Comparing the Cognitive Effects of Repeated Intravenous Ketamine and Electroconvulsive Therapy in Patients With Treatment-Resistant Depression:

A Secondary Analysis of the ELEKT-D Trial

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Abstract

Objective: Electroconvulsive therapy (ECT) has potent antidepressant effects yet can lead to neurocognitive side effects. Ketamine is a rapid-acting antidepressant, which may be an alternative to ECT. Few have directly compared the cognitive effects of ECT and ketamine treatment.

Methods: We compared cognitive effects of intravenous ketamine and ECT in patients with treatment-resistant depression (TRD), collected through a multisite, randomized trial conducted between April 2017 and November 2022 (the ELEKT-D study). Participants received 6 IV ketamine treatments or 9 ECT sessions. Cognitive functioning was assessed through 4 validated cognitive tasks at pre- and posttreatment visits. The Squire Memory Complaint Questionnaire (SMCQ) and Global Self-Evaluation of Memory (GSE-My) were used to measure changes in memory functioning. Responders (those who achieved ≥50% reduction in depressive symptoms) were evaluated again at 1-, 3-, and 6-month follow-up visits.

Results: In the intent-to-treat sample (N = 365), ECT recipients performed significantly worse than ketamine recipients on all cognitive tasks at end of treatment ($P < .001$), with no significant differences in task performance associated with response to either treatment. Among responders, we observed no significant group differences at 1-, 3-, and 6-month follow-up. Analyses of subjective memory questionnaires were mixed. SMCQ scores improved for both groups with ketamine recipients reporting greater functional gains; ketamine-treated patients reported improvements in GSE-My scores while ECT-treated patients reported a decline in GSE-My scores. Within-group analyses in the ketamine group found improvements in executive functioning and cognitive flexibility. This survived adjustments for changes in depression, suggesting partial independence of cognitive and mood effects.

Conclusions: Patients treated with ketamine demonstrated superior cognitive functioning compared with those treated with ECT following a 3-week treatment course, with no differences between treatments observed among responders in follow-up. Findings support the short-term superiority of ketamine on cognitive functioning and the long-term cognitive safety of both treatments for TRD.

Trial Registration: ClinicalTrials.gov identifier: NCT03113968.

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Major depressive disorder (MDD) affects 5%–17% of individuals throughout their lives,[1] and those with MDD often suffer cognitive dysfunction in addition to the characteristic mood disturbances.[2–4] While existing antidepressants are considered effective, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial aimed to determine which oral antidepressants were most effective. This trial has shown that roughly 1 in 3 with MDD are unresponsive to prescribed antidepressant medications, while another

Clinical Points

- With interventional treatments for treatment-resistant depression (TRD) expanding, determining the appropriate treatment for a given patient depends on a number of factors including cognitive side effects.
- Both electroconvulsive therapy and ketamine are effective treatment options for those with TRD in the long term, but ketamine could be the more suitable choice for patients worried about cognitive performance or susceptible to cognitive dysfunction.

third receive suboptimal symptom reduction.[5] Those unresponsive to at least 2 different first-line antidepressant treatments are generally considered to suffer from treatment-resistant depression (TRD).[5]

Electroconvulsive therapy (ECT) is highly effective for TRD, with response rates over 50% in many trials.[6–8] Despite advances in ECT administration techniques, cognitive impairment remains a concern, particularly regarding memory loss.[9,10] Many negative effects on cognition appear transient, with performance returning to baseline levels or higher over the weeks or months following an acute ECT series.[9–12] However, concerns remain regarding ECT's negative impact on cognition, contributing to the pursuit of novel alternatives for TRD.

Ketamine has generated considerable therapeutic interest as a rapid antidepressant. Existing research has found short courses of ketamine to have a neutral[13–15] or positive[16–19] effect on cognitive performance. However, these studies have generally evaluated small samples. Further, ketamine has been associated with negative cognitive and neurological changes in primate models using therapeutic doses at a higher frequency,[20] and among high-dose recreational users, where studies have found episodic memory and attentional dysfunction after discontinuation even as semantic memory recovered.[21]

Here, we investigate in depth the comparative cognitive outcomes among patients with TRD randomized to a course of ECT or intravenous (IV) ketamine, as part of the ELEKT-D trial.

METHODS

Trial Design and Procedure

The current study analyzed neurocognitive data from the Patient-Centered Outcomes Research Institute (PCORI)-funded ELEKT-D clinical trial; the detailed research design and primary results of this study have been published[22] (ClinicalTrials.gov identifier: NCT03113968). Briefly, patients with TRD were randomized to receive ECT (9 total treatments, beginning with right unilateral lead placement) or IV ketamine (6 total treatments, 0.5 mg/kg over 40 minutes) over 3 weeks; for CONSORT diagram, see Anand et al.[22] Psychological and cognitive functioning were assessed at baseline and end of treatment (EoT). Those who responded to either treatment (ie, ≥50% improvement as measured by the Quick Inventory of Depressive Symptomatology Self-Report [QIDS-SR-16][23]) repeated cognitive testing at 1-, 3-, and 6-month follow-up visits. Written and informed consent was obtained from all participants prior to participation in the study, and each site's institutional review board approved a standard consent form and protocol.

Patient Eligibility

Key inclusion criteria included (1) an MDD diagnosis, (2) a Montgomery-Asberg Depression Rating Scale score >20 at baseline,[24] (3) a baseline Montreal Cognitive Assessment (MoCA) ≥18,[25] and (4) 2 or more lifetime adequate trials of antidepressants or augmentation strategies. Key exclusion criteria included a diagnosis of bipolar disorder, schizophrenia, MDD with psychotic features, a pervasive developmental disorder, or any neurodegenerative disorder.

Cognitive Functioning

The MoCA, a brief multidomain tool for detecting cognitive impairment, was the cognitive screening measure for the ELEKT-D trial, with a possible score range of 0–30. The MoCA was also completed at EoT and follow-up visits. The Hopkins Verbal Learning Test-Revised (HVLT-R)[26] was used to assess verbal learning and episodic memory, captured by the total and delayed recall scores. The Stroop Color and Word Test (Stroop)[27] was used to measure executive functions such as processing speed, selective attention, and cognitive flexibility. The Controlled Oral Word Association Test (COWAT)[28] was used to measure speeded verbal fluency. We used counterbalanced forms for HVLT-R, MoCA, and COWAT at baseline and EoT to minimize practice effects. Partial results of the HVLT-R task were previously reported in the primary manuscript and are repeated here for clarity and completeness.[22] Two self-report questionnaires were used to assess subjective changes in memory over the course of treatment. The Squire Memory Complaint Questionnaire (SMCQ),[29] where scores range from −72 to +72, was completed at each study and follow-up visit, and the Global Self-Evaluation of Memory (GSE-My),[30] a 7-point scale evaluating memory function since beginning treatment, was completed from visit 2 onward. The North American Adult Reading Test-35 (NAART-35),[31] a single-word oral reading task, was administered at visit 1 to attain an estimation of premorbid ability.

Statistical Analysis

Ordinary least-squares estimates were used to compare the mean change in raw score from baseline to

EoT for total and delayed recall HVLT-R, Stroop interference, MoCA, COWAT, and SMCQ between the ECT and ketamine groups. As the collection of the GSE-My began after baseline, least-square estimates of each group at EoT were compared. Adjusted models controlled for covariates of site, baseline QIDS-SR-16, change in depression severity (change in QIDS-SR-16 score), and baseline cognitive performance. Additional exploratory analyses were used to compare change in cognitive performance between responders and nonresponders to each treatment at EoT, using the same adjusted models with change in depression severity removed given the collinearity of QIDS score and response. To evaluate the persistence of changes in cognitive performance between baseline and EoT, we fitted the least-square mean score for each cognitive measure in a mixed-effect model to evaluate change over time among responders from baseline through the 6-month follow-up. The model included a random intercept at the participant level. The covariates were selected based on clinical judgment. Least-square mean scores for the full sample were assessed for both subjective measures of memory (SMCQ and GSE-My). The Benjamini-Hochberg approach was applied to account for multiple comparisons.

Exploratory within-group analyses were used to evaluate ketamine's effects on cognition. Ordinary least-squares regression analyses compared changes in mean cognitive performance (*t* statistics) from baseline to EoT. Linear regression was used to assess relationships between depression severity (measured by QIDS-SR-16), concomitant medications, and cognitive changes. Models adjusted for age, sex, education, and estimated intelligence (via NAART-35).

RESULTS

Descriptive statistics, including demographic variables, concurrent medications, and comorbid conditions of study participants, are reported in Table 1. For responder characteristics, see Supplementary Table 1. The intention-to-treat sample comprised 365 participants, 191 of whom were female (52.3%) and 319 (87.4%) of whom identified as European American or White. The sample participants had a mean age of 46.0 years (SD = 14.5), and the average age at first depressive episode was 19.4 years (SD = 11.4). Antidepressants were the most common concurrent medication, taken by 82.4% of participants assigned to the ECT condition and 85.1% of those assigned to the ketamine condition. The most common comorbid psychiatric condition was generalized anxiety disorder, reported by 200 (54.8%) participants. At EoT, there were 70 ECT responders (41.2%) and 108 ketamine responders (55.4%) based on change in QIDS-SR-16.

Between-Group Cognitive Outcomes Following Treatment

Following treatment, the ketamine group outperformed the ECT group on the HVLT-R total (mean difference = 5.35; corrected $P < .001$), HVLT-R delayed recall (mean difference = 8.57; corrected $P < .001$), Stroop interference (mean difference = 4.03; corrected $P < .001$), COWAT (mean difference = 7.78; corrected $P < .001$), and MoCA (mean difference = 1.10; corrected $P < .001$; Figure 1). At EoT, both treatment groups reported improved memory functioning on the SMCQ; however, while ECT recipients' scores had increased 15.08 points, ketamine recipients' scores had increased 21.51 points (mean difference = 6.43; corrected $P < .001$). For the GSE-My, the ketamine group reported significantly better treatment-associated memory changes at EoT compared to the ECT group (mean difference = 0.94; corrected $P < .001$). While there was no significant difference in GSE-My at visit 2, from visit 3, through EoT, ECT recipients reported a significant worsening in treatment-related memory functioning compared to ketamine recipients (corrected $P < .001$; Figure 2B).

Exploratory Between-Group Cognitive Outcomes Between Responders and Nonresponders

At the EoT visit, there was no significant difference between responders and nonresponders to either treatment on the HVLT-R Total, HVLT-R Delayed Recall, Stroop interference, COWAT, or MoCA ($P > .05$). Regardless of treatment response, performance scores had declined on all objective cognitive tasks at EoT for those who received ECT. Ketamine nonresponders had worse scores compared to baseline on the MoCA (mean change = 0.39) and HVLT-R Delayed Recall (mean change = −1.46); however, scores did not differ significantly from those of responders. There were significant differences between responders and nonresponders to both ketamine and ECT on the subjective cognitive measures ($P < .001$). Mean change in SMCQ at EoT was 6.29 for ECT nonresponders, 14.86 for ketamine nonresponders, 19.85 for ECT responders, and 31.23 for ketamine responders, indicating the greatest improvement in subjective cognitive functioning among ketamine responders. The mean difference in GSE-My scores between responders and nonresponders was 0.55 ($P < .001$) and 0.69 ($P < .001$) for ketamine and ECT recipients, respectively, indicating better subjective cognitive functioning among responders for both treatment groups.

Longer-Term Cognitive Outcomes Among Responders

Among responders (who were followed for 6 months following acute treatment), there were no group

Table 1.

Demographic and Clinical Factors of the Sample (N=365)

	ECT (N = 170)	Ketamine (N = 195)	SMD
Age, mean ± SD, y	46.6 ± 14.1	45.6 ± 14.8	0.07
Years of education, mean ± SD	15.8 ± 2.4	15.4 ± 2.8	0.14
Sex, n (%)[a]			0.04
Male	83 (48.8)	91 (46.7)	
Female	87 (51.2)	104 (53.3)	
Racial identity, n (%)[a]			0.14
African American	10 (5.9)	10 (5.1)	
White	151 (88.8)	168 (86.2)	
Other	9 (5.3)	17 (8.7)	
Hispanic identity, n (%)[a]			0.30
Hispanic	7 (4.1)	24 (12.3)	
Non-Hispanic	163 (95.9)	171 (87.7)	
BMI, mean ± SD	30.5 ± 7.9	29.5 ± 7.4	0.13
Comorbidities, n (%)			
GAD	91 (53.5)	109 (55.9)	0.05
PTSD	43 (25.3)	37 (19.0)	0.15
OCD	15 (8.8)	9 (4.6)	0.17
Substance use	12 (7.1)	10 (5.1)	0.08
Age at onset of first depressive episode, mean ± SD, y	19.2 ± 11.2	19.6 ± 11.6	0.04
Baseline QIDS, mean ± SD	18.5 ± 4.2	17.9 ± 4 .1	0.08
Baseline MADRS, mean ± SD	32.6 ± 6.1	32.4 ± 6.2	
Baseline cognitive performance, mean ± SD			
NAART-35 Standard Score	89.5 ± 8.8	88.0 ± 10.2	0.15
MoCA Total Score	26.5 ± 2.6	26.7 ± 2.7	0.06
HVLT-R Delayed Recall	37.8 ± 14.7	39.1 ± 14.6	0.09
HVLT-R Total Score	35.9 ± 12.7	36.4 ± 13.4	0.04
COWAT	38.9 ± 10.6	36.9 ± 11.0	0.19
Stroop Word Reading Total Score	86.5 ± 17.3	88.4 ± 18.6	0.11
Stroop Color Reading Total Score	62.5 ± 12.8	64.5 ± 12.7	0.16
Stroop Interference Total Score	37.8 ± 11.0	39.8 ± 11.4	0.19
Concomitant psychiatric medications, n (%)			
Antidepressants	140 (82.4)	166 (85.1)	0.08
Benzodiazepines	56 (32.9)	58 (29.7)	0.07
Anticonvulsants	43 (25.3)	54 (27.7)	0.05
Antipsychotics	48 (28.2)	57 (29.2)	0.02
Lithium	23 (13.5)	19 (9.7)	0.12
Responders (≥50% improvement on QIDS-SR-16), n (%)[b]	70 (41.2)	108 (55.4)	0.29

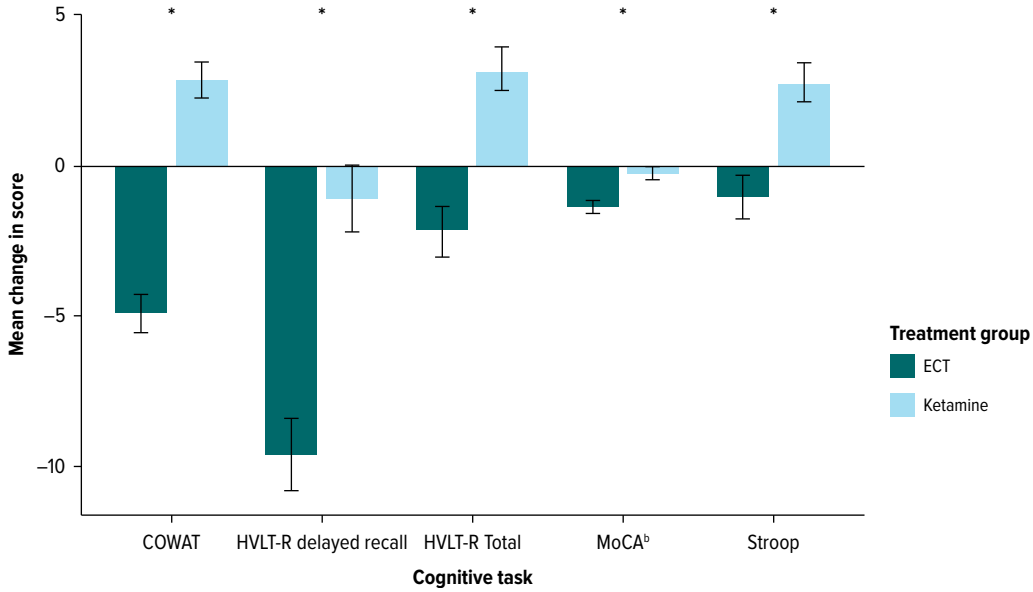
[a]Data are derived from participant self-report.
[b]Characteristics by response are available in Supplementary Table 1.
Abbreviations: BMI = body mass index, COWAT = Controlled Oral Word Association Test, ECT = electroconvulsive therapy, GAD = generalized anxiety disorder, HVLT-R Total = Hopkins Verbal Learning Test Revised Total, HVLT-R Delayed Recall = Hopkins Verbal Learning Test Revised Delayed Recall, MADRS = Montgomery-Asberg Depression Rating Scale, MoCA = Montreal Cognitive Assessment, NAART-35 = North American Adult Reading Test-35, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder, QIDS-SR-16 = 16-item Quick Inventory of Depressive Symptomatology Self-Report, SMD = standardized mean difference, Stroop = Stroop Interference Condition.

differences in SMCQ-rated memory functioning during the 6-month follow-up period (Figure 3A). Regarding the GSE-My, responders who received ECT reported lower subjective memory performance by visit 3, and this difference persisted for up to 6 months following the acute treatment period (Figure 3B). No significant group differences in performance on the HVLT-R, Stroop, COWAT, or MoCA were seen among responders at months 1, 3, and 6. Generally, ketamine responders maintained the performance gains observed at EoT. Despite impaired performance at EoT, ECT responders showed no significant difference from ketamine responders in performance at any follow-up visit on all cognitive tasks assessed (see Supplementary Figure 1).

Within-Group Analysis of Ketamine

Within-group analysis of patients in the ketamine group showed stable or improved performance from baseline to EoT (Figure 4). There was no change in scores for the HVLT-R Total, HVLT-R Delayed Recall, or MoCA. Significant improvements were observed for Stroop Word Reading ($P < .001$, Cohen $d = 0.31$), Color

Figure 1.
Mean Change in Performance by Task and Treatment[a]



[a]Ordinary least-square estimates of change in raw score from baseline to end of treatment for participants receiving ECT (N = 170) and ketamine (N = 195). All models controlled for site, baseline depression severity, change in depression severity, and baseline cognitive performance. Error bars represent standard errors.
[b]MoCA represents change from screening to end of treatment.
*$P < .001$ Benjamini-Hochberg adjusted significance.
Abbreviations: COWAT = Controlled Oral Word Association Test, ECT = electroconvulsive therapy, HVLT-R Total = Hopkins Verbal Learning Test Revised Total, HVLT-R Delayed Recall = Hopkins Verbal Learning Test Revised Delayed Recall, MoCA = Montreal Cognitive Assessment, Stroop = Stroop Interference Condition.

Reading ($P < .001$, Cohen $d = 0.40$), Interference ($P < .001$, Cohen $d = 0.40$), and COWAT ($P < .001$, Cohen $d = 0.47$). SMCQ-rated memory showed significant improvement, with a mean increase of 23.9 points from baseline to EoT ($P < .001$, Cohen $d = 0.94$). These improvements persisted after adjusting for changes in depression severity.

DISCUSSION

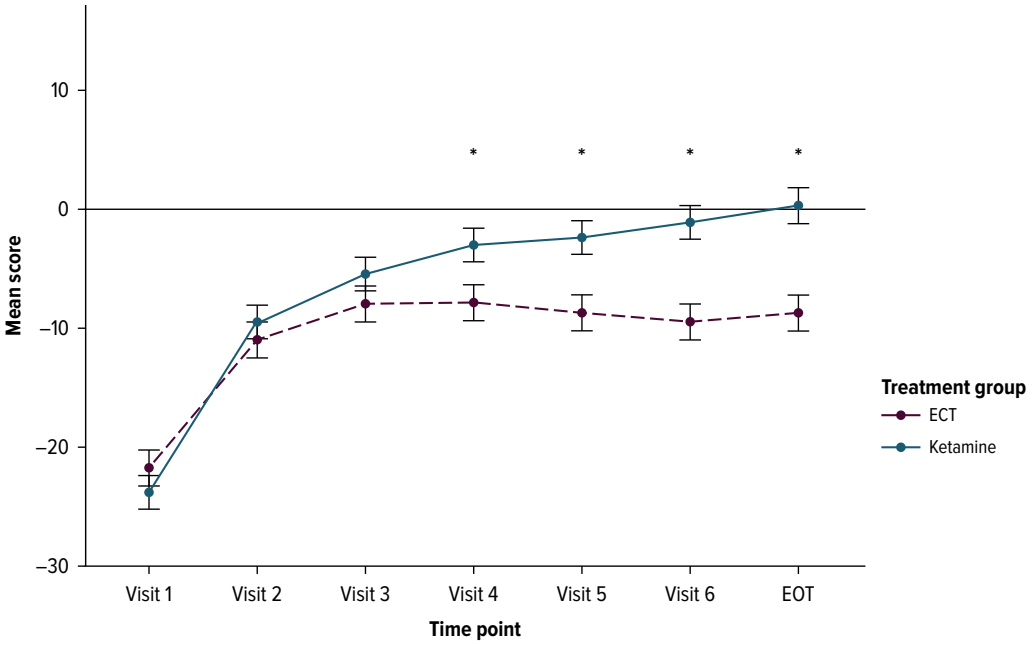
The present study examined neurocognitive effects of ECT and ketamine treatment for TRD in a large, randomized, clinical trial focusing on cognitive effects following an acute treatment series as well as longitudinal changes over a 6-month follow-up period among responders. Participants who received ECT showed significantly worse cognitive performance on all tasks compared to those who received ketamine following an acute treatment course, controlling for change in depression severity. No significant difference in change in cognitive performance from baseline was observed between responders and nonresponders on any objective cognitive task, but significant differences were seen on both subjective scales. Among responders, ketamine patients maintained cognitive performance gains throughout the follow-up period, while ECT patients improved from EoT through follow-up with no significant group differences in cognitive task performance at 6 months. Outcomes from subjective memory questionnaires were mixed. While ketamine recipients reported improved functioning on both scales, ECT recipients showed modest improvements on the SMCQ and endorsed worsening memory function on the GSE-My. Within-group analysis of patients treated with ketamine showed improvement in cognitive performance on measures of verbal fluency and cognitive flexibility. Analysis showed that these improvements persisted when controlling for changes in depression severity.

Our results found no indication of deleterious cognitive effects after 6 IV ketamine treatments at a dose of 0.5 mg/kg, while 9 sessions of ECT were associated with broad-spectrum reductions in cognitive performance at EoT. Our findings echo those of past naturalistic cohort studies[19] and randomized control trials[32,33] where cognition and memory were preserved or improved following ketamine and worsened with ECT. Previous studies with smaller sample sizes investigating multidose ketamine for TRD have similarly reported stable[13,14] or improved[16–19] performance on cognitive tasks

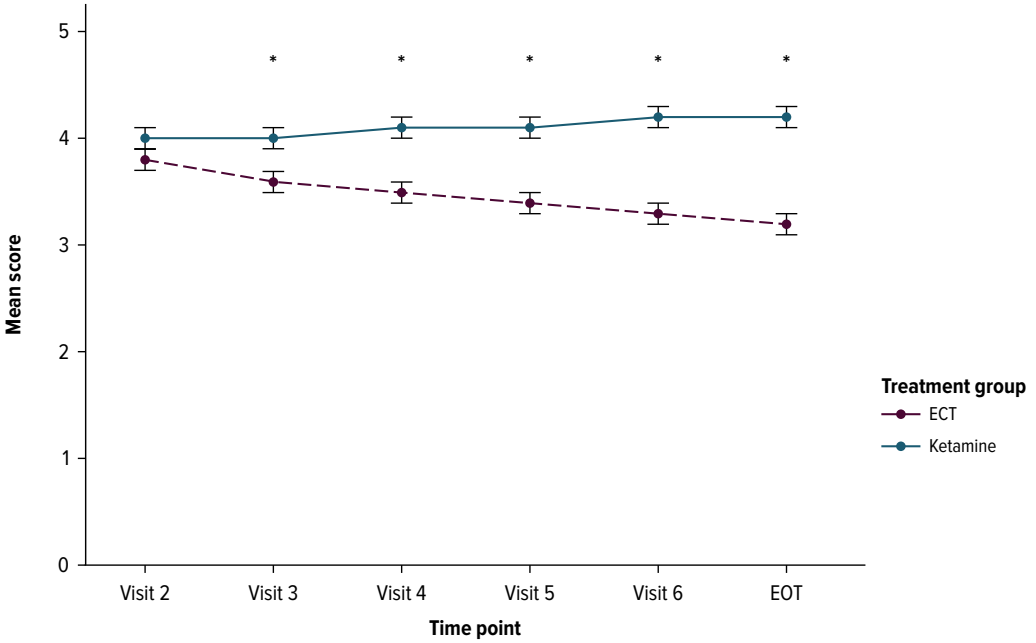
Figure 2.

Change in (A) SMCQ and (B) GSE-My Over Time by Treatment Group (Full Sample)

A. Change in SMCQ[a,b]



B. Change in GSE-My[c,d]



[a]Mixed-effect model of least-square means showing change from visit 1 (baseline) to end of treatment (EOT) for the self-reported memory functioning from the Squire Memory Complaint Questionnaire (SMCQ) for participants receiving ECT (N = 170) and racemic ketamine (N = 195).
[b]SMCQ scores range from −72 to +72; higher scores indicate better self-rated memory functioning. Error bars are standard error of the mean.
[c]Mixed-effect model of least-square means showing change from visit 2 to end of treatment (EOT) for the treatment-related changes in memory functioning from the Global Self-Evaluation of Memory (GSE-My) for participants receiving ECT (N = 170) and racemic ketamine (N = 195).
[d]GSE-My scores range from 1 to 7; higher scores indicate better perceived memory associated with treatment. Error bars are standard error of the mean.
*$P < .001$ (adjusted).

following an induction course of ketamine, consistent with the posttreatment improvements on tasks like the COWAT and Stroop observed in our exploratory analyses. Moreover, the durability of gains in cognitive flexibility captured by the Stroop when controlling for depression, and the absence of a significant difference in performance between ketamine responders and nonresponders at EoT, supports the partial independence of ketamine's cognitive and mood effects found in previous studies.[34,35] Our cognitive findings align with those of a recent pooled analysis of cognitive data from 900 participants from phase 3 studies of intranasal esketamine, which supported the cognitive safety of short-term and maintenance esketamine treatment for TRD.[36]

Post-ECT performance loss was observed on all cognitive tasks at EoT regardless of treatment response, and subsequent performance equaling or exceeding baseline scores during follow-up among responders is consistent with the findings of a previous meta-analysis, which reported significantly reduced performance across cognitive tasks within 3 days of a course of ECT and the return of performance within 2 weeks.[37] Thus, our findings align with those of previous smaller studies and meta-analyses that deterioration in cognitive performance following a course of ECT is transient and does not produce long-term multidomain impairment measurable by standardized tasks.[9,37,38] The pattern of cognitive impairment and recovery observed in our sample may relate to the neuroplasticity hypothesized to result from ECT treatment,[39] resulting from temporary disruption of established neurocircuitry in key regions for mood, memory, and cognition with performance recovering as neural connections stabilize.[10,40] However, further research is needed to fully elucidate ECT's effects as they relate to mood and neuroplasticity.

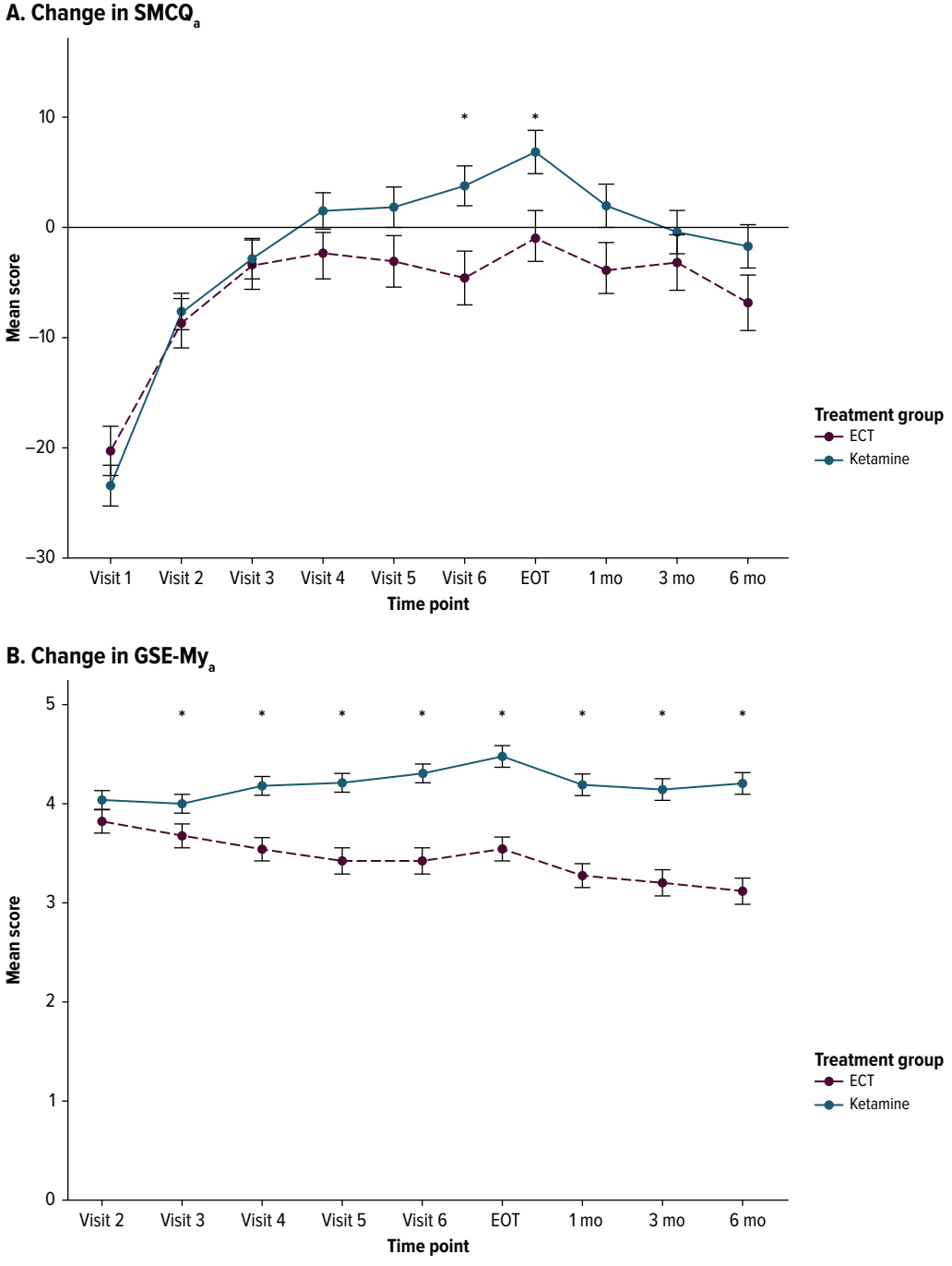
The mixed findings regarding the 2 measures of subjective memory serve to highlight the dichotomous effects of ECT and ketamine treatment on memory functioning. The SMCQ and GSE-My scores of ketamine recipients increased from first completion to EoT, which were retained or improved, respectively, among responders during follow-up. Thus, beyond the objective cognitive performance benefit over ECT, ketamine was associated with generalized and activity-specific improvements in self-reported memory that tangibly affected patient-perceived daily functioning. Notably, ECT recipients also reported improved SMCQ scores at EoT regardless of treatment response, that while lower than the gains associated with ketamine at this time point, indicate that both treatments offer some immediate gains in functional capacity related to memory. However, SMCQ score improvement among the ECT group appeared to plateau from visit 3 through EoT, and through follow-up among responders. The delta between ketamine and ECT-derived gains in SMCQ observed in our sample, coupled with ECT responders' return to pretreatment performance on a verbal learning and memory task, may relate to SMCQ questions pertaining to respondents' functional autobiographical memory. Impaired autobiographical memory, retrograde amnesia, and anterograde amnesia for the period following treatment are common adverse effects of ECT,[37,38] though their prevalence is believed to be reduced by right unilateral lead placement.[9] Thus, full spectrum relief from cognitive dysfunction may have been stymied by ECT's negative effect on these specific functional domains. Despite this, relief from cognitive symptoms of depression is apparent when considering the 13.56-point difference between responders and nonresponders to ECT at EoT.

This interpretation is further supported by the inverse pattern of GSE-My scores between treatment groups, with ketamine recipients reporting consistent perceived treatment-related memory improvement while ECT recipients indicated worsening memory function with each successive study visit. The apparent discrepancy between the gains captured by the SMCQ and losses reported on the GSE-My has been observed in previous longitudinal research into ECT's subjective memory effects, wherein questionnaires measuring changes in specific operational abilities find improvement, while scales which ask participants to retrospectively provide an open-ended impression of functioning may capture nonspecific perceived dysfunction.[30] Furthermore, both self-report measures may show expectation effects related to negative societal perceptions of ECT's effects on memory[41]; however, patient-perceived functional impairments following ECT have been well documented in the literature[38] and warrant more direct investigation in future studies.

The findings of the present study, which constitutes the largest known comparison of the cognitive effects of ECT and ketamine within a randomized trial, provide support for the long-term cognitive safety of both ketamine and ECT, with responders to both treatments showing stable or improved performance on objective measures throughout follow-up. However, the subacute functional superiority of the ketamine group regarding objective and subjective cognitive performance and persistent improvements in GSE-My-rated memory functioning associated with treatment throughout the study lend support for the preferential use of ketamine over ECT in this population particularly those citing cognitive concerns or predisposed to cognitive dysfunction. Given the burden of cognitive dysfunction in MDD,[3] and its tendency to persist beyond the remission of mood symptoms,[9] the present findings can help inform clinical decision-making for treatment of this population. As an *N*-methyl-D-aspartate receptor antagonist, ketamine, like esketamine, is hypothesized to improve depressive symptoms through induction of neuroplasticity.[36] The findings supporting partial

Figure 3.

Change in (A) SMCQ and (B) GSE-My Over Time by Treatment Group (Responders Only)[a]



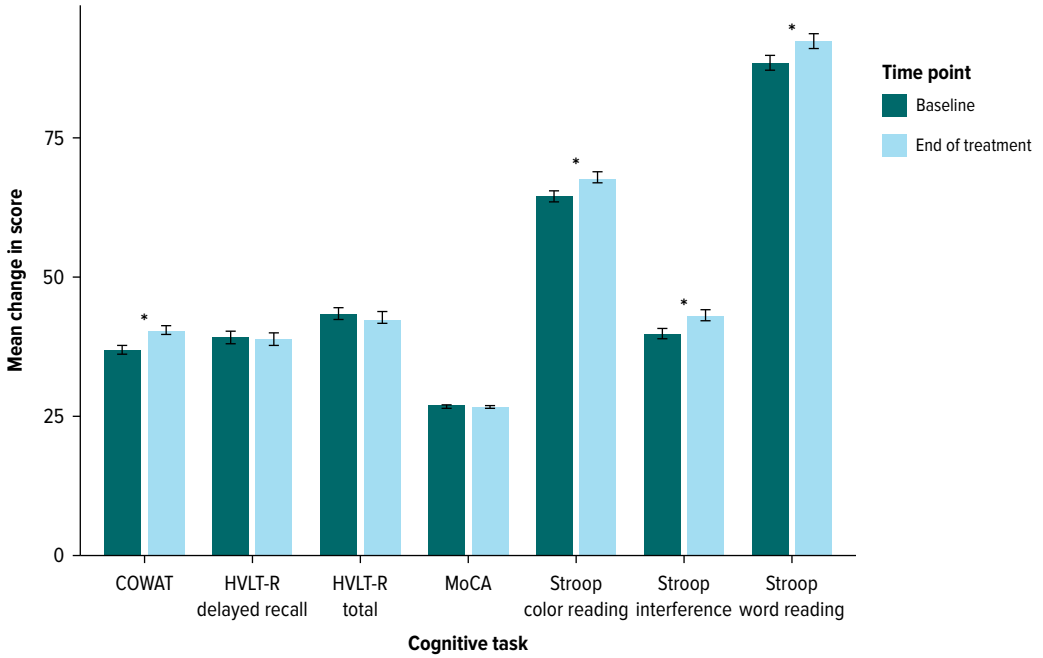
[a]Mixed-effect model of least-square means showing change among responders from first collection to end of treatment (EOT), and follow-up visits at 1 month, 3 months, and 6 months posttreatment completion, as rated on the Squire Memory Complaint Questionnaire (SMCQ; part A) and Global Self-Evaluation of Memory (GSE-My; part B) for ECT (N = 70) and racemic ketamine (N = 108). Response constituted a reduction ≥50% on the QIDS-SR-16. GSE-My scores range from 1 to 7; higher scores indicate better perceived memory associated with treatment.

*$P < .001$ (corrected).

Abbreviations: ECT = electroconvulsive therapy, QIDS-SR-16 = 16-item Quick Inventory of Depressive Symptomatology Self-Report.

Figure 4.

Change in Cognitive Performance Before and After Ketamine Treatment[a]



[a]Least-squares means analysis of cognitive performance (*t* score) for those randomized to the ketamine arm of the ELEKT-D trial (N = 195) at before and after 6 intravenous ketamine infusions. Baseline MoCA performance was collected at the screening visit. Models include age, education, NAART-35 derived IQ, gender, and change in depression severity (as measured by QIDS-SR-16) as covariates. Higher scores indicate better performance. Error bars are standard error. Missing data at end of treatment: Stroop, 31; HVLT-R, 8; MoCA, 8; COWAT, 6.

*$P < .001$.

Abbreviations: COWAT = Controlled Oral Word Association Test, HVLT-R Total = Hopkins Verbal Learning Test Revised Total, HVLT-R Delayed Recall = Hopkins Verbal Learning Test Revised Delayed Recall, MoCA = Montreal Cognitive Assessment, NAART-35 = North American Adult Reading Test-35, Stroop = Stroop Interference Condition.

independence of mood and cognitive improvement among ketamine recipients highlight the importance of investigating the cognitive effects of this class of antidepressants, particularly their use in combination with psychotherapeutic and cognitive restructuring interventions.[13,36]

Strengths, Limitations, and Future Directions

The present study represents the largest known study comparing the neurocognitive effects of ECT and multidose racemic ketamine in TRD, detailing objective and subjective changes in cognitive functioning in the subacute period as well as longitudinally among responders. An additional strength of the study is the use of multiple cognitive measures and alternate forms. Furthermore, all analyses reported here were subject to correction for multiple comparisons, strengthening the findings of this study. Notably, several limitations of the current analysis require comment. As a post hoc analysis of data from an existing noninferiority trial, these findings should be considered preliminary. The open-label design, absence of placebo control, lack of task-based measurement for autobiographical memory, lack of formal comparison between right unilateral and bilateral completers, and progression into the follow-up limited only to treatment responders reduce the scope of interpretation.

Future research should explore ketamine's neuroplastic potential and its viability as intervention target, as well as work to better characterize the discrepancy in long-term objective and subjective memory functioning following ECT.

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