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Intravenous ketamine for late-life treatment-resistant depression: a pilot study of tolerability, safety, clinical benefits, and effect on cognition

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Abstract

Background: Evidence-based treatment options for late-life treatment-resistant depression (TRD) are limited. Ketamine is a promising treatment for TRD; however, there is a paucity of data on its safety and efficacy in older adults.

Methods: In this pilot clinical trial, 25 adults aged ≥60 years with TRD received IV ketamine openly twice a week for 4 weeks; partial responders at the end of this acute phase were eligible to receive weekly infusions for 4 more weeks in a continuation phase. Acceptability, tolerability, and safety, including adverse and serious adverse events (AEs and SAEs), blood pressure changes, dissociation, craving, in addition to rates of depression response and remission were evaluated. The NIH Toolbox Cognitive Battery was used to assess specific measures of executive function (EF) and overall fluid cognition.

Results: Completion rates were 88% for the acute phase and 100% for the continuation phase. No AEs resulted in participant discontinuation, and there were no SAEs. Treatment-emergent elevation of blood pressure, dissociation, and craving were transient and did not result in any participant discontinuation. Depressive symptoms improved significantly and 48% of participants responded. During the acute phase, the EF measures and the fluid cognition composite score improved (Cohen's d=0.61), and these improvements were sustained in the continuation phase.

Conclusion: This pilot study suggests that repeated IV ketamine infusions are well-tolerated and are associated with improvement in depression and EF in older adults with TRD. These promising findings need to be confirmed and extended in a larger randomized controlled trial.

Registration: ClinicalTrials.gov identifier: NCT04504175

Keywords: Treatment-resistant depression; Geriatric; Intravenous ketamine, cognition

Introduction

Treatment resistant depression (TRD) is typically defined as having failed two antidepressant trials of adequate dosage and duration (1). In older adults, TRD is associated with poor long-term outcomes including disability, cognitive dysfunction(2), and excess mortality from suicide (3-7). For older adults with TRD, treatment options supported by evidence from randomized-controlled trials (RCTs) are limited to aripiprazole augmentation, with weaker evidence supporting the use of lithium augmentation, combination of antidepressants, repetitive transcranial magnetic stimulation (rTMS), and electroconvulsive therapy (ECT) (3, 8-10). In the largest to date, pragmatic comparative effectiveness trial in older adults with TRD, remission rates with commonly used pharmacotherapy strategies were <30% (11). In this context, additional treatment options for TRD in older adults are needed.

Ketamine, a racemic mixture of s- and r- enantiomers, is an anesthetic agent that blocks *N*-methyl-D-aspartate (NMDA) glutamate receptors. Its use as an antidepressant is a promising new treatment for TRD: an infusion of 0.5 mg/kg over 40 minutes produces a rapid antidepressant response in younger adults with TRD (12), improving mood and quality of life, and reducing suicidality (13-15). Ketamine also has potential pro-cognitive effects in TRD, as one of its putative antidepressant mechanisms is a rescue of prefrontal circuit dysfunction through synaptogenesis (16). Thus, understanding the impact of ketamine treatment on executive function (EF) in late-life TRD is central to the risk-benefit analysis of ketamine in older adults and has implications for understanding its mechanism in the management of late-life depression.

In younger adults, serial infusions at twice weekly frequency provide a more sustained antidepressant response than once per week infusions (17). However, there are minimal data on the short-term effects of ketamine in older adults, and none on its long-term effects despite

safety concerns about its potential negative effects on cognition. These concerns are based on observational studies in ketamine abusers and the known cognitive vulnerability of older adults to medications (18-20). The existing literature on IV ketamine in TRD in older adults consists only of two case series with 6 and 53 patients (21, 22). A randomized controlled trial of subcutaneous ketamine was conducted in 16 older patients with TRD using incremental doses of subcutaneous ketamine at 0.1, 0.2, 0.3, 0.4, and 0.5 mg/Kg. (23). Subcutaneous ketamine was well-tolerated and more effective at the higher doses (≥ 0.2 mg/Kg). Esketamine, the s-enantiomer of ketamine, is FDA-approved for TRD, but concerns exist about its use, including its high price generating doubts about its cost-effectiveness (24), poor bioavailability compared to IV ketamine (25-50% for esketamine vs. 100% for IV ketamine) (25), efficacy data with 81% of the response attributable to placebo (26), and the possibility that the r-enantiomer accounts for some of ketamine's antidepressant action – directly or via its active metabolites (27-30). The TRANFORM-3 study, a placebo-controlled RCT of esketamine as an augmentation strategy for TRD in older adults, did not show a statistically significant difference between esketamine plus antidepressant versus placebo plus antidepressant (31), although the improvement was comparable to that seen in younger adults (32).

Given the lack of data on IV ketamine in older adults with TRD, we conducted a pilot study to examine its acceptability, tolerability, and safety, and secondarily its clinical benefit and impact on depression and cognition in general, and EF in particular, in older adults with TRD. To our knowledge, this is the first clinical trial evaluating acute and continuation IV ketamine in this population. We hypothesized that ketamine infusions would be both acceptable (as measured by completion rates) and well tolerated and safe (as measured by adverse events [AEs], serious AEs [SAEs], changes in vital signs, craving, and dissociation). We also hypothesized that IV ketamine would lead to clinical improvement in both depression and overall cognitive performance, in particular in EF.

Methods

This was a multisite pilot study with 25 participants, five enrolled at each of five sites (Columbia University and the New York State Psychiatric Institute, University of California at Los Angeles, University Health Network and University of Toronto, University of Pittsburgh, and Washington University in St. Louis). This study was approved by the local IRBs of each study site (ClinicalTrials.gov identifier: NCT04504175).

Participants

Participants were recruited between October 13, 2020 and November 6, 2021. They were community-dwelling men and women age 60 years and older with TRD, defined as an episode of major depressive disorder (MDD) without psychotic features (diagnosed by the Structured Clinical Interview for the Diagnostic and Statistical Manual, 5th edition [SCID-5]) that had persisted despite ≥2 trials of adequate dosage and duration with antidepressants from different classes in the current episode (including at least one evidence-based second-line treatment) as determined by the Antidepressant Treatment History Form (ATHF) (33). Participants were also required to have moderate to severe depressive symptoms based on a Patient Health Questionnaire 9-item (PHQ-9) (34) score of ≥15 at baseline. A co-morbid anxiety disorder was not an exclusion criterion. Exclusion criteria included: a clinical diagnosis of dementia or a score ≥10 on the Short Blessed Test (35); a diagnosis of a schizophrenia-spectrum disorder or bipolar disorder; a personality disorder that would interfere with safe participation based on the judgement of the research team; a current alcohol or substance use disorder (determined by the Alcohol Use Disorders Identification Test (AUDIT) (36) and Drug Abuse Screening Test (DAST) (37), respectively) to rule out current alcohol or substance use disorder in the past 3 months or lifetime use of recreational ketamine or other dissociative agent (e.g., PCP); use of naltrexone, memantine, or any medication that could be considered relatively contraindicated if used with

ketamine; high risk for imminent suicide that could not be managed safely in the clinical trial; any physical condition affecting IV ketamine safety or tolerability or that would interfere with participation in the study i.e., life expectancy < 1 year because of terminal illness, unstable angina, or inadequately controlled hypertension).; and baseline systolic blood pressure (BP) >150 mmHg or diastolic BP >90. Participants who presented with elevated BP were referred to their healthcare provider for hypertension management and later re-assessed for eligibility. The evidence for the potential interaction between ketamine and medications belonging to the benzodiazepine or antipsychotic classes is limited, and these are commonly used medications in this patient population. Therefore, participants taking these types of medications were not excluded. For patients taking benzodiazepines, the total daily dose had to be at 2-3 mg/day equivalent of lorazepam and patients were asked to try to take less at bedtime and to try to hold the morning of the treatments. Similarly, concurrent antipsychotics medications were reviewed and allowed to be continued. For those taking aripiprazole, we recommended a reduction of higher doses to 5mg. “

Overall Study Design

Potential participants were identified from patient registries and through referrals from behavioral health and primary care providers. All participants provided written informed consent. They had to be on a stable oral antidepressant dosage for at least 4 weeks prior to the start of the infusions and continued their oral antidepressant at the same dosage for the duration of the infusions.

For the acute phase, participants received ketamine IV twice weekly for 4 weeks. At the end of the acute phase, those who achieved a Montgomery-Asberg Depression Scale (MADRS) (38) total score <10 or ≥ 30% reduction from baseline MADRS total score proceeded to the continuation phase, which consisted of an additional 4 weeks of once-a-week IV ketamine.

Participants whose MADRS score had not decreased to a total score <10 or by at least 30% from baseline did not proceed to the continuation phase of the study and their participation ended.

Intervention

Ketamine infusion: Participants' weight was confirmed prior to each infusion to calculate the ketamine dose (0.5 mg/kg of body weight). Participants refrained from solid food for 6 hours prior to the infusion, with nothing to drink for 2 hours prior the infusion. An IV line was inserted into the upper extremity by research personnel. Ketamine was infused over 40 minutes using an IV infusion pump. Heart rate, BP, pulse, and pulse-oximetry were measured every 10 minutes during the infusion and every 20-30 minutes for up to two hours following the infusion. These safety ratings were repeated prior to discharge. In addition, participants were monitored for incidence of dissociation and other psychotomimetic symptoms using the first six questions of the Clinician-Administered Dissociative States Scale (CADSS) (39) pre-infusion and 40 and 90 minutes after the start of each infusion. After resolution of any psychotomimetic symptoms or BP elevation, and IV removal, participants were discharged. Transportation to and from infusion visits was arranged for participants.

Clonidine co-administration: To prevent or reduce the severity of potential psychotomimetic/dissociative and hypertensive effects of ketamine, clonidine (could be administered before or during the ketamine infusions (up to 0.6 mg pre-treatment and up to 0.3 mg during the infusion) (14). Based on the investigators' and participants' choice, some participants received clonidine prophylactically (if there were concerns about significant dissociation or changes in blood pressure prior to the infusion), while some participants received clonidine if they experienced dissociation or an elevated BP after their first treatment. No other rescue medications were used for management of nausea, blood pressure, or agitation.

Outcomes

As described above, participants were monitored during the ketamine infusion sessions during which tolerability and safety measures (including dissociation and vital signs) were collected. In addition, participants were assessed at three time points during the study: baseline, end of acute phase, and end of continuation phase. Assessments included measures of craving, clinical benefit, and cognitive performance.

General adverse events: In addition to monitoring of vital signs, adverse events were recorded using an adverse event form. Treatment-emergent hypertension was defined as SBP >160 or DBP >100. Participants were also asked to notify the study team of new symptoms, illnesses, or other problems.

Dissociative effects and craving: As per above, dissociative symptoms were measured using the first six questions of the CADSS, with each item scored from 0-4 and a total score >4 considered to indicate dissociation (39). Craving was assessed using the participant-rated 4-question Craving Scale. The questions ask about the strength of the urge to take more ketamine than prescribed, how mood or anxiety levels affect any urge to take more ketamine, how often participants find themselves thinking about the next ketamine dose, and how much ketamine is being craved. Responses range from scores of 0 to 100.

Depression: Response was defined as ≥50% reduction in baseline MADRS total score, and remission was defined as a MADRS score <10 based on the MADRS completed at baseline, end of acute phase, and end of continuation phase. Participants who did not complete the acute phase of the study were classified as non-responders and non-remitters. We also assessed changes in MADRS scores.

Cognitive performance: At baseline, end of acute phase, and end of continuation phase, we also administered the NIH Toolbox Cognition battery, a computerized neuropsychological assessment battery. The following tests were used to assess several cognitive domains: Dimensional Change Card Sort Test (DCCS; cognitive flexibility and EF); Flanker Inhibitory Control and Attention Test (EF); List Sorting Working Memory Test (EF); Picture Sequence Memory Test (episodic memory); and Pattern Comparison Processing Speed Test (processing speed) (40). We also analyzed the three specific EF measures calculated and the Fluid Cognition Composite Score, an overall composite score based on the five above measures (40), as possible markers of ketamine's mechanism of action.

Data Analysis:

Participants with data available at baseline and the end of the acute phase were included in the analysis. Baseline characteristics were summarized descriptively; we computed response and remission rates and change in cognitive scores during the acute phase. For each subject, we computed the Spearman correlation between CADSS (40 minutes after infusion) and infusion number, treating infusion number as an ordinal variable (1, ..., 12). We then averaged over the subjects to obtain an average Spearman correlation. We analyzed changes (from baseline to end of acute phase and from end of acute phase to end of the continuation phase for those who went on to the continuation phase)in MADRS score and the EF measures and fluid cognition composite score using paired t-tests along with the corresponding 95% confidence intervals (Cis), and Cohen's d values.

To assess whether changes in EF measures were associated with treatment response during the acute phase, we fit linear models with each EF measure as the response and with responder status as the primary predictor, adjusting for baseline EF measures, education, and

gender. Since NIH Toolbox measures are age-adjusted, we did not add age to these models. We also fit similar models in which we considered remitter status or used the change in MADRS score during the acute phase as the primary predictors.

Approximate normality of the numerical variables was assessed visually using histograms or Q-Q plots, and the Shapiro-Wilk test. We conducted a complete case analysis to analyze change in each toolbox measure. For change over the acute phase for a given measure, we used data from those subjects with complete information at both baseline and at the end of the acute phase. For change over the continuation phase, we used data from those subjects with complete information at both the end of the acute phase and at the end of the continuation phase.

Results

The participants' mean (SD) age was 71.5 (4.9) years, 13/25 (52%) reported being female, and all reported being of European descent. Overall, they were well-educated with a mean (SD) of 16.2 (1.9) years of education. They had a moderate degree of physical comorbidities with a mean (SD) total score on the Cumulative Illness Rating Scale-Geriatric (CIRS-G) of 8.1 (5.4), and had moderately severe depression with an average MADRS score of 24.4 (7.9) prior to treatment (Table 1). The mean ATHF score for adequate trials was 3.3, sd = 1.4.

Completion Rates

Twenty-two of 25 (88%) participants completed the acute phase infusion schedule. Of the 3 that dropped out of completing the acute phase of the study, 2 did not want to continue due to poor response and one did not want to give a reason.

Fifteen participants were eligible for the continuation phase and 15 (100%) entered and completed it.

Tolerability and Safety

AEs and SAEs: There were no treatment related SAEs. Two (8%) participants reported nausea with vomiting and headache, which were mild and manageable.

Cardiovascular AEs: Five (25%) participants experienced infusion-related transient hypertension and 8 (32%) received clonidine co-administration as pre-treatment during every infusion due to concern for elevation in blood pressure, with one participant reporting dry mouth, possibly related to clonidine use. No infusions were discontinued because of elevated BP, or any other AEs.

Dissociation: All participants experienced some dissociative symptoms during at least one of the infusions, which peaked at approximately 40 minutes and resolved within 90 minutes after the start of the infusions. In our sample, CADSS scores seemed to decrease over time after multiple infusions (Figure 1). We obtained a Spearman correlation of -0.28 with a corresponding 95% percentile bootstrap confidence interval of (-0.43, -0.12) based on 1000 bootstrap samples from the original data. No participants dropped out due to inability to tolerate the infusions. Of the 8 participants who received clonidine for blood pressure management, one had noted a subjective reduction in dissociative symptoms with subsequent treatments.

Craving: Two (8%) participants reported some craving with scores of 50-100 on the first 3 questions of the Craving Scale; four (16%) other participants indicated having thoughts about their next dose with scores of 10-50 on the Craving Scale.

Clinical Benefit

Of the 25 participants who started the study, 15 (60%) experienced ≥ 30% reduction in MADRS and thus were eligible to participate in the 4-week continuation phase, which all of them entered and completed. Figure 2 shows the MADRS scores at baseline, end of acute phase, and end of continuation phase, stratified by whether or not a ≥ 30% reduction in MADRS score occurred from baseline to the end of the acute phase. The mean change in MADRS total score between baseline and end of acute phase was a decrease of 9.4 points, with 95% CI (6.46, 12.32) Cohen's d value -1.19, and paired t-test statistic -6.66 (df = 22) with $p < 0.01$. For those continuing on, the mean change in MADRS total score between the start and end of the continuation phase was an increase of 3.5 points with 95% CI (0.38, 6.56), Cohen's d value of 0.95, and paired t-test statistic 2.41 (df = 14) and $p = 0.03$. At the end of the acute phase, 12/25 (48%) met criteria for response and 6/25 (24%) for remission. At the end of the continuation phase, 7/15 (47%) met criteria for response and 4/15 (27%) for remission.

Cognition

Cognitive assessments were completed for 23 participants. Table 2 presents results from the paired t-tests for changes in cognitive measures during the acute phase. There was improvement in the Fluid Cognition Composite Score (Cohen's d value 0.61, indicating a medium-large effect size), and the three measures of EF: Flanker, DCCS, and List Sorting Working Memory subtests.

Linear models of the relationship between each EF measure and responder/remitter status, during the acute phase, showed no evidence of significant differences in adjusted changes in EF measures between responders and non-responders or between remitters and non-remitters (Supplement Table 1); in addition, there was no significant association between change in any of the EF measures and change in MADRS scores (Supplement Table 2).

Table 3 presents results from the paired t-tests for changes in cognitive measures during the continuation phase. There were no statistically significant changes in any of the EF measures, with the magnitude of Cohen's d effect sizes for these changes ranging from 0.07 to 0.33 (small effect sizes).

The age-corrected fluid cognition composite score increased (improved) during the acute phase (Cohen's d – 0.61) and showed no evidence of change (Cohen's d = -0.13) during the continuation phase (See Figure 3).

Discussion

This pilot study of IV ketamine in older adults with TRD yields four main observations. First, the study demonstrated good acceptability of IV ketamine by older adults with TRD, as indicated by high completion rates in both the acute and continuation phases. Second, IV ketamine was both well tolerated and safe: AEs were rare and did not prevent the continued use of IV ketamine in any participant and the use of clonidine help with the management of blood pressure changes seen during the infusions. Third, our results suggest IV ketamine may be beneficial, with 48% of participants achieving response and 24% remission following 4 weeks of twice per week treatment, an effect which was maintained during continuation treatment. Fourth, participants' EF improved significantly during the four-week acute treatment, similar to findings in younger adults (14). Improvement in EF was not statistically associated with response, remission, or change in depressive symptoms during the acute phase. Additionally, in participants whose depression improved and who were included in the continuation phase, the acute improvement in EF was sustained during the four-week continuation phase. No deleterious impact on overall fluid cognitive performance was observed following 4 weeks of twice weekly acute infusions or 4 additional weeks of weekly continuation infusions. These are similar findings to what has been observed in younger adults receiving IV ketamine where sympathomimetic and psychomimetic

changes were observed, but they were not sustained and were generally tolerated (41, 42). Similarly, there was no worsening of cognitive functioning with IV ketamine treatment in younger (43). Taken together, these preliminary results support that IV ketamine is a promising treatment for TRD in older adults and is associated with improvement in EF, at least in the short term. This is important given the paucity of research and the limited, evidence-based treatment options for TRD in older adults.

Acute exposure to low doses of NMDA antagonists produces a NMDA receptor hypofunction state that is associated with transient neuronal injury (41), which is age-dependent (i.e., it appears to be more severe in older animals), and cognitive impairment (40, 42). While these cognitive effects are transient and not detectable once the NMDA antagonist would no longer be expected to be present (43, 44, 66), observational studies in ketamine abusers suggest the potential for cognitive impairment with long-term use (59-61). The lack of evidence in this study of ketamine inducing cognitive impairment over 8 weeks of serial infusions is reassuring that repetitive exposure as used in this prospective study does not carry a risk of cognitive impairment initially identified in observational studies.

The strengths of this pilot study include the use of both acute and continuation phases, its multi-site nature, the use of a computerized neuropsychological battery to evaluate both fluid cognition and EFs at three timepoints, and the protocolized treatment facilitating the generalizability of findings. Limitations include the small sample size, the lack of racial or ethnic diversity, no adjustment for multiple testing, and the absence of randomization and a placebo-control or comparison treatment. Additionally, the study participants were in the “young-old” cohort, as the mean age was 71.5 years (SD 4.9) and thus, findings may not be generalizable to older patients. The findings may not be generalizable to patients with other characteristics, such as those with more treatment resistant depression or are acutely suicidal. Accordingly, the

improvement in EF during the acute phase may have been due to a practice effect, independent of the specific effects of ketamine. However, there was no improvement in information processing speed or immediate memory, for which there was the same amount of practice. Thus, our findings should be considered preliminary, generating the hypothesis, rather than establishing, that IV ketamine treatment can improve EF in older adults with TRD. A larger, adequately powered, RCT is now needed to extend the results of our pilot study and confirm the tolerability, safety, and efficacy of IV ketamine in older adults with TRD (45). This future study should also evaluate further putative treatment mechanisms and examine whether its benefits are maintained beyond 8 weeks.

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Figure 1. Mean scores on the Clinician-Administered Dissociative States Scale (CADSS) before, during, and after each infusion in acute and continuation phases

Legend: CADSS scores were collected pre-infusion, and 40 and 90 minutes after the start of the infusions.

Figure 2. Montgomery -Asberg Depression Rating Scale (MADRS) scores trajectories in participants with less than 30% reduction and participants with 30% or greater MADRS reduction over time.

Legend: (Left) Spaghetti plots of the trajectories of MADRS scores for participants with less than 30% MADRS score reduction between baseline and acute phase end. (Right) Spaghetti plots of the trajectories of MADRS score in those with 30% or greater MADRS reduction between baseline, acute phase end, and continuation phase end .

Figure 3. Age-correct fluid cognition composite score trajectories in participants with less than 30% reduction and participants with 30% or greater MADRS reduction over time.

Legend: (Left) Spaghetti plots of the trajectories of age-corrected fluid cognition composite scores for participants with less than 30% MADRS score reduction between baseline and acute phase end. (Right) Spaghetti plots of the trajectories of age-corrected fluid cognition composite score in those with 30% or greater MADRS reduction between baseline, acute phase end, and continuation phase end

Table 1. Baseline characteristics of the 23 participants who completed the acute phase

Age (mean (SD))	71.5 (4.9)
Sex: Male (%)	11 (47.8)
Race: White (%)	23 (100.0)
Ethnicity: Non-Hispanic (%)	22 (95.7)
CIRS-G Total (mean (SD))[a]	8.1 (5.4)
MADRS Total (mean (SD))	24.4 (7.9)
Education: Years (mean (SD))	16.2 (1.9)
DCCS (mean (SD))	98.2 (13.9)
Flanker (mean (SD))	82.7 (9.0)
List Sorting (mean (SD))[b]	101.0 (15.6)
Picture Sequence Memory (mean (SD))	102.5 (13.2)
Pattern Processing Speed (mean (SD))	87.7 (17.7)
Fluid Cognition Composite (mean (SD)) [b]	92.4 (13.7)

Abbreviations: CIRS-G: Cumulative Illness Rating Scale-Geriatric, MADRS: Montgomery-Asberg Depression Scale, DCCS: Dimensional Change Card Sort Test, Flanker: Flanker Inhibitory Control and Attention Test, List Sorting: List Sorting Working Memory Test. Picture Sequence Memory: Picture Sequence Memory Test, Pattern Processing Speed: Pattern Comparison Processing Speed Test, Fluid Cognition Composite: Fluid Cognition Composite Score.

[a]1 participant is missing baseline CIRS-G
[b]4 participants are missing baseline List Sorting and Fluid Cognition Composite scores

Table 2. Change in NIH Toolbox Cognitive Battery measures during the acute treatment phase

	n	Mean Change (95% CI)[a]	t (df)[b]	p-value[b]	Cohen's d[c]
Executive Function					
Dimensional Change Card Sort Test	23	+6.61 (1.43, 11.78)	2.65 (22)	0.02	0.48
Flanker	23	+5.43 (2.25, 8.61)	3.54 (22)	<0.01	0.61
List Sorting	19	+8.63 (2.40, 14.86)	2.91 (18)	<0.01	0.55
Immediate Memory					
Picture Sequence Memory	22	+1.73 (-4.96, 8.41)	0.54 (21)	0.60	0.14
Information Processing Speed					
Pattern Processing Speed	23	+3.00 (-3.10, 9.10)	1.02 (22)	0.32	0.17
Fluid Cognition Composite	17	+7.59 (2.85, 12.32)	3.40 (16)	<0.01	0.61

Abbreviations. Flanker: Flanker Inhibitory Control and Attention Test, List Sorting: List Sorting Working Memory Test. Picture Sequence Memory: Picture Sequence Memory Test, Pattern Processing Speed: Pattern Comparison Processing Speed Test, Fluid Cognition Composite: Fluid Cognition Composite Score.
[a]End of acute phase - baseline
[b]t-test statistic (df = degrees of freedom) and p-value from paired t-test
[c]Cohen's d computed as (mean at week 4 – mean at baseline)/standard deviation at baseline

Table 3. **Change in NIH Toolbox Cognitive Battery measures during the continuation treatment phase**[a]

	n	Mean Change (95% CI)[b]	t (df)[c]	p-value[c]	Cohen's d
Dimensional Change Card Sort Test	15	-5.47 (-11.65, 0.71)	-1.90 (14)	0.08	-0.30
Flanker	15	2.00 (-1.17, 5.17)	1.35 (14)	0.20	0.17
List Sorting	12	-2.00 (-10.25, 6.25)	-0.53 (11)	0.60	-0.15
Picture Sequence Memory	15	4.67 (-1.49, 10.83)	1.63 (14)	0.13	0.33
Pattern Processing Speed	15	1.60 (-7.68, 10.88)	0.37 (14)	0.72	0.07
Fluid Cognition Composite	11	-2.09 (-8.4, 4.21)	-0.74 (10)	0.48	-0.13

Abbreviations. Flanker: Flanker Inhibitory Control and Attention Test, List Sorting: List Sorting Working Memory Test. Picture Sequence Memory: Picture Sequence Memory Test, Pattern Processing Speed: Pattern Comparison Processing Speed Test, Fluid Cognition Composite: Fluid Cognition Composite Score.

[a] Participants were eligible for the Continuation phase if they completed the acute phase and had a Montgomery-Asberg Depression Rating Scale ≥30% reduction from baseline

[b]End of continuation phase – end of acute phase

[c]t-test statistic (df = degrees of freedom) and p-value from paired t-test

[d]Cohen's d computed as (mean at week 8 – mean at week 4)/standard deviation at week 4