our ability to examine the sensitivity of individual sub-items. Additionally, the present study was not able to include a measure on autobiographical memory, while retrograde amnesia is a major concern for patients and occurs regularly post-ECT (33, 34). Nonetheless, no sub-item on retrograde memory is included in the MMSE, so it is unlikely that the MMSE would be sensitive in identifying patients who experience side-effects in the domain of retrograde memory.

Given the low sensitivity of the MMSE, we propose reconsidering the prominence of the MMSE in ECT practice and cognitive monitoring guidelines, advocating for a more comprehensive approach to assess ECT-induced cognitive changes. Our findings could

contribute to the development of evidence-based guidelines and to the enhanced monitoring of cognitive side-effects in patients with depression undergoing ECT.

Acknowledgements

This study (with project number 60-63600-98-903, PI A Dols) was supported in part by The Netherlands Organization for Health Research and Development (ZonMW). RJT Mocking is funded by an ABC Talent Grant, ZonMW GGZ Fellowship, Starter Grant and Nationaal Plan Hoofdzaken.

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.

Declaration of interest

The authors report no biomedical financial interests or potential conflicts of interest.

Data availability

According to European law (General Data Protection Regulation), data containing potentially identifying or sensitive patients' information are restricted. However, for academic researchers, data could be available on request via the Dutch ECT Consortium (DEC) Board: dutchectconsortium.nl (a.dols@umcutrecht.nl) or via the corresponding author.

References

1. Weiner RD, Reti IM. Key updates in the clinical application of electroconvulsive therapy. Int Rev Psychiatry. 2017;29(2):54-62.

2. Semkovska M, McLoughlin DM. Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. Biol Psychiatry. 2010;68(6):568-77.

3. Verwijk E, Comijs HC, Kok RM, Spaans HP, Stek ML, Scherder EJ. Neurocognitive effects after brief pulse and ultrabrief pulse unilateral electroconvulsive therapy for major depression: a review. J Affect Disord. 2012;140(3):233-43.

4. Andrade C, Arumugham SS, Thirthalli J. Adverse Effects of Electroconvulsive Therapy. Psychiatr Clin North Am. 2016;39(3):513-30.

5. Rasmussen KG. What Type of Cognitive Testing Should Be Part of Routine Electroconvulsive Therapy Practice? J ect. 2016;32(1):7-12.

6. Moirand R, Galvao F, Lecompte M, Poulet E, Haesebaert F, Brunelin J. Usefulness of the Montreal Cognitive Assessment (MoCA) to monitor cognitive impairments in depressed patients receiving electroconvulsive therapy. Psychiatry Res. 2018;259:476-81.

7. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189-98.

8. Verwijk E, van Kessel M, Obbels J, Kroes M. Neurobiologie en neuropsychologie van cognitieve effecten. Leerboek Elektroconvulsietherapie. 2019:247-74.

9. Landry M, Moreno A, Patry S, Potvin S, Lemasson M. Current Practices of Electroconvulsive Therapy in Mental Disorders: A Systematic Review and Meta-Analysis of Short and Long-Term Cognitive Effects. J ect. 2021;37(2):119-27.

10. Fernie G, Bennett DM, Currie J, Perrin JS, Reid IC. Detecting objective and subjective cognitive effects of electroconvulsive therapy: intensity, duration and test utility in a large clinical sample. Psychol Med. 2014;44(14):2985-94.

11. Obbels J, Vansteelandt K, Verwijk E, Dols A, Bouckaert F, Oudega ML, et al. MMSE Changes During and After ECT in Late-Life Depression: A Prospective Study. Am J Geriatr Psychiatry. 2019;27(9):934-44.

12. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695-9.

13. Galea M, Woodward M. Mini-Mental State Examination (MMSE). Aust J Physiother. 2005;51(3):198.

14. Rohde P, Noorani R, Feuer E, Lisanby SH, Regenold WT. Electroconvulsive Therapy Across Nations: A 2022 Survey of Practice. J ect. 2024;40(2):96-104.

15. Bodnar A, Krzywotulski M, Lewandowska A, Chlopocka-Wozniak M, Bartkowska-Sniatkowska A, Michalak M, Rybakowski JK. Electroconvulsive therapy and cognitive functions in treatment-resistant depression. World J Biol Psychiatry. 2016;17(2):159-64.
16. Loef D, van Eijndhoven P, van den Munckhof E, Hoogendoorn A, Manten R, Spaans HP, et al. Pre-treatment predictors of cognitive side-effects after treatment with electroconvulsive therapy in patients with depression: A multicenter study. J Affect Disord. 2024;349:321-31.
17. van Eijndhoven P, Tendolkar I, Loef D, Rovers J, Somers M, Spaans H-p, et al. Precision Electroconvulsive Therapy (PET) project: tackling (cost) effectiveness and patients perspectives. medRxiv. 2024:2024.03. 21.24304665.
18. Van den Broek WW, Birkenhäger T, De Boer D, Burggraaf J, van Gemert B, Groenland T. Richtlijn elektroconvulsietherapie. Dutch Association for Psychiatry. 2010.
19. Saan R, Deelman B. Dutch version of the Rey auditory verbal learning test. Groningen: Department of Neuropsychology, RUG, provisional manual. 1986.
20. Luteijn F, Van der Ploeg F. Handleiding groninger intelligentietest (git). Lisse, the Netherlands: Sweitz & Zeitlinger. 1983.
21. Mulder J, Dekker P, Dekker R. Handleiding Woord-Fluency Test/Figuur-Fluency Test. Nederland, Leiden, Leiden: PITS. 2006.
22. de Vent NR, Agelink van Rentergem JA, Schmand BA, Murre JM, Huizenga HM. Advanced Neuropsychological Diagnostics Infrastructure (ANDI): A Normative Database Created from Control Datasets. Front Psychol. 2016;7:1601.
23. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-9.
24. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23(1):56-62.
25. Leucht S, Fennema H, Engel RR, Kaspers-Janssen M, Szegedi A. Translating the HAM-D into the MADRS and vice versa with equipercentile linking. J Affect Disord. 2018;226:326-31.
26. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol. 1991;59(1):12-9.
27. Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. J Thorac Oncol. 2010;5(9):1315-6.
28. Rajji TK, Miranda D, Mulsant BH, Lotz M, Houck P, Zmuda MD, et al. The MMSE is not an adequate screening cognitive instrument in studies of late-life depression. J Psychiatr Res. 2009;43(4):464-70.
29. Poldrack RA, Huckins G, Varoquaux G. Establishment of Best Practices for Evidence for Prediction: A Review. JAMA Psychiatry. 2020;77(5):534-40.

30. McElhiney MC, Moody BJ, Steif BL, Prudic J, Devanand D, Nobler MS, Sackeim HA. Autobiographical memory and mood: effects of electroconvulsive therapy. Neuropsychology. 1995;9(4):501.

31. Semkovska M, McLoughlin DM. Retrograde autobiographical amnesia after electroconvulsive therapy: on the difficulty of finding the baby and clearing murky bathwater. J ect. 2014;30(3):187-8; discussion 9-90.

32. Hermida AP, Goldstein FC, Loring DW, McClintock SM, Weiner RD, Reti IM, et al. ElectroConvulsive therapy Cognitive Assessment (ECCA) tool: A new instrument to monitor cognitive function in patients undergoing ECT. J Affect Disord. 2020;269:36-42.

33. Fraser LM, O'Carroll RE, Ebmeier KP. The effect of electroconvulsive therapy on autobiographical memory: a systematic review. J ect. 2008;24(1):10-7.

34. Obbels J, Verwijk E, Bouckaert F, Sienaert P. ECT-Related Anxiety: A Systematic Review. J ect. 2017;33(4):229-36.

Table 1. Baseline demographic, clinical and treatment characteristics.

	All participants N=426	Reliable change in the MMSE		p-value of difference between groups
		Declined n=36	Not declined n=390	
Demographic characteristics				
Age, mean (SD), range	64.0 (15.8), 21 -92	71.8 (15.0)	63.2 (15.7)	p=0.002
Sex, Female, n (%)	266 (62.4)	25 (69.4)	241 (61.8)	p=0.364
Level of education:				p=0.230
lower, n (%)	122 (32.1)	9 (37.5)	113 (31.7)	
medium, n (%)	118 (31.1)	10 (41.7)	108 (30.3)	
high, n (%)	140 (36.8)	5 (20.8)	135 (37.9)	
Clinical characteristics				
Bipolar disorder, n (%)	50 (11.7)	3 (8.3)	47 (12.1)	p=0.507
Previous depressive episodes, mean (SD)	2.2 (2.8)	3.7 (3.6)	2.1 (2.7)	p=0.025
Duration of current episode in months, mean (SD)	15.3 (27.0)	10.8 (9.8)	15.8 (28.2)	p=0.786
Age at onset of first depression, mean (SD)	46.3 (20.7)	54.0 (23.1)	45.7 (20.4)	p=0.058
With psychotic features n (%)	181 (43.1)	16 (44.4)	165 (43.0)	p=0.864
MMSE before, mean (SD), range	26.2 (3.9)	26.0 (3.3)	26.2 (4.0)	p=0.753
MMSE after, mean (SD), range	26.8 (3.8)	19.4 (4.9)	27.5 (2.9)	p<0.0001
ECT characteristics				
Number of ECT sessions, mean (SD)	12.2 (6.6)	9.3 (5.3)	12.5 (6.7)	p=0.009
Patients treated bilateral or switched to bilateral, n (%)	145 (41.2)	9 (31.0)	136 (42.1)	p=0.246
Depression measures				
MADRS before, mean (SD)	31.7 (8.9)	31.2 (6.7)	31.7 (9.0)	p=0.761
MADRS after, mean (SD)	12.2 (10.4)	13.0 (11.9)	12.1 (10.2)	p=0.960
Remission, n (%)	202 (50.2)	19 (55.9)	183 (49.7)	p=0.492
Response, n (%)	233 (64.4)	21 (65.6)	212 (64.2)	p=0.876

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). Abbreviations: MMSE=Mini Mental State Examination; ECT=electroconvulsive therapy; MADRS=Montgomery–Åsberg Depression Rating Scale.

Table 2. Score and Reliable Change Index of extended neuropsychological measure from before to after electroconvulsive therapy.

	Score before, mean (SD)	Score after, mean (SD)	Paired samples T-test comparing means before and after	Reliable change index		
				Declined, n (%)	Stable, n (%)	Improved, n (%)
Delayed recall (n=164)	6.8 (3.9)	6.3 (3.6)	t=2.03, p=0.044	28 (17.1)	126 (76.8)	10 (6.1)
Category fluency (n=227)	18.1 (6.8)	16.8 (6.3)	t=3.14, p=0.002	41 (18.1)	165 (72.7)	21 (9.3)
Letter fluency (n=202)	28.1 (11.6)	25.6 (11.3)	t=3.64, p<0.001	27 (13.4)	164 (81.2)	11 (5.4)

Table 3. Sensitivity and specificity of the Mini Mental State Examination (MMSE) in identifying all patients who did and did not experience a significant decline in the extended neuropsychological measures, respectively.

	Delayed recall	Category fluency	Letter fluency	All extended neuropsychological measures combined
Sensitivity MMSE (95%CI) Specificity MMSE (95%CI)	3.6% (0-10.4) 95.6% (92.1-99.0)	7.3% (0-15.3) 95.7% (92.8-98.6)	11.1% (0-23.0) 96.6% (93.9-99.3)	6.6% (1.0-12.2) 95.6% (92.5-98.8)

Figure 1. Pie charts of patients who showed a reliable decline in the Mini Mental State examination (MMSE) versus in the extended neuropsychological measures: delayed recall, category fluency (CF), and letter fluency (LF). The absolute numbers per category are displayed.

Figure 2. Receiver Operating Characteristics (ROC) curves of the Mini Mental State Examination (MMSE) difference score predicting a significant decline in each of the extended neuropsychological measures: delayed recall, category fluency (CF), and letter fluency (LF).