Neurocognitive performance and serial intravenous subanesthetic ketamine in treatment-resistant depression

Paulo R. Shiroma1,2, C. Sophia Albott1,2, Brian Johns2,3, Paul Thuras1,2, Joseph Wels4 and Kelvin O. Lim1,2

1 Mental Health Service Line, Minneapolis VA Medical Center, Minneapolis, MN, USA
2 Department of Psychiatry, University of Minnesota Medical School, Minneapolis, MN, USA
3 Department of Psychiatry, North Memorial Medical Center, Minneapolis, MN, USA
4 Department of Anesthesiology, Minneapolis VA Medical Center, Minneapolis, MN, USA

Abstract

The N-methyl-D-aspartate glutamate receptor antagonist ketamine has demonstrated rapid antidepressant effects in treatment-resistant depression (TRD). However, evaluation of ketamine’s neurocognitive aspects in TRD has started to be explored. This study aims to (1) examine baseline neurocognitive performance and change in severity of depressive symptoms through six ketamine infusions, (2) examine the neurocognitive effects after completion of serial infusions and whether changes were associated to relapse to depression. Six IV infusions of 0.5 mg/Kg ketamine over 40 min were conducted on a Monday–Wednesday–Friday schedule during a 12-d period on 15 patients with TRD followed by a 4-wk observational period. Neurocognitive functioning was assessed using the CogState battery at baseline and at each follow-up visit. Tasks were designed to test attention, memory (working, visual, and verbal), speed of processing, and set shifting. The likelihood of response through six infusions was greater among depressed subjects with lower attention at baseline ($F(1,13)=5.59, p=0.034$). Significant improvement was found in scores of visual memory ($F(4,33.82)=5.12, p=0.002$), simple working memory ($F(4, 24.85)=3.29, p=0.027$) and complex working memory ($F(4, 32.76)=4.18, p=0.008$) after the last ketamine infusion. However, neurocognitive changes were accounted for by improvement in the severity of depressive symptom. The acute neurocognitive effect after completion of repeated infusions was not associated with the likelihood of subsequent relapse during follow-up. Our findings suggest a potential baseline neurocognitive predictor of ketamine response and the apparently lack of short-term neurocognitive impairment after completion of six ketamine infusions in TRD.

Key words: glutamate, ketamine, treatment-resistant depression, veterans.

Introduction

Ketamine, a non-competitive, high-affinity antagonist of the N-methyl-D-aspartate (NMDA) type glutamate receptor used for induction and maintenance of anesthesia (Green and Li, 2000), has been recently investigated for its high efficacy and rapid antidepressant effect. However, side effects of ketamine have raised some concerns. In 2013, the United Kingdom government upgraded ketamine from a Class C drug to a Class B drug based on recommendations from the Advisory Council on the Misuse of Drugs concerning bladder damage on ketamine drug users with ‘more research needed on the long-term neurocognitive effects’.

Studies in healthy subjects suggested that subanesthetic doses of ketamine as a psychopharmacologic probe disrupt information encoding that occurs during drug administration but does not impair recall for previously learned information (Morgan et al., 2004; Krystal et al., 2005). Other studies have found evidence for selective impairments in aspects of executive functioning (Krystal et al., 1994b; Morgan et al., 2009), while no impairments have been reported (Morgan et al., 2004; Parwani et al., 2005). Ketamine administration at subanesthetic doses appears to carry a very low risk of adverse events in experimental psychopharmacology studies (Perry et al., 2007). These findings are consistent with the lack of long-term effects reported with anesthetic doses of ketamine (Corssen et al., 1971; Moretti et al., 1984).

Given recent interest of ketamine use in treatment-resistant depression (TRD), the neurocognitive effects has just started to be explored. Murrough and
colleagues (Murrough et al., 2013b) reported impairments in memory recall immediately after a single ketamine infusion was completed. The strategy of repeated ketamine infusions suggest that more than a single infusion achieve better antidepressant outcomes (Murrough et al., 2013a; Rasmussen et al., 2013; Shiroma et al., 2014); however, the short-term neurocognitive effects after completion of treatment are not known.

This study aims to (1) examine the association of baseline neurocognitive performance and the change in severity of depressive symptoms through six consecutive infusions among TRD subjects, (2) examine the neurocognitive effects of serial ketamine infusions during follow-up and whether changes in neurocognition were associated to relapse from antidepressant response.

Methods

Participants

Adult subjects participated in an open-label study of repeat ketamine infusion conducted over 12 d at the Special Diagnostic and Treatment Unit (SDTU) of the Minneapolis VA Medical Center followed by a 4-wk follow-up period. Subjects were recruited by direct referral from clinicians in the Mental Health and Primary Care Clinics. Participants were men and women aged 18 to 70 years with recurrent Major Depressive Disorder (MDD) without psychotic features confirmed by a Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996). Severity of depressive symptoms was defined by a 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) score greater than or equal to 14. Patients were considered with TRD if symptoms from current major depressive episode (MDE) failed to improve from at least two adequate antidepressant trials of different pharmacological classes. A systematic evaluation of antidepressant trials was assessed by the Antidepressant Treatment History Form (rating antidepressant trial ≥3; confidence rating ≥3) (Sackeim, 2001). If present, current pharmacological antidepressant dosages including augmenting agents were stable for at least 2 months prior to beginning the study.

Patients were excluded owing to inability to speak English; inability or unwillingness to provide written informed consent; moderate to severe cognitive impairment defined by Mini Mental State Examination (MMSE) (Folstein et al., 1975) scores ≤26; current or lifetime diagnosis of post-traumatic stress disorder, acute stress disorder, psychosis-related disorder, bipolar disorder I or II disorder, substance-induced disorder, any mood disorder owing to a general medical condition or any Axis I disorder other than MDD that was judged to be the primary presenting problem; diagnosis of Parkinson’s disease, dementia of any type, multiple sclerosis, seizures or other central nervous system (CNS)-related disorders; history of moderate/severe traumatic brain injury; comorbid substance use, abuse or dependence within 6 months of assessment plus negative urine toxicology screen test; clinically unstable medical illness including but not limited to history of or current myocardial ischemia or arrhythmias, severe pulmonary secretions, history of or current closed angle glaucoma, congestive heart failure or angina, significant renal or hepatic impairment, scheduled elective surgery or other procedures requiring general anesthesia during the study, uncontrolled hypertension; current use of barbiturates or narcotic medications; pregnancy (confirmed by baseline lab test), the initiation of female hormonal treatments within 3 months of screening, or inability or unwillingness to use a medically accepted contraceptive method for the duration of the study; active suicidal ideation judged to cause imminent danger.

Baseline assessments were ascertained within one week of first ketamine infusion. The Minneapolis VA Medical Center Institutional Review Board approved the study, and written informed consent was obtained from all subjects before participation. Steps to minimize coercion or undue influences included information about voluntary participation and withdrawal during the study, information on risks and benefits, and ample opportunities for discussion. The investigational aspect of ketamine for TRD was highlighted during the consent process namely that no further ketamine treatment would be provided beyond the study period. All participants were advised to discuss available clinical interventions to treat TRD with their primary psychiatrist after completing the study. Patients were financially compensated for their participation.

Rating scales and procedures

Study design

Participants completed six IV infusions of ketamine on a Monday–Wednesday–Friday schedule over a 12-d period. Patients who met response criteria by the last dose of ketamine were followed weekly for 4 consecutive weeks or until relapse was observed. During this follow-up period, patients continued with similar dosages from pre-study antidepressant regimen. Response was defined as ≥50% improvement from baseline depression score as measured by the Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Remission was established by a MADRS score ≤9. Relapse was defined as <50% of baseline MADRS score at that follow-up visit.

Infusion procedures

On the day of infusion, subjects arrived in the morning after an overnight fast. An indwelling catheter was placed in the non-dominant arm for ketamine administration. Digital pulse oxymetry, respiratory rate, heart rate, and blood pressure was recorded every 10 min for 1 h beginning 10 min before infusion. Based on the dose, rate of
Neurocognitive performance and serial intravenous subanesthetic ketamine in treatment-resistant depression

Neurocognitive assessment

All participants completed a 2-h battery of cognitive tests at baseline and at each follow-up visit. The neurocognitive testing was selected from the CogState battery (www.cogstate.com) (Collie et al., 2003a). For each test within this battery, the stimuli consisted of playing cards. Tasks were designed to test attention, memory (working, visual, and verbal), speed of processing, and set shifting. The tests were selected because of their brevity, demonstrated utility for within-subjects experimental designs, for the parametric properties of their outcome measures, and their use in psychopharmacology trials (Snyder et al., 2005; Falleti et al., 2006). Furthermore, the CogState battery was can be administered repeatedly using many alternate forms and still acceptable test–retest reliability without generating significant practice effects (Collie et al., 2003b; Falleti et al., 2006). The neurocognitive tasks were administered in a fixed sequence presented on laptop computers in a quiet room to minimize distracting noise. Responses were indicated by pressing keys on the laptop or using a computer mouse if preferred. Brief descriptions of the tasks are provided in Table 1 with further details to be found elsewhere (Maruff et al., 2009; Fredrickson et al., 2010).

Each of these cognitive tasks yields multiple outcome measures. We selected a single primary outcome from each test in the battery that has been shown to be optimal for the detection of change as it contains only a small probability of floor or ceiling effects and no restriction in the range of possible performance values. The outcome measures are normally distributed or corrected to normality through the use of mathematical transformation (e.g. logarithmic base 10, or square root arcsine proportion correct).

Data analysis

Linear mixed models using maximum likelihood estimation and an unstructured covariance structure were used to analyze change in MADRS scores over time, examining both simple change and change controlling for baseline cognitive measures. Mixed models were also used to examine change in neurocognitive performance over time. In all models assessing change over time both the intercept and time were random effects with intercept, time and other covariates, depending on specific analysis, as fixed effects. Finally, logistic regression models were employed to examine the effects of change in neurocognitive performance as predictors of depression relapse following treatment. As the analysis on cognitive performance was exploratory, the study was not powered to detect differences in this matter.

Results

Demographic and clinical characteristics

Demographics and baseline characteristics of the study sample are presented in Table 2. All 15 patients were male; 14 were Caucasians. On average, the sample age was 52 years, had 15 years of education, were chronically depressed with onset of first MDE at age 32, had at least three lifetime episodes of major depression, and presented moderate to severe symptoms of depression (17-item HDRS mean score=20.3, s.d.: 4.3) during a current episode of 17 months. Eleven subjects had at least one first degree relative with mood disorder; three had a past history of substance disorder; 11 had at least one
<table>
<thead>
<tr>
<th>Neurocognitive function</th>
<th>Cognitive task</th>
<th>Objective</th>
<th>Outcome</th>
<th>Measure type</th>
<th>Range of values for the variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Identification Task (IDN)</td>
<td>Identify whether the card presented is red</td>
<td>Transformed reaction times for correct responses. (Lower score=better performance)</td>
<td>Speed</td>
<td>2 to 5</td>
</tr>
<tr>
<td></td>
<td>One Back Task (ONB) (Simple working memory)</td>
<td>Identify whether a card is the same to the one just before</td>
<td>Transformed proportion of correct responses. (Higher score=better performance)</td>
<td>Accuracy</td>
<td>0 to 1.57</td>
</tr>
<tr>
<td></td>
<td>Two Back Task (TWOB) (Complex working memory)</td>
<td>Identify whether a card is the same to the one two cards before</td>
<td>Transformed proportion of correct responses. (Higher score=better performance)</td>
<td>Accuracy</td>
<td>0 to 1.57</td>
</tr>
<tr>
<td></td>
<td>Groton Maze Learning Test (GML) (Spatial working memory)</td>
<td>Find the hidden pathway in a 10×10 grid of tiles</td>
<td>Total number of errors made in attempting to learn the same hidden pathway on five consecutive trials at a single session. (Lower score=better performance)</td>
<td>Accuracy</td>
<td>0 to infinity</td>
</tr>
<tr>
<td>Visual memory</td>
<td>Continuous Paired Associate Learning Task (CPAL)</td>
<td>Find the correct location of the object</td>
<td>Total number of errors across five rounds. (Lower score=better performance)</td>
<td>Accuracy</td>
<td>0 to infinity</td>
</tr>
<tr>
<td></td>
<td>One Card Learning Task (OCL)</td>
<td>Identified whether a card has been seen before in the task</td>
<td>Transformed proportion of correct responses. (Higher score=better performance)</td>
<td>Accuracy</td>
<td>0 to 1.57</td>
</tr>
<tr>
<td></td>
<td>Groton Maze Learning Test – Delayed Recall (GMR)</td>
<td>Remember the hidden pathway learned previously in a 10×10 grid of tiles</td>
<td>Total number of errors made in remembering the maze pathway after a delay. (Lower score=better performance)</td>
<td>Accuracy</td>
<td>0 to infinity</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>International Shopping List Task (ISL)</td>
<td>Remember items read from a shopping list</td>
<td>Total number of correct responses made in remembering the list on three consecutive trials at a single session. (Higher score=better performance)</td>
<td>Accuracy</td>
<td>0 to infinity</td>
</tr>
<tr>
<td></td>
<td>International Shopping List Task: Delayed Recall (ISRL)</td>
<td>Remember items from previously read shopping list</td>
<td>Total number of correct responses made in remembering the list after a delay. (Higher score=better performance)</td>
<td>Accuracy</td>
<td>0 to infinity</td>
</tr>
<tr>
<td>Speed of processing</td>
<td>Groton Maze Chase Test (GMCT)</td>
<td>Chase the target in a 10×10 grid of tiles</td>
<td>The total number of correct moves made per second. (Higher score=better performance)</td>
<td>Accuracy</td>
<td>0.01 to infinity</td>
</tr>
<tr>
<td></td>
<td>Detection Task (DET)</td>
<td>Identify once the a card is flipped over and face up</td>
<td>Mean of transformed reaction times for correct responses. (Lower score=better performance)</td>
<td>Speed</td>
<td>2 to 5</td>
</tr>
<tr>
<td>Set shifting</td>
<td>Set-Shifting Task (SETS)</td>
<td>Identify whether a card is the target stimulus dimension (a color or a number).</td>
<td>Total number of errors across five rounds. (Lower score=better performance)</td>
<td>Accuracy</td>
<td>0 to infinity</td>
</tr>
</tbody>
</table>
psychiatric hospitalization; four had prior suicidal attempts; and two had received electroconvulsive therapy for depression.

Out of 15 subjects enrolled in the study, one dropped out after the first infusion owing to decreased energy and increased irritability, and another patient dropped out after two infusions owing to dissatisfaction with the expected therapeutic effect from ketamine. Analysis for the neurocognitive effects of serial ketamine infusions during follow-up and possible association with relapse from antidepressant response was limited to those 13 patients that completed six ketamine infusions.

Antidepressant outcomes

For the sample of 13 subjects, the within-subject change in MADRS score over six ketamine infusions was statistically significant (F(5, 65) = 37.8, p < 0.0001) where the severity of depressive symptoms at baseline (mean MADRS score = 29.9, S.D. = 2.3) decreased after the last infusion (mean MADRS score = 7.0, S.D. = 2.3). Out of 13 subjects who completed all six infusions, 12 (92.3%) achieved response criterion and nine (69.2%) remitted. After the first infusion, three subjects responded (23%) and one subject remitted (7.7%). Seven subjects reached response and six remitted after receiving three or more infusions. Of the 12 patients who responded after six infusions, MADRS scores were obtained weekly for 4 wk. Five out of 13 patients remained in response status throughout the four weeks of follow-up. The mean time for those six subjects who relapsed after the last ketamine infusion was 16 d (range 7–28 d). Four patients relapsed within one week after the last infusion.

Baseline neurocognitive performance predictors of change in MADRS score over six ketamine infusions

We conducted a linear mixed model analysis with MADRS change score over time from baseline as the dependent variable, baseline neurocognitive tasks, age, age at onset of first MDE, duration of current depressive episode, family history of mood or substance use disorder, and current depressive episode as predictors. Performance in attention at baseline and age at onset of MDE were significant predictors of change in severity of depressive symptoms over six infusions. The likelihood of response through six ketamine infusions was greater among depressed subjects with lower attention at baseline (F(1, 13) = 5.59, p = 0.034) and younger age at onset of first MDE (F(1, 13) = 5.59, p = 0.034). Verbal memory scores at baseline was a marginally significant predictor of improvement from depression through repeated ketamine treatment.

Table 2. Demographic and clinical characteristics of patients with treatment-resistant depression

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>#1</th>
<th>#2</th>
<th>#3</th>
<th>#4</th>
<th>#5</th>
<th>#6</th>
<th>#7</th>
<th>#8</th>
<th>#9</th>
<th>#10</th>
<th>#11</th>
<th>#12</th>
<th>#13</th>
<th>#14</th>
<th>#15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>28</td>
<td>55</td>
<td>69</td>
<td>52</td>
<td>32</td>
<td>41</td>
<td>66</td>
<td>67</td>
<td>57</td>
<td>53</td>
<td>64</td>
<td>62</td>
<td>69</td>
<td>43</td>
<td>23</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Education, years</td>
<td>14</td>
<td>14</td>
<td>23</td>
<td>14</td>
<td>14</td>
<td>17</td>
<td>19</td>
<td>14</td>
<td>14</td>
<td>12</td>
<td>13</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>First degree relative with mood disorder, yes/no</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Psychiatric hospitalizations, no</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Past substance disorder, yes/no</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>History of suicide attempts, yes/no</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>History of ECT, yes/no</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Length of current episode, months</td>
<td>18</td>
<td>24</td>
<td>9</td>
<td>7</td>
<td>12</td>
<td>36</td>
<td>15</td>
<td>36</td>
<td>20</td>
<td>9</td>
<td>15</td>
<td>24</td>
<td>9</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Baseline HDRS score</td>
<td>19</td>
<td>18</td>
<td>23</td>
<td>16</td>
<td>17</td>
<td>19</td>
<td>18</td>
<td>19</td>
<td>25</td>
<td>14</td>
<td>18</td>
<td>28</td>
<td>27</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Baseline MADRS score</td>
<td>29</td>
<td>30</td>
<td>30</td>
<td>31</td>
<td>35</td>
<td>27</td>
<td>28</td>
<td>30</td>
<td>37</td>
<td>24</td>
<td>36</td>
<td>24</td>
<td>33</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>MMSE score</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Baseline CGI score</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failed antidepressants during current episode, no</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Demographic and clinical characteristics of patients with treatment-resistant depression
Neurocognitive effects of six ketamine infusions

There were significant changes in repeated neurocognitive performance over time after completion of six ketamine infusions (Fig. 1). Significant improvement was found in scores of visual memory (One Card Learning Task) \((F(4, 33.82) = 5.12, p = 0.002)\), simple working memory (One Back Task) \((F(4, 24.85) = 3.29, p = 0.027)\) and complex working memory (Two Back Task) \((F(4, 32.76) = 4.18, p = 0.008)\) after last ketamine infusion compared to baseline. Other cognitive tasks showed non-significant changes after repeated ketamine infusions (data not shown) with scores showing improvement or not change in cognitive performance from baseline.

We also analyzed whether changes in cognitive tasks after the last ketamine infusion were related to changes in depressive symptoms. When MADRS scores were considered as a covariate, non-significant changes over time were found in visual memory \((F(1, 2.39) = 0.08, p = 0.797)\) and in both simple and complex working memory \((F(1, 2.71) = 0.013, p = 0.917\) and \(F(1, 3.13) = 2.19, p = 0.230)\), respectively).

Neurocognitive performance change after completion of six ketamine infusions

By performing logistic regression analysis, we examined whether changes in neurocognition after completing six ketamine infusions were associated to the likelihood of relapse (defined as MADRS>50% of baseline score) ascertained during subsequent follow-up visits. There was no significant association between changes in scores of neurocognitive testing with chances of relapse at follow-up. Antidepressant outcome as a continuous variable measured by MADRS scores showed similar results.

Discussion

In this open label trial of repeated ketamine infusions for TRD, we found that improvement of depressive symptoms was associated with lower attention at baseline. Completion of six ketamine infusions produced changes in neurocognitive performance through 4 wk of follow-up: this was accounted for by improvement in the severity of depressive symptom over time. Finally, the acute neurocognitive effect of repeated ketamine infusions was not associated with the likelihood of subsequent relapse during the short-term follow-up.

Murrough and colleagues (Murrough et al., 2013b) found that responders to a single ketamine infusion had poorer baseline neurocognitive performance relative to non-responders and, in particular, slower processing speed. Similarly, the current study found that depressed subjects with lower attention at baseline had greater chances to decrease the severity in depressive symptoms during six ketamine infusions. Previous studies on cognitive functions and response to traditional antidepressants, however, have shown results in the opposite direction. For instance, the depression executive dysfunction (DED) model proposes that cognitive impairment, particularly executive dysfunction, is associated with poor response to antidepressant medication in older patients (Alexopoulos et al., 2005). Lower performance in non-executive cognitive functions such as visuo-spatial construction, memory, and processing speed were also
associated with poorer antidepressant response in some populations (McLennan and Mathias, 2010). Whether these discrepancies are related to ketamine’s mechanism of action different from traditional antidepressants will need to be substantiated by further studies.

The current study revealed that serial infusions of ketamine in TRD were not associated with cognitive decline at least in the short-term (4 wk). Whereas Murrough and colleagues (Murrough et al., 2013b) revealed a selective impairment in delayed recall 40 min after a single ketamine infusion in TRD subjects, more recently, Diamond and colleagues (Diamond et al., 2014) examined the effect of repeated ketamine infusions on objective (autobiographical, episodic, and semantic) and subjective memory by conducting an open-label naturalistic study among bipolar and unipolar TRD patients. In contrast to our study, Diamond et al. treated over 3 wk with either three or six ketamine infusion a mixed group of bipolar and unipolar TRD patients. The performance on memory tests was measured 4–7 d as well as 12 and 26 wk after the last infusion. Diamond’s study found no memory deficits after completion of repeated ketamine providing further support to the current study regarding safety aspects of neurocognitive effect of ketamine in TRD. As Diamond et al., pointed out, ‘higher frequency, higher doses or longer duration of ketamine infusions could potentially cause cognitive problems’ and justified further examination.

The NMDA receptor is critical in a form of synaptic plasticity called long-term potentiation (LTP) which is central for learning and memory (Bliss and Collingridge, 1993). Given the principal action of ketamine is at the NMDA receptor, the immediate effect of ketamine use on cognition have been widely investigated. The most robust finding is that a single dose of ketamine induced marked, dose-dependent impairments in working and episodic memory in healthy subjects, which would impact profoundly on users’ ability to function (Fletcher and Honey, 2006; Morgan and Curran, 2006). Deficits in other types of memory such as verbal and semantic memory (Hartvig et al., 1995; Adler et al., 1998; LaPorte et al., 2005; Farwani et al., 2005) as well as attention (Malhotra et al., 1996) and executive function (Krystal et al., 1994a) have also been reported.

The long-term neurocognitive adverse events of ketamine are scarce in the literature where data essentially derived from studies in ketamine drug users. Overall, recreational use defined as average use of 3 d per month, was not associated with impaired cognitive function (Morgan et al., 2009). Similarly, infrequent use (less than four times a week but at least once a month) (Morgan et al., 2009) does not appear to be associated with long-term cognitive impairment. However, frequent ketamine users (more than four times a week) appear to exhibit profound impairments in both short- and long-term memory (Morgan et al., 2012).

Whether memory impairment by heavy ketamine use might abate after cessation of use is unclear. Jansen (Jansen, 1990) described a case in which a subject had persisting impaired recall and attention and a subtle visual anomaly after cessation of long-term high-dose ketamine use. On the contrary, Morgan et al. (Morgan et al., 2009) found in a group of 30 ex-ketamine users who had been abstinent for at least a year that memory impairments may be reversible when individuals stop using the drug. The reversibility of cognitive impairments is supported by reversible neurotoxic effects observed in animals that have been exposed to chronic and high doses of NMDA-receptor antagonists (Popke et al., 2001).

Similar to findings in memory deficits, frequent ketamine user may also show impairments in some aspects of executive functions such as verbal fluency and planning (Morgan et al., 2009). Ketamine has shown to modulate dopamine transmission in the dorsolateral prefrontal cortex (Moghaddam et al., 1997), a system critically involved in working memory and executive functions (Krystal et al., 2005). In fact, chronic recreational ketamine users with no significant performance differences with healthy controls exhibited a regionally selective up-regulation of dopamine 1 (D1) receptor availability in the dorsolateral prefrontal cortex (Narendran et al., 2005). This up-regulation might be an early sign of system dysregulation suggesting a compensating mechanism to dopaminergic deficit in the prefrontal region induced by NMDA antagonist exposure.

The significances of our findings should be evaluated in the scope of the study limitations. The number of subjects is small, all males, and several exclusion criteria were applied. Study results then should be confirmed by larger samples that include sub-populations of TRD subjects (e.g. psychiatric comorbidity) and clinical variables that might modify respond to repeated ketamine infusions. For instance, levels of anxiety were not included in the study. The association between a family history of alcohol abuse and antidepressant response to ketamine previously reported (Phelps et al., 2009; Luckenbaugh et al., 2012) was not confirmed in this study. Future randomized placebo-control studies will be required to determine specificity from findings suggested from this single-arm, open-label design study.

Although we intended to assess the short-term neurocognitive effects after administration of six ketamine infusions, it is not known whether the frequency and the length of continuing treatment (e.g. maintenance) would cause temporary or permanent cognitive deficits, if any. Electroconvulsive therapy, the oldest and most effective treatment for TRD at present (UK ECT Review Group, 2003) might cause persistent cognitive deficits especially in retrograde amnesia of autobiographical information following acute treatment (Rami-Gonzalez et al., 2001; Reisner, 2003; Verwijk et al., 2012). Based on studies on ketamine drug users and neurocognition, the frequency of ketamine administration could be a source of concern when evaluating ketamine risk/benefits as a safe intervention for TRD.
In conclusion, our study revealed association between baseline neurocognitive performance in attention task and the likelihood of antidepressant improvement through a series of ketamine infusions. Most importantly, the study suggested the virtually lack of short-term neurocognitive effect after completion of six ketamine infusions in TRD. Future studies will be required to determine whether neurocognitive side effects will prevent further consideration of ketamine as a possible intervention for refractory depression.

Acknowledgments

Dr Shiroma was supported by the Minneapolis VA Center for Epidemiological and Clinical Research (CECR), a VA Clinical Research Center of Excellence, and the Mental Health Service Line, Minneapolis VA Medical Center. The funding source had no further role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. We are extremely grateful to the staff from Special Diagnostic and Treatment Unit (SDTU) at the Minneapolis VAMC for their support during the conduction of the study.

Statement of Interest

None

References


