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Selective Cognitive Impairments Associated with NMDA Receptor Blockade in Humans

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Hypofunction of the *N*-methyl-D-aspartate receptor (NMDAR) may be involved in the pathophysiology of schizophrenia. NMDAR antagonists like ketamine induce schizophrenia-like features in humans. In rodent studies, NMDAR antagonism impairs learning by disrupting long-term potentiation (LTP) in the hippocampus. This study investigated the effects of ketamine on spatial learning (acquisition) *vs* retrieval in a virtual Morris water task in humans. Verbal fluency, working memory, and learning and memory of verbal information were also assessed. Healthy human subjects participated in this double-blinded, placebo-controlled study. On two separate occasions, ketamine/placebo was administered and cognitive tasks were assessed in association with behavioral ratings. Ketamine impaired learning of spatial and verbal information but retrieval of information learned prior to drug administration was preserved. Schizophrenia-like symptoms were significantly related to spatial and verbal learning performance. Ketamine did not significantly impair attention, verbal fluency, or verbal working memory task performance. Spatial working memory was slightly impaired. In conclusion, these results provide evidence for ketamine's differential impairment of verbal and spatial learning *vs* retrieval. By using the Morris water task, which is hippocampal-dependent, this study helps bridge the gap between nonhuman animal and human NMDAR antagonism research. Impaired cognition is a core feature of schizophrenia. A better understanding of NMDA antagonism, its physiological and cognitive consequences, may provide improved models of psychosis and cognitive therapeutics.
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INTRODUCTION

Glutamate dysfunction, specifically hypofunction at the *N*-methyl-D-aspartate receptor (NMDAR), may be involved in the pathophysiology of schizophrenia (Coyle *et al*, 2003; Krystal *et al*, 2003; Olney and Farber 1995). NMDAR antagonists, such as phencylidine (PCP) and ketamine, induce schizophrenia-like features (ie positive, negative, and cognitive symptoms) in healthy humans (Krystal *et al*, 1994; Newcomer *et al*, 1999) and exacerbate symptoms in patients with schizophrenia (Lahti *et al*, 1995a, b; Malhotra *et al*, 1997). The NMDAR has also been the focus of much research investigating learning and memory. NMDAR hypofunction appears to disrupt learning and memory (for a review, see Newcomer and Krystal, 2001) in a specific way consistent with learning and memory deficits observed in schizophrenia (Holthausen *et al*, 2003; Saykin *et al*, 1991).

Animal studies suggest that NMDAR antagonism impairs the acquisition of information by disrupting long-term potentiation (LTP) in the hippocampus (for a review, see Morris and Davis 1994). Human research suggests that NMDAR antagonism may selectively impair encoding (ie learning) of nonspatial information, but not retrieval of nonspatial information already learned (Hetem *et al*, 2000; Krystal *et al*, 2000). However, these studies only partially characterize the differential effects of NMDAR antagonism on encoding and retrieval of information in humans.

One major aim of this study was to investigate the effects of a noncompetitive NMDAR antagonist, ketamine, on spatial learning and memory in a virtual Morris water task in humans (Astur *et al*, 1998). This task was modeled after the Morris water maze that assesses spatial learning and memory in rodents and is often regarded as the 'gold standard' in testing hippocampal function (Morris, 1981). Several studies have shown that humans use similar spatial strategies as rodents to solve this task (Astur *et al*, 1998; Hamilton *et al*, 2002; Sandstrom *et al*, 1998). Additionally,

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we have shown that this task is sensitive to hippocampal damage in humans in a manner that is similar to the impairments seen following hippocampal damage in rodents (Astur *et al*, 2002).

Consistent with prior research, we investigated the effects of ketamine on learning and memory of verbal information, working memory, attention, and verbal fluency. We hypothesized that ketamine would disrupt learning of verbal and spatial information but not retrieval of previously acquired information. Moreover, we hypothesized that the impairment in learning would be positively correlated with schizophrenia-like symptoms induced by ketamine.

METHOD

Course of Events

This study was double-blind, placebo-controlled, and conducted over two sessions separated by 1–2weeks. Each session consisted of placebo/ketamine administration, magnetic resonance spectroscopy (MRS) scanning (Rowland *et al*, 2005), behavioral ratings, and cognitive assessments, respectively. Behavioral ratings were conducted approximately 30 min, and cognitive testing commenced approximately 45 min following drug administration start when drug levels have been shown to be at steady state with this protocol (Newcomer *et al*, 1999). Each subject was administered ketamine on one day and placebo on another in a block randomized manner.

Subjects

A total of 10 healthy, male subjects completed this study (mean age = 24.7 years; standard deviations (SD) = 3.4). Inclusion/exclusion criteria were: (1) no past or present psychiatric disorder as determined with the Structured Clinical Interview for DSM-IV, Non-Patient Version (SCID-NP; First *et al*, 1995), (2) no first-degree relatives with a diagnosis of a psychotic disorder, (3) no current medical illnesses as determined with a physical exam and laboratory tests, (4) no previous exposure to ketamine or PCP. All subjects gave written informed consent prior to the study and were paid for their participation. This study was approved by the University of New Mexico Human Research Review Committee and the United States Food and Drug Administration.

Drug Administration

Ketamine was administered with a loading dose of 0.27 mg/kg over 10 min and a maintenance dose of 0.00225 mg/kg/min for the remaining extent of the experiment (Newcomer *et al*, 1999). This dose is well below that used for anesthesia and has proven reliable in producing mild schizophrenia-like symptoms with an excellent safety profile (Newcomer *et al*, 1999). Placebo was saline administered in a similar manner as ketamine. Blood pressure, heart rate, and oxygen saturation were monitored continuously by a licensed nurse and physician. Subjects were discharged and allowed to leave the study premises only after they were proven to be fully alert and oriented, ambulating freely, and completely symptom-free (ie all symptom rating scores and all vital signs were back to baseline). Subjects were not allowed to drive to or from the study. To ensure that there were no residual adverse effects or recreational substance use with ketamine-like drugs, subjects were contacted by phone the evening of study participation, as well as 1 week, 1 month, and 3 months following study participation.

Behavioral Assessments

Ratings were obtained by one psychiatrist (JB) with the Brief Rating Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962), the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984), and the Clinician Administered Dissociative States Scale (CADSS; Bremner *et al*, 1998).

Learning and memory. To assess acquisition and retrieval of spatial information, subjects performed three different versions of a virtual Morris water task (Astur *et al*, 1998). Each version was distinct in its cues and dimensions. Details of this task have been presented previously (Astur *et al*, 1998, 2002, 2003). The first water task version was learned prior to the experimental sessions, and was used to assess retrieval. The second and third versions of the tasks were learned during the experimental sessions and were used to assess acquisition. The tasks consisted of a virtual room containing a round pool conceptually split into four quadrants with a platform hidden in one of the quadrants and four starting points. See Figure 1 for illustration.

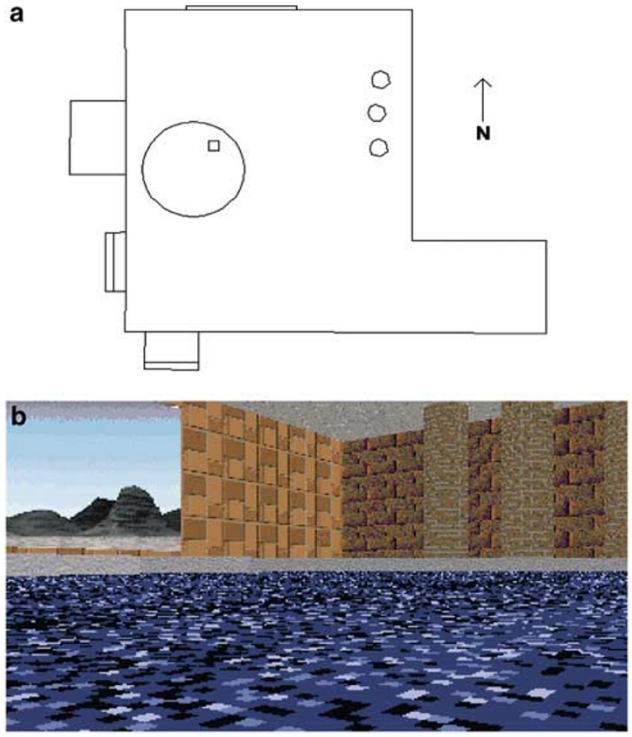

Figure 1 (a) Aerial view of the room and pool. The platform is in the location it would be during a hidden platform trial (ie the northeast quadrant). (b) A view within the pool. The participant is facing the northeast corner.

Participants were told that they would be in a pool filled with water and that the goal was to escape from the water as quickly as possible. This was accomplished by swimming to the hidden platform as quickly as possible. Participants used a joystick to navigate through the pool starting from one of four possible starting points. If the subject moved over the region of the pool where the platform was hidden the platform rose out of the water and the message 'Congratulations. You have escaped from the water' appeared on the computer screen. If the platform was not located within 60 s, the platform rose from beneath the surface of the water so that it was visible, and the message 'Please swim to the red platform' appeared on the screen. At that point, the subject had to swim to the visible platform to complete the trial.

The task consisted of five blocks of four trials totaling 20 trials. The starting point was block randomized. The hidden platform remained in the same location for all 20 trials: this was not revealed to the subjects. Distance traveled and escape latency to the platform were measured. After the 20 trials, a 45 s probe trial was administered. For the probe trial, the platform was removed unbeknown to the participant, and the participant was allowed to search for the platform. The distance traveled in the platform quadrant was measured as an indicator of spatial memory. Following the probe trial, two blocks of four visible platform trials were administered. These trials were identical to the hidden platform trials except that the platform was raised visibly out of the water. This was used as a control for attention, motivational, and motor processes.

Acquisition and retrieval of verbal information were assessed with the Hopkins Verbal Learning Test (HVLT; Lezak, 1995). Three lists of 12 words were administered to the participants. These lists have been proven to be comparable in recognition and retrieval performance (Lezak, 1995; pp 448). One list was learned prior to the experimental sessions and was used to assess retrieval. The other two lists were administered during the experimental sessions and were used to assess acquisition. For this task, the examiner read the words aloud at a 1 s per word pace, after which the participant was asked to recall as many words as possible. For learning the list prior to the experimental sessions, this procedure was repeated until the participant could repeat the list two consecutive times. For the test of retrieval of this list, the participant was asked to recall as many words as possible during both experimental sessions. For acquisition, this procedure was repeated two more times totaling three trials. Delayed recall was assessed 30 min later.

Attention. Attention was assessed with the Stroop Color-Word Interference Test (Lezak, 1995). This task consisted of three timed trials lasting 45 s. For this task, participants (1) read as many color words in black ink as possible; (2) named as many color patches as possible; and (3) named the ink color of different colored words.

Working memory. Verbal and spatial working memory were assessed with forward and backward digit span and spatial spans (from Wechsler Memory Scale III; Lezak, 1995). For digits forward, participants were asked to repeat number sequences that were read aloud at a rate of one number per second. For digits backward, participants were asked to repeat number sequences in a backward fashion. The test consisted of pairs of sequences within items of increasing difficulty. The first item contained two number sequences. The task ended when either the participant failed to repeat two pairs of number sequences or successfully repeated all number sequences. The spatial span forward and backwards was similar to the digit span procedure. However, the sequence to be recalled was a series of positions of blocks pointed to by the examiner. The blocks were arranged in a spatial configuration.

Verbal fluency. Since many studies have shown schizophrenics to be impaired in verbal fluency, performance on the FAS was assessed (Lezak, 1995). Also, ketamine has been shown to disrupt verbal fluency performance (Krystal *et al*, 1994; Adler *et al*, 1998). For this task, participants were asked in three trials to generate as many words as possible in 60 s that started with the letters 'F', 'A', and 'S', respectively.

Data Analyses

Behavioral ratings and cognitive measures were analyzed between conditions (placebo *vs* ketamine) with paired *t*-tests. The virtual Morris task data were analyzed with a 2 (drug) $\times$ 5 (block) repeated measures ANOVAs, and paired *t*-tests for the probe trial. One-tailed tests were used for the learning and memory variables because of the directional hypotheses, whereas two-tailed tests were used for the other variables. The relationships between cognitive and behavior measures where computed with the Pearson product–moment correlations. Adjustments of the critical significance level for multiple comparisons were not made due to the preliminary nature of this study. Analyses were conducted with the Statistical Package for Social Sciences (SPSS) version 11.0 software package.

RESULTS

Behavioral Ratings

Participants experienced schizophrenia-like features associated with ketamine administration as exhibited by an increase in behavioral rating scores. They showed an increase in behavioral rating scores (SANS: $t = 2.5$, $df = 9$, $p < 0.05$; CADSS: $t = 4.6$, $df = 9$, $p < 0.001$; BPRS: $t = 1.7$, $df = 9$, $p = 0.1$). Means and SD are presented in Table 1. Typical reactions reported were visual alterations (colors, texture exaggerated), auditory alterations (sounds

Table 1 Means (SD) for Behavioral Rating Scales

Behavioral scale	Placebo	Ketamine
SANS	3.0 (2.1)	6.6 (3.4)*
CADSS	0.4 (0.8)	18 (12.0)*
BPRS	21.0 (8.2)	25.4 (8.2)**

*$p \leqslant 0.05$; **$p = 0.12$.

intensified), altered time perception (time went by very quickly or slowly), being in a dreamlike state, things moving in slow motion, and body distortions. Decreased facial expression and decreased willingness to engage in conversation were also noted. The intensity of reaction varied among participants.

No subject reported adverse effects or recreational ketamine-like substance use during follow-up phone contact.

COGNITIVE MEASURES

Learning and Memory

Virtual Morris water task. Eight participants completed this task for both experimental sessions. One participant had to abort testing due to feelings of motion sickness and another failed to begin testing due to nausea resulting from the ketamine. Measures of acquisition were latency and distance to swim to the platform for five blocks of four trials, and percent distance traveled in platform quadrant for the probe trial that immediately followed the last block. Distance traveled and latency to the platform were analyzed with 2 (drug) $\times$ 5(block) repeated measures ANOVAs. For distance, a significant drug by block interaction ($F(4, 24) = 3.6$, $p = 0.01$) and a significant main effect for block ($F(4,24) = 7.4$, $p = 0.001$) were found, but, there was no significant main effect of drug $F(4,24) = 1.04$, $p = 0.174$. Follow-up pairwise comparisons revealed a significant difference for Block 1 $t(7) = 2.0$, $p = 0.045$, such that when subjects were administered ketamine they traveled more distance to reach the platform compared to when given placebo (Figure 2). Pairwise comparisons for Blocks 2–5 were not statistically significant. Results were similar for latency to find the platform. A graphical display of mean distance traveled to platform by drug condition is displayed in Figure 2. Results revealed no statistically significant difference between ketamine and placebo for percent distance in platform quadrant for the probe trial. As expected, there was no statistically significant difference between ketamine and placebo conditions in latency to visible platform for Block 1 ($t(7) = 0.67$, $p = 0.53$ or Block 2 ($t(7) = 0.98$, $p = 0.36$.

Retrieval memory for the task learned prior to experimental sessions was measured by the percent distance traveled in the platform quadrant for a probe trial. As predicted, there was no significant difference between ketamine and placebo conditions for percent distance traveled ($t(7) = 0.26$, $p = 0.8$).

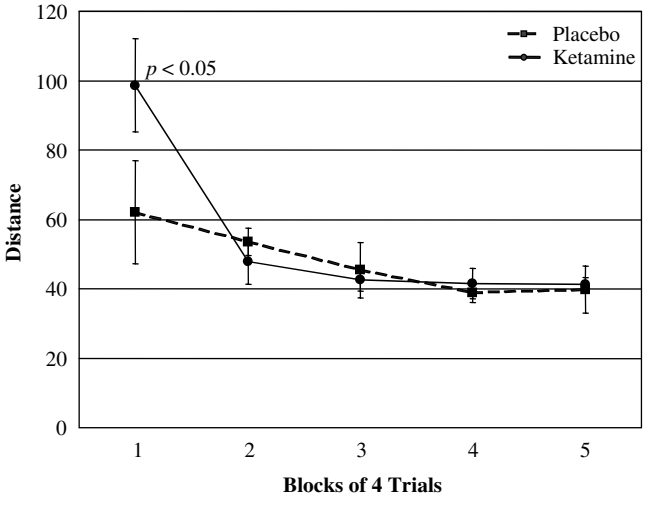

Figure 2 Acquisition task: mean distance traveled to hidden platform by drug group.

Hopkins verbal learning test. Nine subjects completed this task under both drug conditions. Consistent with the hypothesis, subjects administered ketamine were impaired in encoding new words when compared to placebo ($t(8) = 2.0$, $p = 0.0425$). The effect size for this difference was moderate to large (Cohen's $d = 0.77$). Delayed recall of the new word list revealed similar impairment for the ketamine condition ($t(8) = 2.1$, $p = 0.0365$); Cohen's $d = 0.85$). Also consistent with hypothesis, when subjects were asked to recall words from a list learned prior to the experimental sessions, there was no difference among the ketamine and placebo conditions. Means and standard deviations are presented in Table 2.

Attention

Nine participants completed the modified Stroop task under both drug conditions. Participants under the influence of ketamine had lower scores on all conditions of this task. However, results revealed no significant difference between ketamine and placebo conditions for color-word interference. Means and standard deviations are presented in Table 2.

Table 2 Means, Standard Deviations (SD), Statistical Significance (*p*), and Effect Size (*d*) Values for Selective Attention, Working Memory, and Verbal Fluency Performance

Cognitive task	Placebo	Ketamine	*p, d* values
HVLT			
Recall (old list)	11.4 (1.0)	11.4 (0.9)	0.99, 0
Encode (new list)	31.1 (4.2)	28.0 (3.9)*	0.043, 0.77
Delayed recall (new list)	10.8 (1.3)	9.7 (1.3)*	0.037, 0.85
Stroop			
Color-word interference	5.4 (8.9)	3.6 (6.9)	0.5, 0.23
Digit span			
Forward	12.1 (2.2)	12.3 (3.1)	0.6, 0.08
Backward	8.2 (2.6)	8.4 (3.0)	0.7, 0.07
Spatial span			
Forward	9.7 (1.6)	8.9 (2.2)	0.4, 0.42
Backward	9.0 (1.1)	8.0 (1.6)	0.15, 0.74
FAS (total)	48.8 (14.1)	45.7 (13.2)	0.23, 0.23

*$p < 0.05$.

Working Memory

Nine participants completed both digit and spatial spans forward and backward. There were no obvious impairments as illustrated by mean values and statistical tests in digit span forward and backward associated with ketamine administration. However, mean values for spatial span, both forward and backward, were lower for the ketamine compared to the placebo condition, although these differences were not statistically significant. Means and standard deviations are presented in Table 2.

Verbal Fluency

Nine participants completed the FAS task. Examination of total FAS mean scores revealed that subjects administered ketamine produced fewer words. However, this difference was not statistically significant. Means and standard deviations are presented in Table 2.

Behavioral and Cognitive Relationships

Consistent with hypotheses, there was a negative significant correlation between encoding new words on the HVLT and measures on the SANS ($r(8) = -0.698$, $p = 0.018$) and BPRS ($r(8) = -0.64$, $p = 0.031$), but not on the CADSS ($r(8) = -0.386$, $p = 0.152$). Delayed recall of words on the HVLT was also significantly negatively correlated with measures on the SANS ($r(8) = -0.7$, $p = 0.018$) and BPRS ($r(8) = -0.637$, $p = 0.032$), but not the CADSS ($r(8) = -0.289$, $p = 0.225$). Retrieval of already learned words on the HVLT was significantly related to BPRS scores ($r(8) = -0.643$, $p = 0.043$), but not to the SANS ($r(8) = -0.274$, $p = 0.24$) or CADSS ($r(8) = -0.5$, $p = 0.085$). For the Morris water task, only percent distance spent in the target quadrant for the probe trial of the maze previously acquired was negatively related to BPRS ($r(7) = -0.744$, $p = 0.017$) and CADSS ($r(7) = -0.71$, $p = 0.025$) measures. Behavioral measures were not significantly related to performance on other cognitive measures.

DISCUSSION

The purpose of this study was to investigate whether ketamine differentially impairs encoding and retrieval of spatial *vs* nonspatial declarative information in healthy humans. To our knowledge, no other studies have specifically addressed the effects of NMDAR antagonism on encoding *vs* retrieval in both spatial and nonspatial domains in humans. Consistent with our hypotheses, ketamine disrupted learning of new verbal information as exhibited by a significant decrease in HVLT scores. Correspondingly, as predicted, ketamine did not disrupt retrieval of verbal information learned prior to drug administration. These findings replicate a study by Hetem *et al* (2000) that showed ketamine to disrupt learning of new words but not retrieval of previously learned words. They are also consistent with studies showing ketamine to impair verbal memory (Krystal *et al*, 1994; Malhotra *et al*, 1996). The results are also in accordance with previous human research showing ketamine to impair encoding of new rule-based information (ie WCST), but not retrieval if this rule was learned previously (Krystal *et al*, 2000). Similarly, some researchers suggest that learning and memory are particularly impaired in schizophrenia, even when accounting for possible underlying cognitive deficits such as attention and working memory (Holthausen *et al*, 2003; Saykin *et al*, 1991, 1994).

The animal research is rich in establishing evidence that NMDAR antagonism impairs acquisition by disrupting hippocampal LTP, which is often viewed as being one of the mechanisms for memory storage within the brain (for a review, see Morris and Davis, 1994). Classically, hippocampal function is assessed in nonhumans by the Morris water maze, a test of spatial learning and memory (Morris, 1981). NMDAR antagonism has been shown to specifically impair spatial learning but not retrieval of this task in rats (Kant *et al*, 1991; McLamb *et al*, 1990). Interestingly, knockout mice for the NMDAR1 subunit in the CA1 of the hippocampus exhibit deficits in spatial learning of this task (Tsien *et al*, 1996). In our current study, a virtual version of the Morris water task was utilized, and results show that ketamine exposure did not impair retrieval; this is consistent with our hypotheses and with results from rat studies. However, ketamine did disrupt acquisition on this task as revealed by greater distance traveled and longer escape latencies, but this effect was only evident on the first learning block of the task. The differences in acquisition between ketamine and placebo conditions cannot be attributed to sensory, motor, or attention factors since performance on the visible platform condition was comparable. These data dovetail well with schizophrenia because it has been shown that people with schizophrenia show impairments in this task, perhaps due to NMDAR dysfunction (Astur *et al*, 2003).

To our knowledge, this is the first study to assess the differential effects of NMDAR antagonism on spatial acquisition and retrieval in humans. Although a significant difference for the acquisition of the virtual Morris water task between ketamine and placebo conditions did not extend throughout the task, this does not preclude the fact that NMDARs are important for learning. In a review by Nakazawa *et al* (2004), substantial evidence implicates NMDARs, specifically within the hippocampal area CA3, to be essential in the early stages of learning but not always in the later stages of learning. Thus, NMDARs appear to be crucial for the rapid encoding of information, such as that found in one-trial learning. Furthermore, pretraining on the Morris water maze greatly diminishes the impairment effect of NMDAR antagonists in rodents (Bannerman *et al*, 1995; Saucier and Cain, 1995). Thus, our data suggest that NMDAR antagonism disrupt the early stage of learning, as demonstrated by the impaired performance on the first acquisition block of the virtual Morris water task. This issue may best be addressed by using a modified version of the Morris water task (eg delayed matching-to-place, for a review, see Nakazawa *et al*, 2004) that has been demonstrated to be more sensitive to NMDAR antagonism.

While ketamine did not significantly impair performance on working memory, selective attention, or verbal fluency tasks in this study, some trends existed that would suggest significant results in a larger sample size. This is not particularly remarkable because prior studies assessing the effects of ketamine on these cognitive processes have had

mixed results. Some studies have found ketamine to disrupt working memory on N-back tasks (Morgan *et al*, 2004; Adler *et al*, 1998) and backward digit span task (Honey *et al*, 2003), while others found no significant impairment on a spatial working memory task (Newcomer *et al*, 1999), or forward and backward digit spans (Ghoneim *et al*, 1985). Impaired verbal fluency with ketamine administration has been shown in some studies (Adler *et al*, 1998; Krystal *et al*, 1994, 1998) but not others (Krystal *et al*, 1999; Newcomer *et al*, 1999). Some studies have shown ketamine to impair performance on tasks of sustained attention (Krystal *et al*, 1994), while others have not (Krystal *et al*, 2000; Newcomer *et al*, 1999). Consistent with this study, many have shown ketamine not to impair performance on tasks of selective attention (Harborne *et al*, 1996; Newcomer *et al*, 1999; Oranje *et al*, 2000). These conflicting findings are likely due to methodological differences, such as ketamine dose, route of administration (ie bolus *vs* infusion), task differences, and the time when tasks were performed during ketamine administration (ie prior, during, or following steady-state levels). For example, the studies that found such impairments used higher doses (Adler *et al*, 1998; Honey *et al*, 2003; Krystal *et al*, 1994, 1998, 1999, 2000; Morgan *et al*, 2004), and different administration procedures (ie a bolus followed by a maintenance infusion (Adler *et al*, 1998; Honey *et al*, 2003; Krystal *et al*, 1998, 1999, 2000)) when compared to this study. It is likely that working memory, attention, and verbal fluency processes are impaired at higher doses, which would be more compatible with that observed in schizophrenia (Heinrichs and Zakzanis, 1998). However, our findings are consistent with the one study that used similar procedures (Newcomer *et al*, 1999).

Learning and memory impairments in schizophrenia may be related to hippocampal NMDAR abnormalities observed in schizophrenia (Gao *et al*, 2000; Harrison *et al*, 2003). Our results suggest such an association. Significant correlations were found between behavioral ratings and learning and memory variables. The severity of schizophrenia-like symptoms was directly related to poor information encoding. The severity of schizophrenia-like features was not significantly related to performance on selective attention, working memory, or verbal fluency tasks. The majority of studies on the effects of ketamine on cognition fail to report whether the relationship between cognitive performance and symptom ratings was investigated. However, one study found no significant relationship between BPRS measures and performance on word recognition and recall (Malhotra *et al*, 1996), whereas another found a relationship between measures on a thought disorder scale and working memory performance (Adler *et al*, 1998). Whether there is one common neural circuit or an interaction of distributed neural networks involved in ketamine-induced symptoms and learning deficits remain to be determined. Functional neuroimaging studies may help elucidate this issue.

There are several limitations of this study. First, the sample size is small. Data must be acquired on more subjects to substantiate these preliminary findings. Spatial working memory deficits with ketamine administration may prove to be statistically significant with a larger subject number since the effect sizes were of medium magnitude. It is possible that ketamine may disrupt spatial processing in general. Second, only one ketamine dose was administered. It is plausible that working memory, selective attention, and verbal fluency deficits previously reported in some ketamine studies are dose dependent.

This study attempted to determine the impact of NMDAR antagonism on several cognitive processes in healthy humans. Results of this study provide further evidence for a differential effect of NMDAR blockade on acquisition *vs* retrieval of verbal and spatial information with the particular dose of ketamine administered in this study. A unique aspect of this study was the utilization of a hippocampal-dependent task in an attempt to bridge the gap between nonhuman animal and human NMDAR antagonism research.

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