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Ketamine Can Disrupt Episodic Memory (Hours to Days) Consolidation: Effects of Varying Dose and Retention Intervals

Ryan Darius Tabtabai

University of Connecticut - Storrs, ryan.tabtabai@gmail.com

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APPROVAL PAGE

UNIVERSITY SCHOLAR AND HONORS THESIS

KETAMINE CAN DISRUPT EPISODIC MEMORY (HOURS TO DAYS)

CONSOLIDATION: EFFECTS OF VARYING DOSE AND RETENTION

INTERVALS

Presented by

Ryan Darius Tabtabai

Primary University Scholar Advisor (James Chrobak): _____

University Scholar Advisor (David Miller): _____

University Scholar Advisor (Anastasios Tzingounis): _____

Biology Honors Advisor (Kenneth Noll): _____

Psychology Honors Advisor (David Miller): _____

Department of Psychology, Behavioral Neuroscience Division
University of Connecticut
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Abstract

Memory consolidation is the process wherein short-term, episodic memories are converted into stable, long-term representations. Forebrain N-methyl-D-aspartate receptors (NMDARs), particularly frontal cortical and hippocampal receptors, are thought to play a key role in neuronal plasticity and memory consolidation. Ketamine is an NMDA antagonist that disrupts memory, particularly encoding and retrieval processes. Previously we have observed no effect of post-acquisition ketamine treatment (50-100 mg/kg) on memory consolidation in rats performing a delayed-match-to place radial water maze task. The current study reexamined the effects of ketamine (25-100 mg/kg) on memory consolidation in this task over varying retention intervals (4, 24, and 48 hours). Consistent with previous data, no effect of ketamine treatment was seen at the four-hour retention interval. However, errors significantly increased at both the 24 and 48-hour intervals in rats treated with 100mg/kg ketamine. At 48 hours post-treatment, ketamine (25-100 mg/kg) produced a dose-dependent disruption of consolidation. These results indicate that a dose and delay dependent disruption of memory consolidation consequent of ketamine administration. In summary, these studies demonstrate that NMDA antagonism can disrupt consolidation of episodic memories.

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Introduction

Communication between the neocortex and hippocampus is achieved in large part due to glutamate neurotransmission between neurons. Glutamate is the primary neurotransmitter for ninety-percent of the neurons in both the hippocampus and neocortex (8). Glutamate neurons in particular have been shown to play a key role in higher-level cognitive process such as memory and perception within the mammalian brain. Synaptic transmission between these neurons is achieved through the activation of kainate and AMPA receptors, both of which activate sodium (Na⁺) ion channels. Sodium ion influx at the post-synaptic target causes a depolarization that leads to action potential generation. Direct activation of both kainate and AMPA receptors by glutamate therefore serves as the principle means of communication between most neurons in the central nervous system, including both the neocortex and hippocampus.

The N-methyl-d-aspartate (NMDA) receptor serves as another important glutamate receptor. Unlike kainate and AMPA receptors, NMDA receptors are mechanistically attached to a calcium channel. Once activated by glutamate, the NMDA receptor triggers an influx of calcium that initiates a molecular cascade that in turn can enhance the synaptic effects of glutamate at both the kainate and AMPA receptors (14). It is generally accepted that the presence of NMDA receptors is the main mechanism for enhancing synaptic plasticity at glutamate synapses (9). NMDA receptors allow for complex changes in the strength of connectivity among glutamate synapses in the mammalian forebrain.

Long-term potentiation (LTP) is a subset of synaptic plasticity that occurs when connected neurons are synchronously stimulated leading to a sustained increase in

synaptic strength (13). Structural changes within synapses that occur as the result of LTP makes it an ideal candidate for an underlying mechanism of episodic memory acquisition and long-term memory consolidation. NMDA receptors are critical for many types of LTP and serve as a useful point of manipulation to study their role in episodic memory formation (11).

A two-stage model for memory trace development has been proposed that posits that the hippocampus is the site of acquisition for novel spatial information that is subsequently consolidated to the neocortex via LTP (15). As a rat moves around an environment, the rhythmic firing of specific “place cells” within the hippocampus corresponds to the location the rat is in and builds a cognitive map of its position in space (16). During sleep or non-exploratory wakefulness following acquisition, the hippocampus experiences re-activation of large populations of neurons via sharp wave ripples (SPWRs) that lead to a burst of activity in hippocampal efferents, including the neocortex (2, 3, 17). It is widely accepted that SPWRs are responsible for sustained synaptic strengthening by inducing LTP and are theorized to be the underlying physiological mechanism of long-term memory consolidation (18).

The necessity of preceding NMDA activation for successful LTP and memory consolidation has been shown in the literature. Subtle alterations of glutamate neurotransmission at NMDA receptors induces cognitive, including memory, deficits normally associated with schizophrenia (7, 9). A variety of evidence also demonstrates that administration of NMDA antagonists, including ketamine, can produce cognitive impairments in experimental animals without disrupting sensorimotor function (10).

Chrobak and colleagues (2008) examined the effects of ketamine on memory formation, consolidation and retrieval in rats using a task that can access one-trial episodic memory. The task is a delayed-match-to-place (DMP) test using a radial water maze with eight arms that can each serve as a goal by housing a platform that allows the rat to climb out of the water. Changing the location of the goal over several trials assures that the animal is acquiring new episodic memories that can then be tested at various delay intervals after initial exposure. This task also allows for drug administration at different times relative to the first exposure to each goal placement (sample trial) to test encoding, retrieval, and consolidation by administering the drug immediately prior to the sample, immediately prior to the recognition test, or immediately following the sample, respectively. Ketamine administration demonstrated significant dose-dependent (2.5-25 mg/kg) encoding and retrieval deficits. This study, however, failed to observe any effect on post-acquisition drug administration when the episodic memory was tested four hours later. Thus ketamine had no effect on consolidation. This finding conflicts with several studies in literature that detail memory consolidation deficits upon NMDA blockade (4, 5, 6).

The present study re-examined the effects of NMDA receptor blockade on memory consolidation over short (4 hours) and long retention intervals (1-2 days). Specifically, we asked whether post-acquisition ketamine would weaken the memory trace sufficiently to impair recognition performance one and two days after an event in comparison to a four-hour recognition test.

Materials and Methods

Subjects and drugs.

One group (N = 16) of Sprague Dawley rats (Charles River Laboratories, Wilmington, MA) were used in this study. All rats ranged from 4-16 months of age during both training and testing and weighed 300-700 g.

All rats were housed on a 12 h light/dark cycle, in individual Plexiglas pens in a temperature-controlled room. Water was available *ad libitum*. When the rats reached 450 g, their food intake was limited to ≈ 30 g/d. At the time of ketamine treatments, all rats weighed between 450 and 680 g. Ketamine hydrochloride (Ketaset, 100 mg/ml; Fort Dodge Laboratories, Fort Dodge, IA) was prepared in physiological saline (Sal) and administered intraperitoneally immediately following the sample trial. All rats received no more than one ketamine treatment per week. All procedures were performed in accordance with the guidelines set forth by the Institutional Animal Care and Use Committee of University of Connecticut and National Institutes of Health.

Apparatus

A radial water maze was used as the memory task. The maze was housed within a black fiberglass pool (dimensions: 140cm in diameter and 40cm deep). Eight steel arms painted flat black can be added and removed to a central unit. The center of the maze has dimensions of 50cm wide while each arm is 14cm wide and extends 36cm to the outer edge of the pool. The water that filled the pool was at $22 \pm 2^\circ\text{C}$, and the sides of the pool were 18cm above the water level. The goal inside of the water maze consists

of a movable black plastic platform 10 cm in diameter that was submerged 6cm under the water level. The platform was placed at the end of any given arm, allowing the rat to get out of the water. The entire radial water maze was located in a room and was bordered by two walls, a cage rack, and a long table about one meter from the pool on every side.

Delayed match-to-place training

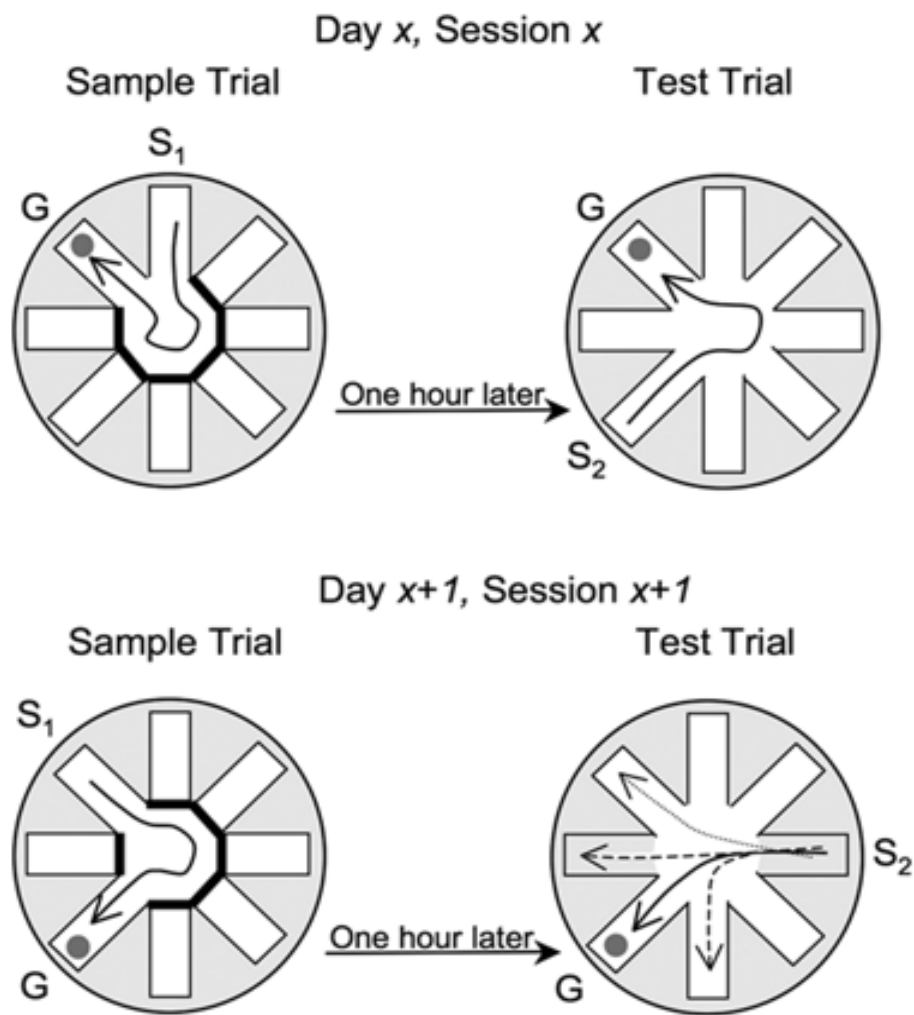
A standard training protocol was employed which consisted of five sessions a week (once per day) of a forced-choice sample trial followed by a test trial (Figure 1). The control sample trial consisted of setting up the radial water maze such that a pre-designated start and goal are the only arms open. Each rat was placed in the start arm and navigated to the goal arm where they were removed and returned to their cages. After one hour, all arms were opened for the test trial and the rats were placed in a new start arm to ensure that memories were being formed based on the spatial position of the goal. Each rat was tested each day during the training period for a total of five sessions per week with different start and goal arms each session. All arms will served as the goal and start arms approximately the same amount of sessions for the entire 24-day training session.

Figure 1 Legend.

DMP training graphic as it appears in the study published by Chrobak et al. (2008).

Delayed-match-to-sample radial water maze task. Each day (Day x , Session x) rats were given one forced-choice sample trial, with access to all but the start (S_1) and goal (G) arm blocked. The goal arm contained a submerged platform. On the test trial (typically 1 h later), all arms were open and a different start (S_2) arm was used to test memory for the spatial location of the current goal location. Typically only one sample and one test trial were given each day. Solid lines depict path to goal. The most common first errors are depicted in Test Trial on Day $x + 1$, Session $x + 1$. Once rats are well trained, the majority of first errors are to one of the arms on either side of the goal (adjacent; dashed line) or to the previous goal arm.

Figure 1:



Dependent Measures

Dependent measures for the experiment were defined as the amount of incorrect arm choices during the test trial, the latency and choice for the sample and test trial, and the first error location during the test trial. The first errors were divided into three different classifications: 1, 2, or 3. A previous error (1) refers to the rat entering a maze arm that served as the “previous goal” (the goal for the pre-test control sample conducted 24 h prior to the weekly test day). An adjacent error (2) refers to a rat entering an “adjacent arm” on either side of the goal location. All other first errors (3) are referred to as “other choice” corresponds to any arm other than the goal arm, previous goal, or an adjacent arm.

Experimental Details

The experimental test procedure began after 12 weeks of training. Over the course of the 8 weeks, rats were administered ketamine on each Tuesday at four different doses [0 (saline), 25, 50, and 100 mg/kg] immediately following the sample trial. Previous research conducted by Chrobak, et al. (2008) showed no evidence of a ketamine drug effect at the 4 h delay, prompting the replication of the experiment at the 24 h delay. An effect was noted at the 100 mg/kg dosage at a 24 h delay, at which point the 4 h delay was tested to officially replicate the previous findings. Even at 100 mg/kg, the subjects experienced no decline in memory function at the 4 h delay, corroborating the findings published by Chrobak et al. (2008). To further investigate the effect of long delays on memory consolidation, drug doses were administered at a 48 h delay. Saline and 100 mg/kg doses of ketamine were administered three times each at retention intervals of 4 h,

24 h, and 48 h. Ketamine doses of 25 mg/kg and 50 mg/kg were administered two times each at retention intervals of 24 h and 48 h. Each test day consisted of the rats running a control sample trial with a goal based on a predetermined schedule. Immediately after the sample trial, the drug dosages were administered and the rats were tested with all maze arms open after the retention interval.

Data analyses.

Error data at all long delays (4 h, 24 h, and 48 h) was analyzed by comparing saline and 100 mg/kg dosages using three paired *t* tests. A repeated-measures one-way ANOVA was employed to analyze error data from the 48 h delay followed by a least significant difference post-hoc test to assess specific control-ketamine treatment comparisons. Analyses were conducted using SPSSX (SPSS, Chicago, IL) or Microsoft (Seattle, WA) Excel on a Windows-compatible computer.

Results

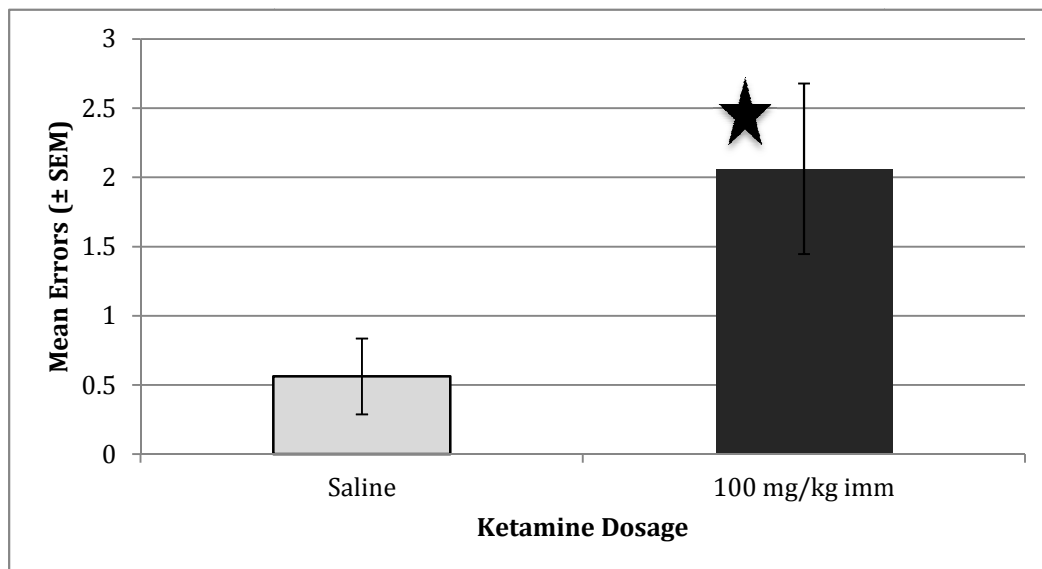
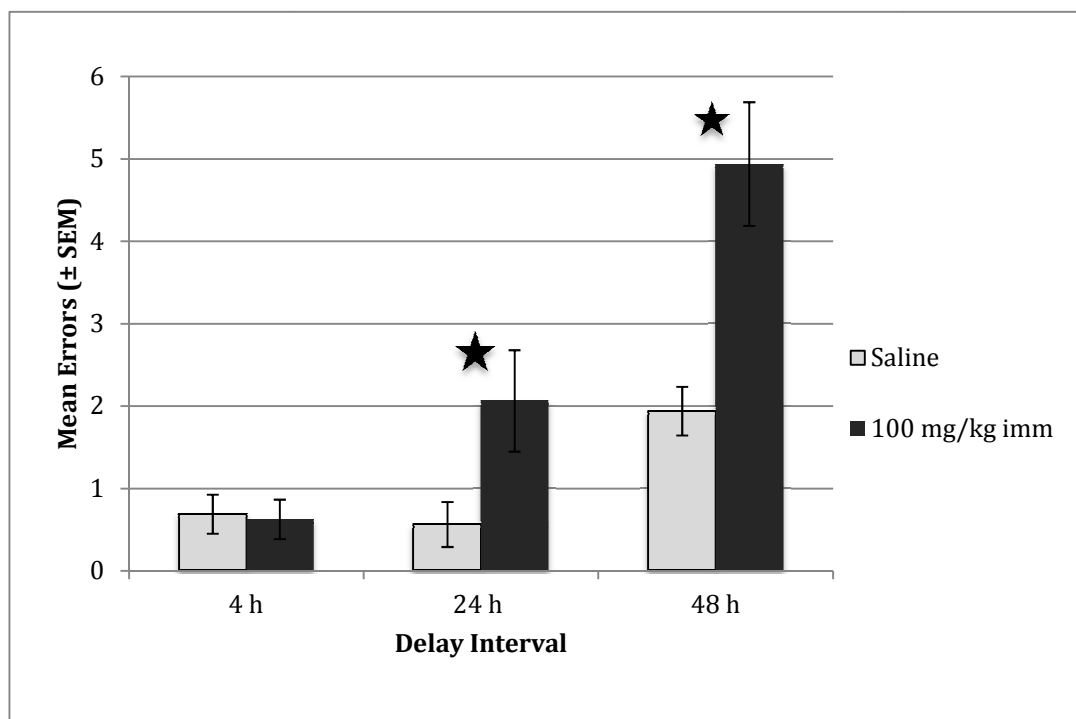
1) Effect of 100mg/kg Ketamine as a Function of Delay

First, we describe the performance of a group of rats ($n = 16$) trained in the DMP radial water maze task at the 24 h delay (Figure 2). A drug effect was seen when errors from both the saline and the 100 mg/kg ketamine dosages were compared using a paired t test ($p < 0.05$). Errors on these trials averaged 0.6 ± 0.3 and 2.1 ± 0.6 for saline and 100 mg/kg doses, respectively. The drug effect at the 24 h delay prompted the examination of any effects the same dose may have at a 4 h delay. Errors at the 4 h delay averaged 0.7 ± 0.2 and 0.6 ± 0.2 for saline and 100 mg/kg doses, respectively ($p > 0.05$). Drug effect was further tested at the 48 h delay yielding mean errors of 1.9 ± 0.3 and 4.9 ± 0.7 for saline and 100 mg/kg doses, respectively ($p < 0.005$).

Figure 2 Legend.

Effect of 100 mg/kg ketamine as a function of delay in a DMP radial water maze task. **A**, Dose effect of 100 mg/kg ketamine at the 24 h delay. Mean errors \pm SEM are derived from the performance of each rat at that delay after having been given either saline or a dose of 100 mg/kg ketamine immediately following the sample trial. * $p < 0.05$ comparing the two drug conditions. **B**, Dose effect of 100 mg/kg ketamine at all delays (4 h, 24 h, and 48 h). Mean errors \pm SEM derived from the rat performance at the 4 h delay yielded no significant drug effect ($p > 0.05$). * $p < 0.05$ and $p < 0.005$ for the 24 h and 48 h delay, respectively. **C**, Mean errors \pm SEM for saline and 100 mg/kg ketamine at all delays (4 h, 24 h, and 48 h).

Figure 2

A**B**

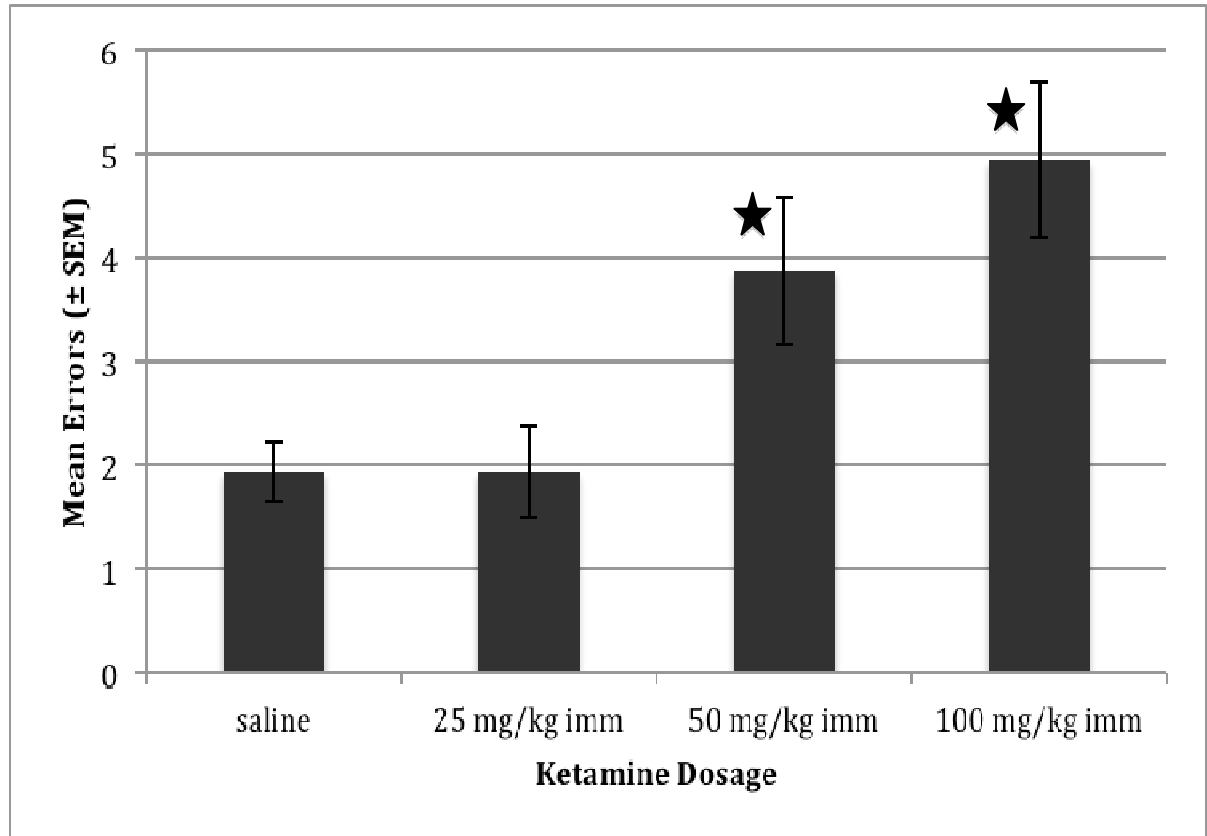
2) Dose Effect at 48 h Delay

The drug effect noted at the 48-hour retention interval was further investigated by examining two other doses of ketamine (25 mg/kg and 50 mg/kg) (Figure 3). An analysis of variance (ANOVA) of mean errors was employed along with a least significant difference posthoc test. Mean errors committed after saline administration was compared to each drug dose to ascertain the presence of a significant difference between doses. The doses of 50 mg/kg and 100 mg/kg both exhibited a drug effect on maze performance when compared to saline ($p < 0.01$ and $p < 0.005$, respectively). The dosage of 25 mg/kg, however, did not exhibit a drug effect ($p > 0.05$).

Figure 3 Legend

Dose effect at a 48 h retention interval. Mean errors \pm SEM derived from rat performance at the test trial following a drug administration immediately following the sample trial. An ANOVA and least significant difference posthoc test were used to analyze mean errors. * $p < 0.01$ and $p < 0.005$ for 50 mg/kg and 100 mg/kg doses when compared to saline, respectively.

Figure 3



3) Other Measures

Table 1 Legend

First choice latency and latency per choice were measured during the test trial to assess additional effects of a 100 mg/kg ketamine dose at all retention intervals. A significant reduction in latency per choice was noted as the result of a drug effect at the retention interval of 48 h and the ketamine dose of 100 mg/kg ($p < 0.05$).

Table 1: Choice Latencies during test trials: effects of saline and ketamine (100 mg/kg) treatment at different retention intervals

	4 Hour	24 Hours	48 Hours
<u>First Choice Test Latency</u>			
Saline	8.13 +/- 1.06	7.81 +/- 1.90	8.69 +/- 1.10
Ketamine	8.00 +/- 0.63	8.00 +/- 1.06	7.50 +/- 0.99
<u>Test Trial Latency/Choice</u>			
Saline	6.28 +/- 0.50	7.88 +/- 1.89	7.03 +/- 0.62
Ketamine	7.57 +/- 0.61	6.28 +/- 0.77	4.79 +/- 0.39 *

All values expressed as mean (+/- SEM). Each rat (N = 16) was tested once at each dose x retention interval condition. * $p < .05$

Table 2 Legend

First choice latency and latency per choice were measured at the 48 h retention interval to assess additional effects of all ketamine doses. A significant reduction in latency per choice was noted as the result of a drug effect at the ketamine dose of 50 mg/kg ($p < 0.01$).

Table 2: Choice Latency: dose effects of ketamine (0, 25, 50 and 100 mg/kg) at 48 hr test trials

48 Hours	
First Choice Test Latency	
Saline	8.69 +/- 1.10
25 mg/kg Ketamine	7.06 +/- 0.96
50 mg/kg Ketamine	8.13 +/- 0.82
100 mg/kg Ketamine	7.50 +/- 0.99
48 Hours	
Test Trial Latency/Choice	
Saline	7.03 +/- 0.62
25 mg/kg Ketamine	5.81 +/- 0.37
50 mg/kg Ketamine	5.31 +/- 0.42 **
100 mg/kg Ketamine	4.79 +/- 0.39 *

All values expressed as mean (+/- SEM). Each rat (N = 16) was tested once at each dose x retention interval condition. * $p < .05$, ** $< .01$.

Discussion

In the present study, the DMP maze task was employed to provide unique episodic memories at the beginning of every test day by positioning the goal platform in one of the eight radial arms. With only a brief exposure to the sample trial, the rats were able to create a short-term memory trace of the goal's position while exploring the maze. Ketamine injection immediately following the sample trial blocked NMDA receptors and should theoretically block the consolidation of short-term memories into more stable long-term memories. The results from the present study suggest that the consolidation process is dynamic and that the short-term memories may be more stable than previously suggested.

Data from the four-hour retention interval does not show any effect of ketamine on mean errors committed during the test trial. It is safe to assume that the 100 mg/kg dose of ketamine blocked NMDA receptors for the entirety of the retention interval making the occurrence of LTP resulting in consolidation highly unlikely. A possible explanation for the absence of a drug effect is that the short-term representation of the goal's location was stable enough to last the entire retention interval without sustaining significant decrements over time. Ketamine also does not appear to have an effect on episodic memories once acquired during spatial exploration. A blockade of NMDA receptors leads to a deficit in synaptic plasticity and would only affect memory processes that depended on changing synaptic structure. Memory trace acquisition during the sample trial and consolidation following said trial should therefore be affected by the blockade. Once the short-term memory trace was formed through synaptic strengthening

between “place cells” within the hippocampus, however, the blockade of NMDA receptors would have no effect on the trace’s stability.

At the 24 h retention interval a clear drug effect can be seen due to the increase in mean errors. At this delay, consolidation is necessary to preserve episodic information that would otherwise be lost as short-term memories breakdown. A consolidation event that occurred at some point during the delay was hindered by the NMDAr blockade, leading to the increase in mean errors committed during the test trial.

A drug effect is also seen at the 48 h retention interval as mean errors more than doubled when rats were given a dose of 100 mg/kg of ketamine. This increase in mean errors is proportional to the increase in time for the retention interval which suggests that interfering with consolidation produces long-term memories that either do not accurately represent the episodic memory or are less stable over time. The possibility also remains that some rats lost all memory of the goal location and simply reverted back to the serial searching behavior wherein the rat checks each arm in order until the goal is found. This later theory is supported by the significant reduction in latency per choice at 50 and 100 mg/kg ketamine doses. A smaller mean choice latency is indicative of fear resulting from complete loss of the goal location memory trace.

Consolidation is unique among the memory processes because it is extended in time as compared to the limited time frames of the encoding and recall of an event that occur in a moment. Past research has shown evidence for the presence of SPWRs during both sleep and quiet (non-exploring) wakefulness (19), although no evidence has demonstrated the relative importance of SPWRs occurring soon after a “to-be-remembered” event as compared to SPWRs occurring later in an extended retention

period. From an experimental design perspective, injecting high doses of ketamine immediately after the sample trial allowed for several hours of NMDAr blockade in between acquisition of the new memory and its retrieval during the test trial. Once the effects of the ketamine wore off, however, the rats would be free to consolidate their short-term memories. Longer retention intervals of 24 to 48 h would allow for ample time for the memory to be consolidated before retrieval was necessary during the test trial. There is a significant drug effect at these delays, suggesting that the short-term representation supporting recognition memory at a four hour retention test is likely sufficiently degraded by high dose ketamine treatment and unable to support long-term memory performance (eg, 24-48 hrs).

In the future, it would be pertinent to follow the experimental design used by Girardeau, et al. (2009) that offered much more certainty as to when consolidation was occurring by monitoring the presence of SPWRs within the rats (12). An electrode array implanted within the hippocampus that was filtered in the ripple-band and compared to a threshold level of activity was used to identify the onset of SPWRs. Electrical stimulation of the hippocampal commissure interrupted the neuronal activity within the hippocampus, silencing the remainder of the SPWR. Results of the experiment showed decrement to memory consolidation when all SPWRs were interrupted following initial exposure to a maze task. To study the immediate effects that an NMDAr blockade would have on SPWRs and resulting memory consolidation, a cannula could be implanted near the hippocampus and setup to release an NMDA antagonist at the initiation of all SPWRs. A highly potent NMDA antagonist such as MK801 could be used because the specificity of drug administration would remove the need for injecting a large dose immediately

following the sample trial. The original design was limited to ketamine due to the fact that large doses of MK801 cause neurotoxicity (20). A tonic administration of ketamine via intraventricular cannula may also assure that consolidation is impaired over the entirety of the retention interval, although it would be hard to prove a complete blockade of NMDA receptors during consolidation events.

The results of this study demonstrate that post-training blockade of NMDA receptors can weaken long-term representation of a spatial memory as evidenced by increased errors during test sessions with extended (24 h and 48 h) retention intervals. Consolidation may not be necessary for shorter (4 h) retention intervals during which, the short-term memory trace is stable enough to successfully direct the rats to the goal in the test trial without a significant increase in errors committed. Another possibility is that the strength of a degraded memory trace is sufficient to support memory performance at a four hour retention interval, but high-dose ketamine treatment speeds the degradation of that memory trace to the point that it is insufficient to support accurate performance at 24 or 48 hours. Ketamine administration immediately following a “to-be-remembered” event can block memory consolidation in a dose-delay dependent manner.

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