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KETAMINE IMPAIRS MULTIPLE COGNITIVE DOMAINS IN RHESUS MONKEYS

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Abstract

Available evidence suggests that recreational use and abuse of the dissociative anaesthetic ketamine is increasing. Characterization of the cognitive risks of ketamine exposure contributes substantially to understanding this growing public health threat. Although prior human studies demonstrate that ketamine impairs a range of cognitive skills, investigation in nonhuman models permits more precise exploration of neurochemical mechanisms which may underlie detrimental behavioral effects. Adult male rhesus monkeys (7) were trained on a neuropsychological battery including tests of memory (delayed match-to-sample, DMS; self-ordered spatial search, SOSS), reaction time (RT), reinforcer efficacy and sustained attention (progressive ratio, PR) and fine motor coordination (bimanual motor skill, BMS). Battery performance was then serially challenged with acute doses of ketamine (0.3, 1.0, 1.78 mg/kg IM). Ketamine impaired DMS and SOSS in a dose $\times$ difficulty dependent manner with the most difficult task conditions disrupted at the 1.0 and 1.78 mg/kg doses. Thus, both visual recognition memory and working memory indices were affected. Ketamine also slowed RT and BMS performance and interfered with PR performance at the 1.78 mg/kg dose. Overall the present findings confirm that ketamine interferes with multiple aspects of cognition at subanesthetic doses in monkeys.

Keywords

MEMORY; NMDA; CANTAB; CLUB DRUG

1. Introduction

Recreational use and abuse of the dissociative anaesthetic ketamine (Ketalar®, Ketaset®) is not new (Jansen 2001), however the available evidence suggests that such use of ketamine has increased substantially in recent years (Colfax et al. 2001; Dalgarno and Shewan 1996; Garfield et al. 2001; Mansergh et al. 2001; Mattison et al. 2001; Riley et al. 2001; Weir 2000). Ketamine functions as a non competitive antagonist of *N*-methyl-D-aspartate (NMDA) glutamatergic receptors which play a crucial role in long-term potentiation, a putative cellular mechanism subserving memory (for review see Huang and Stevens 1998;

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Nicoll and Malenka 1999). This mechanism is intuitively a general one, thus interference with NMDA function would be predicted to produce widespread impairment of memory. Studies have shown that noncompetitive NMDA antagonists interfere with performance of memory tasks in a number of species (e.g., Buffalo et al. 1994; Ghoneim et al. 1985; Morris et al. 1986) and furthermore, the chronic abuse of ketamine may be associated with persisting impairment of memory and other cognitive functions (Curran and Monaghan 2001; Jansen 1990) in humans. Therefore, the exploration of the cognitive impact of ketamine exposure is of interest to further delineate the possible health risks of ketamine abuse and the role that NMDA receptors may play in various aspects of behavior.

Subanaesthetic doses of ketamine have been administered in a number of human neuropsychological studies as a putative model of psychosis (Curran and Monaghan 2001; Curran and Morgan 2000; Ghoneim et al. 1985; Grunwald et al. 1999; Hetem et al. 2000; Krystal et al. 2000; Krystal et al. 1994; Malhotra et al. 1996; Newcomer et al. 1999) and in such studies ketamine has been shown to interfere with recall and recognition memory for words and nonverbal stimuli (Adler et al. 1998; Ghoneim et al. 1985; Grunwald et al. 1999; Hetem et al. 2000; Malhotra et al. 1996) as well as working memory (Adler et al. 1998) and executive function (Krystal et al. 2000). There is some evidence that ketamine does not affect attentional processes (Adler et al. 1998; Newcomer et al. 1999; Oranje et al. 2000), digit span (Ghoneim et al. 1985; Grunwald et al. 1999) or spatial memory (Newcomer et al. 1999), thus ketamine may interfere only selectively with cognition.

Such acute drug-challenge investigations in human subjects are necessarily limited, however, in terms of the breadth of pharmacological investigations that may be performed in the same subjects. Investigations utilizing nonhumans more readily permit the evaluation of extensive dose-response functions, direct within-subjects comparison of the effects of multiple alternate drug challenges, and the use of combined drug challenges to further delineate the behavioral effects of psychoactive drugs. Because the macaque monkey may be readily trained to perform a wide range of behavioral tasks concurrently (Paule et al. 1990; Voytko 1993; Weed et al. 1999), it is an ideal model for comprehensive characterization of cognitive status following a variety of CNS challenges. Investigation of the effects of ketamine on a range of behavioral procedures in monkeys might therefore contribute substantially to understanding of the risks posed by ketamine to cognitive function in a more mechanistic manner than is possible with human studies.

The behavioral effects of phencyclidine (PCP), dizocilpine (MK-801) and ketamine have been characterized in a number of studies in monkeys (Buffalo et al. 1994; Byrd et al. 1987; Frederick et al. 1995; Harder et al. 1998; Ogura and Aigner 1993; Rupniak et al. 1992; Thompson et al. 1987). While all three compounds share noncompetitive NMDA antagonist properties, ketamine has substantially lower affinity for the NMDA receptor (Parsons et al. 1996; Sihver et al. 1998) and the available direct comparison studies suggest that ketamine is approximately one-tenth as behaviorally potent as PCP in monkeys performing operant tasks (Brady et al. 1980; Byrd et al. 1987; Thompson et al. 1987). Prior monkey studies have generally focused on one or two behavioral or operant measures rather than an array of measures as is common in human studies and the multi-task studies did not evaluate PCP and MK-801 but not ketamine (Buffalo et al. 1994; Frederick et al. 1995). In sum, there is

relatively little evidence regarding the effects of ketamine on behavioral function in nonhuman primates available for comparison with profiles in human volunteers or ketamine abusers.

The present study was designed to evaluate the cognitive effects of acute ketamine exposure in rhesus monkeys, trained to concurrently perform a number of behavioral tasks comprising a nonhuman primate neuropsychological test battery (Weed et al. 1999). Rhesus monkeys' performance on tests from this battery have been previously demonstrated to be sensitive to the effects of pharmacological manipulation (Taffe et al. 2002a; Taffe et al. 1999; Taffe et al. 2002b; Weed and Gold 1998). Use of this battery serves a number of specific purposes for the present investigation. First, this study will investigate the effects of ketamine, concurrently, on a range of behaviors much as has been done previously for PCP and MK-801 but not ketamine. Second, this test battery has been derived from one used in various human studies, thus behavioral profiles may be compared to prior results from human populations with traumatic, developmental or other known brain insults (see Weed et al. (1999) for review). Thus since the behavioral assays used here may be more directly related to specific brain regions or mechanisms (unlike the tests used in the Buffalo et al. (1994) and Frederick et al. (1995) studies) additional information regarding the behavioral effect of noncompetitive NMDA antagonists will result. Here, it is predicted that ketamine will interfere specifically (i.e., in a dose $\times$ difficulty dependent manner) with pattern recognition memory and spatial working memory as assessed with the delayed match-to-sample and self-ordered spatial search procedures respectively, since humans challenged with ketamine are impaired on tasks associated with similar cognitive constructs (Adler et al. 1998; Ghoneim et al. 1985; Grunwald et al. 1999; Hetem et al. 2000; Malhotra et al. 1996).

Evaluation of the behavioral effects of ketamine in monkeys trained on the test battery serves a number of additional goals. It will provide an important extension of our previous study of the effect of muscarinic blockade on these battery tasks (Taffe et al. 1999), and a complement to our contrast of scopolamine and ketamine effects (Taffe et al. 2002b) on a new memory test with proposed sensitivity and specificity for Alzheimer's Disease (Fowler et al. 2002; Swainson et al. 2001). Together these efforts explore the possible unique or overlapping contributions of muscarinic and NMDA mechanisms to the regulation of cognition with a particular emphasis on learning and memory. Thus, this work serves a continuing goal of determining the role various neurotransmitter systems and subsystems play in cognitive function across a range of performance domains in a single preclinical model. Furthering this understanding will also assist in the interpretation of behavioral outcome in continuing studies of the effects of neurotropic virus infection (e.g., Gold et al. 1998; Weed and Gold 2001), exposure to putative neurotoxicants (e.g., Taffe et al. 2002a; Taffe et al. 2001) and chronic exposure to drugs of abuse by generating neuropharmacological profiles of performance analogous to the profiles generated by evaluating various human populations on similar tasks. Finally, this study is a necessary preliminary for the generation of a chronic-exposure, nonhuman model of the cognitive risks associated with recreational use and abuse of ketamine.

2. Methods

2.1. Subjects

Eight adult male rhesus monkeys (*Macacca mulatta*) served as subjects. The monkeys were approximately 5 years of age and weighed 6.5–8.0 kg at the beginning of the study. Animals were individually housed and fed in the home cage after completion of the daily testing session. The animals' normal diet (Lab Diet 5045, PMI Nutrition International) was supplemented with fruit or vegetables four days per week and water was available *ad libitum* in the home cage. Principles of laboratory animal care (Clark et al. 1996) were followed, and all protocols were approved by the Institutional Animal Care and Use Committee of The Scripps Research Institute. The monkeys had extensive training on all components of the behavioral test battery and 4 of the subjects had received acute doses of scopolamine in a study conducted 3 months prior to their participation in the present study (Taffe et al. 2002b). All animals had previously been immobilized with ketamine in doses of approximately 5–10 mg/kg (i.m.), no less than semiannually for the purposes of routine care and health monitoring. Three animals had not been trained to final performance criteria on one task each (#289, RT; #325, DMS; #333, SOSS), consequently testing on the relevant task was omitted for those animals. One animal (#329) failed to complete at least 50% of the battery tasks following initial administration of the lowest two challenge doses of ketamine and was discontinued from the study. Thus the number of subjects contributing to the analysis of each behavioral task ranges from N=6 to N=7.

2.2. Behavioral Testing

Behavioral performance was evaluated using a battery of tests designed to model specific cognitive domains in rhesus monkeys (Weed et al. 1999). The battery included tests of learning (visuo-spatial paired-associate learning; vsPAL), memory (delayed match-to-sample; DMS, self-ordered spatial search; SOSS), sustained attention and reinforcer efficacy (progressive ratio; PR), reaction time (RT) and bimanual motor coordination (bimanual motor skill; BMS). Performance on tests of this battery has previously been shown to be differentially sensitive to acute drug manipulation (Taffe et al. 2002a; Taffe et al. 1999; Taffe et al. 2002b; Weed and Gold 1998). Animals were tested five days per week with three tasks being completed each day in alternation as is outlined in Table 1.

2.2.1. Apparatus—For behavioral testing, animals were transferred to the testing room in transport cages similar to the home cage but modified by the removal of several bars from the front of the cage to allow the animal to easily reach out. The transport cage was placed in front of a touch-sensitive computer monitor on which various stimuli were presented. All animals had been previously trained to reach out of the cage to touch the location on the screen at which visual stimuli were presented to obtain a food pellet reward. The stimulus presentation and response detection were controlled by a micro-computer equipped with a version of the Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition, Cambridge, UK) designed for use with non-human primates. A dispenser delivered 190 mg flavored pellets (Noyes Precision Pellets; Research Diets, Inc., New Brunswick, N.J.) to a bin mounted on the front of the cage after correct responses were made. A white-noise generator remained on in the testing room during each behavioral

session. The test battery consists of six behavioral tasks. Five of the tasks (vsPAL, DMS, SOSS, RT, PR) are part of the non-human primate CANTAB and require monkeys to respond by touching the touch-sensitive computer screen and are reinforced with the delivery of food pellet reinforcers. The sixth task (BMS) requires the animal to extract raisins from holes in a transparent polycarbonate board. Comprehensive descriptions of the procedural details have been previously reported (Weed et al. 1999).

2.2.2. Visuo-Spatial Paired-Associate Learning (vsPAL)—The PAL task is a memory task involving learning to associate a given pattern with a particular spatial location on a trial by trial basis. Procedural details and the effects of this ketamine challenge study on this particular task have been previously described (Taffe et al. 2002b).

2.2.3. Delayed Match-to-sample (DMS)—The DMS task is a recognition memory task involving sets of visual discriminations. A sample stimulus is presented in the center of the screen and the animal must make an observing touch to its location within 30 seconds otherwise the trial is scored as a sample omission error and a 4 sec inter-trial delay is initiated. After a touch, the screen is blanked and following a variable retention interval (0, 16, 32 or 64 sec) four choice stimuli are presented in the corners of the screen. One stimulus is identical to the sample stimulus and the others are novel. A touch directed to the choice stimulus that is identical to the sample is followed by reinforcer delivery and scored as a correct choice. Touches directed to one of the novel (incorrect or “foil”) stimuli score as an error and initiate a 4 sec inter-trial delay. The non-matching stimuli are constructed such that one stimulus shares color (but not shape) information with the sample stimulus, one stimulus shares shape (but not color) information with the sample and one stimulus shares neither color nor shape information. Thus, analysis of error responses to the three foil categories may be used to determine if the subject has remembered partial stimulus information. This new analysis which has not been incorporated in prior rhesus studies using this battery is made possible by using the delayed *match-to-sample* variant rather than the delayed *nonmatch-to-sample* (DNMS) variant of the task. In addition to the four retention interval conditions, a simultaneous condition is included in which the sample stimulus remains present after the observing touch and while the choice stimuli are presented. A session consists of 10 trials at each retention interval (plus 10 simultaneous trials) presented in randomly intermixed fashion for a total of 50 trials. The software utilizes 469 shapes and 7 colors to ensure that discriminations are unique for approximately 120,000 trials. Performance accuracy is measured as a proportion of correct choices to all choices (i.e., both sample and choice omission errors are excluded from the accuracy calculation). For presentation and analysis purposes, performance scores (accuracy, errors, latency) are collapsed across the shorter (0, 16 sec) and longer (32, 64 sec) trial types because previous experience with this task, as well as the DNMS variant of the task, has shown that while consistent ordering of performance on all four delays is unlikely with this group size, performance on the longer two delays is consistently worse than performance on the shorter two delays (Taffe et al. 2001; Taffe et al. 1999; Weed et al. 1999).

2.2.4. Self-Ordered Spatial Search (SOSS)—In each trial of the SOSS task, two, three or four small colored rectangles (boxes) are displayed on the screen in positions randomly

allocated from 16 possible locations. The animal must touch a box within 30 seconds of stimulus onset. After each successful touch, the color of the touched box is briefly (100 ms) changed and then the screen is blanked and a reinforcer is delivered. After a 2 second delay, the boxes are re-displayed and the animal must touch a box which has not previously been touched in the trial. The trial is completed when the animal has either touched all boxes without a repetition (correct), touched a box that had previously been selected in that trial (error) or failed to touch a box within 30 seconds of stimulus presentation (omission). Errors and omissions are followed by a tone and a 4 second screen blank. After an inter-trial interval of 5 seconds, another trial is presented with stimuli in new (randomly allocated) positions. A session consists of 40 trials grouped into 6 blocks by trial type as follows: 5 (2 boxes), 7 (3 boxes), 7 (4 boxes), 8 (3 boxes), 8 (4 boxes), 5 (2 boxes). Accuracy scores are calculated for each trial type by dividing the number of correctly completed trials by the number of trials in which there was at least one response (i.e., errors of omission are excluded from the calculation). A choice latency score (calculated for successfully completed trials only) is derived from the average time required for the monkey to make a selection of a box following each presentation of the trial stimuli for correct responses only. Finally, a measure of search strategy (for trials consisting of more than 2 boxes) is derived from the order of responses on each correct trial. To calculate the strategy score, the distance (in screen pixels) between each sequential box selection is summed for each successfully completed trial. Since box locations for each trial are randomly allocated, this distance is then represented as a proportion of the difference between the shortest and longest possible routes for a given trial. In essence, a strategy score approaching 0% represents an animal consistently choosing to respond sequentially to the next-closest box, whereas a strategy score approaching 100% represents consistently choosing the most-distant box from the previous choice. This novel analysis of search strategy in this task is similar to the “proximity strategy” described by Collins and colleagues (Collins et al. 1998) but has the advantage of providing comparable scores independent of either the number of boxes per trial or the location of the boxes in a given trial. Analysis of SOSS performance of 28 monkeys trained on this task in this laboratory shows a strong negative correlation between strategy score and trial completion accuracy both between animals and across training duration (data not shown) suggesting that employing a strategy of sequentially choosing an unselected box closest to the previously selected box results in improved task performance.

2.2.5. Reaction Time (RT)—For the RT task, a response lever (BRS/LVE, Laurel, MD) is mounted below the monitor and in front of the transport cage. For each trial a grid of five circles, or target locations, connected by lines is presented in white on the screen. The monkey initiates the trial by holding down the lever. After a pseudorandomly-variable delay lasting between 0.75 and 2.5 seconds, a yellow circle appears within one of the five target locations and is removed after 20, 100 or 1000 msec. Touching the appropriate circle within 2 seconds results in reinforcer delivery. The interval between target onset and the monkey’s release of the lever (release latency) and the interval between target onset and the monkey’s touch of the target location (response latency) is recorded in milliseconds. The interval required to move from lever to the target location (movement time) is calculated by subtracting the release latency from the response latency.

2.2.6. Progressive-Ratio (PR) Schedule of Reinforcement—In the PR task a large colored rectangle is presented in the center of the screen and the animal must touch the rectangle for reinforcer delivery. The response requirement starts at 1 and increments by arithmetic progression within blocks of 8 reinforcers and by geometric progression between blocks of 8 (i.e., the first successive 8 ratios increase by 1, the second successive 8 increase by 2, the third successive 8 increase by 4, etc.) The session is terminated after 10 minutes, or earlier if 3 minutes elapse following a response. The interval between session start and the last response emitted is recorded as the “time-to-last-response” measure (i.e., there is no true “breakpoint” in this version of the PR procedure). The last completed response ratio, the number of reinforcers earned, the total number of responses made and the response rate are also recorded.

2.2.7. Bimanual Motor Skill Task (BMS)—A transparent polycarbonate board drilled with 15 holes is filled with raisins and mounted perpendicular to the door of the transport cage. The hole diameter is such that for efficient retrieval of raisins, the animal must push the raisin partially out of the hole with one finger before retrieving it. With training, animals universally adopt a strategy of pushing the raisin with one hand while retrieving it with the other hand, thus entailing bimanual dexterity. The time required to retrieve all 15 raisins is recorded by stopwatch.

2.3 Drug Challenge Procedure

As described above, animals were tested five days per week using an alternating schedule of the battery tasks (i.e., DMS/RT/BMS; PR/SOSS/BMS; PR/PAL/BMS or PAL/RT/BMS) in sessions lasting approximately 60 minutes. Prior to initiation of the drug study, animals were injected with saline on Tuesdays, Thursdays and Fridays for 2 weeks or until performance was not different from performance on noninjection days (Mondays and Wednesdays). The effect of ketamine on performance of the test battery was subsequently determined by serially administering acute doses (0.3, 1.0, 1.78 mg/kg, i.m.) 5 minutes prior to test sessions on Tuesdays and Fridays. For intramuscular injection, ketamine HCl (Ketaset®, 100 mg/ml solution) was diluted with saline to obtain a constant injection volume of 0.1 ml/kg. The vehicle (physiological saline, 0.1 ml/kg) was administered 5 minutes prior to Thursday test sessions. Thus, in a given three week period the DMS, SOSS and PAL tasks were tested twice under baseline conditions, once after vehicle and twice following ketamine administration. The effect of each dose was evaluated twice, in an ascending/descending order, for each task combination.

2.4 Data Analysis

Statistical analysis of the SOSS (trial completion, response latency and strategy score) and DMS (choice accuracy, choice latency, match-color errors, match-shape errors, nonmatch errors) data was conducted by randomized block analysis of variance (ANOVA) with repeated measures factors of drug treatment condition and trial difficulty (DMS, retention interval; SOSS, number of boxes). Post-hoc analyses of significant main effects or interactions found in the randomized block ANOVAs were conducted with the Tukey-Kramer procedure. The RT (response latency, movement time; expressed as a percentage of baseline for each individual), PR (the number of reinforcers acquired, the latency of the last

response, total number of responses, response rate) and BMS (retrieval latency) data were analyzed using repeated measures ANOVA with a single factor of drug treatment condition. Since the RT data were normalized to the baseline condition, there were only 4 levels of the drug treatment condition incorporated in this analysis. Post-hoc analyses of any significant main effects were conducted using the Dunnett procedure with vehicle as the control comparison condition. All analyses were conducted using a commercial statistical software package (GB-STATv7.0; Dynamic Microsystems, Silver Spring MD) and in all tests the criterion for significance was $p < 0.05$.

3. Results

3.1 DMS

Choice accuracy in the DMS task was significantly decreased by increasing the retention interval and by the administration of ketamine as is illustrated in Figure 1. Performance remained substantially above chance responding (i.e., 25%), however, for all conditions and trial types. The ANOVA confirmed a significant main effect of retention interval [$F_{2,10} = 9.744$; $p < 0.05$], drug treatment condition [$F_{4,20} = 13.051$; $p < 0.05$] and the interaction [$F_{8,40} = 2.650$; $p < 0.05$]. Post hoc analysis of these effects confirmed that the 1.0 and 1.78 mg/kg doses of ketamine impaired choice accuracy on the long retention interval trials and only the 1.78 mg/kg dose impaired performance on the short retention interval trials, compared with performance on these trials following vehicle administration. In a similar fashion, accuracy on long retention interval trials was significantly lower than on either short-interval or simultaneous trials following 1.0 mg/kg ketamine, and lower than simultaneous trials following 1.78 mg/kg ketamine.

Analysis of the error categories demonstrated some small but potentially illustrative differences. Monkeys have a tendency to make fewer errors directed at the completely novel foil stimulus compared with the foils which share shape or color information with the sample under baseline and vehicle conditions, as is illustrated in the lower panels of Figure 1. The longer retention intervals significantly increased the proportion of non-match [$F_{2,10} = 5.666$; $p < 0.05$] and match-to-shape [$F_{2,10} = 12.326$; $p < 0.05$] errors but did not affect match-to-color errors [$F_{2,10} = 0.391$; $p = 0.69$]. Ketamine administration significantly increased all error types (non-match [$F_{4,20} = 3.763$; $p < 0.05$]; match-to-shape [$F_{4,20} = 4.470$; $p < 0.05$] and match-to-color [$F_{4,20} = 6.759$; $p < 0.05$]). Post hoc analysis confirmed a significant increase (relative to both vehicle and the other trial types) in non-match errors for long retention interval trials following the 1.0 mg/kg dose. Similarly, more match-to-shape errors were made for long retention interval trials (relative to simultaneous trials) following the 1.78 mg/kg dose. There were no drug effects on the retention interval relationship of match-to-color errors, since post hoc exploration failed to confirm any pair-wise differences. Finally, there was a significant main effect of retention interval [$F_{2,10} = 43.314$; $p < 0.05$], but not ketamine [$F_{4,20} = 0.658$; $p = .63$] on choice latency.

3.2 SOSS

Successful trial completion in the SOSS task was ranked by task difficulty and impaired by the administration of ketamine, as is depicted in Figure 2. Monkeys were significantly less

likely to complete a 4-box trial in comparison with 2- or 3-box trials under each drug treatment condition as confirmed by a significant main effect of number of boxes [$F_{2,10} = 76.750$; $p < 0.05$] and post-hoc comparison of performance within each treatment condition. Ketamine induced a dose-dependent decrement in performance, as confirmed by a significant main effect of drug treatment condition [$F_{4,20} = 12.657$; $p < 0.05$] and a significant interaction between the drug treatment and difficulty factors [$F_{8,40} = 7.893$; $p < 0.05$]. Post-hoc analysis of these effects confirmed that the highest two doses of ketamine significantly reduced trial completion accuracy for 3- and 4-box trials in comparison with vehicle performance, whereas the accuracy of 2-box performance was not significantly affected. Ketamine also increased choice latency as was confirmed by a significant main effect of drug condition [$F_{4,20} = 6.629$; $p < 0.05$]. Interestingly, the effect on latency was limited to the highest dose for 2-box trials only. Finally, ketamine impaired search strategy as was confirmed by a significant main effect of drug condition on the strategy score [$F_{4,20} = 4.817$; $p < 0.05$]. Post hoc exploration of this effect failed to confirm any pair-wise differences however analysis of the marginal means confirmed that the strategy score collapsed across trial type was impaired at the 1.0 mg/kg dose, relative to vehicle.

3.3 RT

Ketamine significantly increased movement time [$F_{3,15} = 17.883$; $p < 0.05$], however a trend for increased release latency failed to reach statistical significance [$F_{3,15} = 0.017$; $p = .11$] as is illustrated in Figure 3. Monkeys achieved a mean release latency of 285 milliseconds (SEM = 21 milliseconds) and movement time of 512 milliseconds (SEM = 78 milliseconds) under baseline conditions. Post hoc exploration confirmed that the highest two doses of ketamine significantly increased movement time relative to vehicle treatment. Inspection of the individual dose-response curves indicated that 5/6 monkeys exhibited >10% increase of movement time at the 1.78 mg/kg dose whereas only 2/6 exhibited >10% increase of release latency (data not shown). Thus ketamine may indeed increase release latency more consistently at a slightly higher dose.

3.4 PR

Ketamine significantly decreased PR performance in terms of the time-to-last-response [$F_{4,24} = 7.685$; $p < 0.05$], number of reinforcers acquired [$F_{4,24} = 14.043$; $p < 0.05$], the total number of responses [$F_{4,24} = 6.028$; $p < 0.05$] and the response rate [$F_{4,24} = 6.226$; $p < 0.05$], as illustrated in Figure 4. The final completed response ratio was also decreased by ketamine ([$F_{4,24} = 7.259$; $p < 0.05$], data not shown). Post hoc analysis of all measures confirmed that ketamine significantly altered PR performance relative to vehicle levels only after the highest dose administered. The time-to-last-response was preserved at the 1.0 mg/kg dose where there was a trend for all other PR measures to be lowered.

3.5 BMS

Ketamine interfered with BMS performance as is illustrated in Figure 5. Post hoc analysis of a significant main effect of drug condition [$F_{4,24} = 8.579$; $p < 0.05$] confirmed that the time required to retrieve all 15 raisins after the highest dose of ketamine was significantly longer than for the vehicle or baseline conditions.

4. Discussion

The present findings show that subanaesthetic doses of ketamine interfere with multiple aspects of behavioral performance in rhesus monkeys, much as has been reported with humans (Curran and Monaghan 2001; Curran and Morgan 2000; Ghoneim et al. 1985; Grunwald et al. 1999; Hetem et al. 2000; Krystal et al. 2000; Krystal et al. 1994; Malhotra et al. 1996; Newcomer et al. 1999). Dose related decrements in performance were observed in all of the behavioral tests, thus ketamine interfered with the retention of visual information (DMS), spatial working memory (SOSS), ballistic motor response (RT), fine motor coordination (BMS) and sustained attention (PR) at the highest, but not the lowest, dose administered. Ketamine related decrements in performance of the memory tasks interacted with task difficulty which indicates a specific effect of the drug on the memory aspects of task performance. In addition, the memory tasks were significantly impaired following a ketamine dose which did not significantly alter performance on the RT, BMS or PR tasks which suggests that memory performance is particularly sensitive to the effects of ketamine.

Ketamine impaired accuracy in the DMS task on the longer retention interval trials at a dose which did not affect performance on shorter retention interval trials, and shorter retention interval trials at a dose which did not affect simultaneous trials. This pattern suggests that ketamine interferes specifically with the retention of visual information across time as opposed to other aspects of the task (e.g., stimulus perception, the match-to-sample rule) which are shared across trial types. Similarly, ketamine impaired SOSS performance in a dose $\times$ difficulty dependent manner as well, in this case indicating that ketamine interferes specifically with the spatial working memory aspects of the task (as opposed to nonmnemonic aspects such as stimulus detection, the ability to accurately touch the boxes, etc.) The analysis of error subtypes in the DMS task suggested that when making an incorrect choice monkeys base their decision on at least partially correct information (either shape or color) more often than not since responses to the “shared color” or “shared shape” foil stimuli were more common than responses to the completely novel foil. In addition, this analysis demonstrated that memory for the color, as opposed to shape, properties of the stimuli were the most resistant to interference from either a longer retention interval or ketamine challenge. Analysis of the search strategy in the SOSS task suggested a potentially important additional effect of ketamine on procedural memory. Viewed together, our present and prior (Taffe et al. 2002b) findings are not consistent with attempts to link ketamine effects to distinct memory constructs (e.g., “working memory”, “episodic memory”, “recognition memory”, etc) nor to specific stimulus domains (e.g., object versus spatial memory) in a differentiable way as has been attempted in some human studies. Rather, the present data suggest that the NMDA receptor is involved in multiple types of memory, thus suggesting that the role of the NMDA receptor might best be considered as supporting “lower level” or more general aspects of memory. This is perhaps an unsurprising conclusion since the type of cellular mechanism proposed to support memory function, i.e., LTP, is intuitively a general mechanism.

Ketamine produced a clear impairment of motor responses in the RT procedure which was not indicated by the choice latencies generated in the DMS and SOSS tasks. Likewise, ketamine interfered with fine motor coordination in the BMS task, thus ketamine interferes

with multiple aspects of motor function. The RT observation in particular also makes a more general point that response latencies generated in the context of more complex tasks (i.e., learning or memory) may not be particularly sensitive indicators of psychomotor ability and confirm the utility of a battery of more specific tasks. One important implication of the ketamine effect on the BMS task, which was assessed at the end of the testing session, is that despite the relatively short duration of action of ketamine in nonhuman primates, behaviorally significant levels of the drug persisted throughout the testing session as was predicted by a report on the time-course of ketamine effects on non-operant behaviors (Shiigi and Casey 1999). Performance in the PR procedure was also impaired by ketamine with all dependent measures significantly reduced at the highest dose administered. Although this version of the PR is time-limited, the fact that the time-to-last-response under vehicle and baseline conditions was consistently under the 10 minute limit indicates that this measures functions in an analogous manner to a true breakpoint. Therefore an interesting observation was the monotonic decrement in response rate, total responses and reinforcers acquired in contrast with the preservation of the time-of-last-response measure at the intermediate 1.0 mg/kg dose. This disconnect, combined with the observation that monkeys were observed in some cases to continue to respond without consuming the food pellets acquired (this has also been observed under scopolamine challenge) suggests that traditional interpretations of a reduction in “motivation” and “reinforcer efficacy” are insufficient to completely describe the phenomenon. It is likely that this procedure in part reflects the degree of sustained attention to task demands.

The present findings are also generally consistent with previous reports of the behavioral effects of noncompetitive NMDA antagonists in nonhuman primates. Ketamine decreased operant response rates in the present PR task much as with PCP, dizocilpine and ketamine in prior studies (Brady et al. 1980; Byrd et al. 1987; Paule 1994). Ketamine also increased the rate of forgetting in the DMS procedure in a dose dependent fashion similar to findings reported by Paule and colleagues (Buffalo et al. 1994; Paule 1994). One finding which is inconsistent with prior reports is that while ketamine disrupted single trial acquisition (DMS, SOSS; also see the initial-attempt data from the vsPAL procedure (Taffe et al. 2002b)), *repeated* acquisition was unaffected in vsPAL procedure (see the overall-attempt data in Taffe et al. 2002b). In contrast to our findings, prior studies in monkeys have shown that ketamine, PCP and MK-801 disrupt two different repeated-acquisition procedures (Buffalo et al. 1994; Paule 1994; Thompson et al. 1987). In one other multiple-task study conducted by Buffalo and colleagues, repeated-acquisition was more sensitive than delayed match-to-sample to the effects of MK-801 (Buffalo et al. 1994). In aggregate, however, the present findings are similar to previous investigations in human and nonhuman primates, thus the model is appropriate for further investigation into the relationships between the behavioral and pharmacological effects of ketamine.

Although the present study examined the behavioral effects of ketamine only, the consistent use of the testing battery permits comparison with prior studies. Of particular interest is a comparison with the effects of muscarinic cholinergic blockade, a strategy which has been used extensively to model memory failure in nonhuman models (see Bartus, 2000, for review), since ketamine increases acetylcholine release in the frontal cortex and

hippocampus of rodents (Nelson et al. 2002; Sato et al. 1996; Wang et al. 2000) and can directly inhibit M1 muscarinic cholinergic receptors *in vitro* (Durieux and Nietgen 1997). (That study also suggested that the preservative benzethonium chloride, which is included in the commercial preparations Ketalar® and Ketaset®, may potentiate ketamine inhibition of M1 muscarinic cholinergic receptors however in the absence of any *in vivo* behavioral evidence such concerns are unlikely to account for the present results.) Finally, evidence suggests that behaviorally inactive doses of scopolamine and ketamine may act synergistically to impair recognition memory in nonhuman primates (Matsuoka and Aigner 1996). In comparison with our previous observations regarding the effects of scopolamine on the test battery measures (Taffe et al. 1999), ketamine induced a similar level of impairment of the SOSS and BMS tasks, less impairment of the RT task and greater impairment of PR. (The scopolamine study employed the delayed non-match-to-sample variant which has a 50% chance rate, thus the current DMS data are not directly comparable). In a direct comparison of the effects of scopolamine on vsPAL performance, ketamine did not prevent learning of pattern-location associations whereas scopolamine impaired learning in a dose- and difficulty-dependent manner (Taffe et al. 2002b). Thus, the learning component of vsPAL, and the RT and PR tasks, are most sensitive to differences between ketamine and scopolamine challenge. Future combined-challenge studies would be required to determine if ketamine and scopolamine interfere with SOSS and DMS in an independent or synergistic manner which may be important for full understanding of the mechanisms by which ketamine interferes with cognition.

Evidence of enhanced striatal dopamine release following ketamine derived from PET studies (Breier et al. 1998; Smith et al. 1998; Vollenweider et al. 2000) would have predicted a psychomotor stimulant effect (as with PCP), however there was little evidence for this in the present results. Specifically, release latencies in the RT procedure and response latencies in the other tasks were not decreased following any dose of ketamine but have been observed to be decreased following challenge with d-amphetamine or nicotine (unpublished observations). Furthermore, the preserved time-to-last-response in the PR procedure, combined with a trend for slowed response rate and fewer reinforcers acquired, observed at the intermediate dose suggests that sustained attention was relatively insensitive to ketamine. This interpretation is consistent with observations of preserved percent-task-completed and the overall number of responses in the vsPAL procedure (Taffe et al. 2002b). Thus, the current findings would be most consistent with recent evidence that ketamine does not produce increases in extracellular dopamine in the striatum of macaques as measured by microdialysis (Adams et al. 2002; Tsukada et al. 2000), and rationales that the PET findings may not constitute evidence for ketamine-evoked increases in dopamine release (Kegeles et al. 2002).

In conclusion, recreational exposure to subanaesthetic doses of ketamine is likely to induce wide-ranging compromise of cognitive function ranging from mnemonic to attentional to motor domains. Even if such acute compromise of function is short lasting, it may produce significant secondary and tertiary health risks ranging from disruption of the ability to operate a motor vehicle to poor decisions regarding risky sexual behavior which may be of

particular importance for ketamine using subpopulations (Colfax et al. 2001; Mansergh et al. 2001; Mattison et al. 2001).

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Delayed Match to Sample

Figure 1.

Effect of ketamine on DMS performance. The mean ($\pm$ SEM; N=6) proportion of correct choices (upper panel) was reduced in a dose- and delay-dependent manner consistent with the interpretation that ketamine increased the rate of forgetting. Under baseline conditions, errors directed to the nonmatching foil stimulus were less likely than errors directed to the foil stimuli matched in either color or shape to the sample. Ketamine did not significantly increase the latency of responses. There are four choice stimuli in this procedure thus 25% correct represents chance responding. Filled symbols indicate a significant difference from vehicle performance within trial type. * indicates a significant difference from simultaneous trials, and ‡ indicates a significant difference from short delay trials, within a treatment condition. See text for full description of the statistical analysis.

Self-Ordered Spatial Search

Figure 2.

Effect of ketamine on SOSS performance. The mean ($\pm$ SEM; N=6) proportion of correct trials (upper panel) was reduced in a dose- and difficulty-dependent manner consistent with the interpretation that ketamine interfered with spatial working memory. Response latency (middle panel) was only significantly increased for 2-box trials at the highest dose of ketamine. Utilization of an optimized search strategy associated with improved performance was also impaired by ketamine (lower panel). Filled symbols indicate a significant difference from vehicle performance within trial type. * indicates a significant difference from 2-box trials, ‡ indicates a significant difference from 3-box trials, within a treatment condition and § indicates a significant difference from vehicle, collapsed across trial type. See text for full description of the statistical analysis.

Reaction Time

Figure 3.

Effect of ketamine on RT performance. The latencies were normalized relative to baseline scores (i.e., the dashed horizontal line indicates baseline performance) for each individual. The mean ($\pm$ SEM; N=6) movement time was significantly increased by ketamine however release latency was not significantly affected. * indicates a significant difference of the indicated dose from vehicle performance. See text for full description of the statistical analysis.

Progressive Ratio

Figure 4.

Effect of ketamine on PR responding. The highest dose of ketamine significantly impaired mean ($\pm$ SEM; N=7) reinforcers acquired and the time-to-last-response (upper panel) as well as the number of responses and the response rate (lower panel). * indicates a significant difference of the indicated dose from vehicle performance. See text for full description of the statistical analysis.

Bimanual Motor Skill

Figure 5.

Effect of ketamine on BMS performance. The highest dose of ketamine significantly impaired the mean ($\pm$ SEM; N=7) time required to retrieve 15 raisins. * indicates a significant difference of the indicated dose from vehicle performance. See text for full description of the statistical analysis.

TABLE 1

Schedule for the Drug Challenges

	Monday	Tuesday	Wednesday	Thursday	Friday
Week 1	DMS/RT/BMS Baseline	vsPAL/RT/BMS 0.30 mg/kg	PR/SOSS/BMS Baseline	DMS/RT/BMS Vehicle	PR/vsPAL/BMS 1.0 mg/kg
Week 2	PR/SOSS/BMS Baseline	DMS/RT/BMS 0.30 mg/kg	vsPAL/RT/BMS Baseline	PR/SOSS/BMS Vehicle	DMS/RT/BMS 1.0 mg/kg
Week 3	PR/vsPAL/BMS Baseline	PR/SOSS/BMS 0.30 mg/kg	DMS/RT/BMS Baseline	vsPAL/RT/BMS Vehicle	PR/SOSS/BMS 1.0 mg/kg
Week 4	DMS/RT/BMS Baseline	vsPAL/RT/BMS 1.78 mg/kg	PR/SOSS/BMS Baseline	DMS/RT/BMS Vehicle	PR/vsPAL/BMS 1.78 mg/kg
Week 5	PR/SOSS/BMS Baseline	DMS/RT/BMS 1.78 mg/kg	PR/vsPAL/BMS Baseline	PR/SOSS/BMS Vehicle	DMS/RT/BMS 1.78 mg/kg
Week 6	vsPAL/RT/BMS Baseline	PR/SOSS/BMS 1.78 mg/kg	DMS/RT/BMS Baseline	PR/vsPAL/BMS Vehicle	PR/SOSS/BMS 1.78 mg/kg
Week 7	DMS/RT/BMS Baseline	vsPAL/RT/BMS 1.0 mg/kg	PR/SOSS/BMS Baseline	DMS/RT/BMS Vehicle	PR/vsPAL/BMS 0.30 mg/kg
Week 8	PR/SOSS/BMS Baseline	DMS/RT/BMS 1.0 mg/kg	PR/vsPAL/BMS Baseline	PR/SOSS/BMS Vehicle	DMS/RT/BMS 0.30 mg/kg
Week 9	vsPAL/RT/BMS Baseline	PR/SOSS/BMS 1.0 mg/kg	DMS/RT/BMS Baseline	PR/vsPAL/BMS Vehicle	PR/SOSS/BMS 0.30 mg/kg

The schedule required to double-determine the effects of 3 doses of ketamine on all battery tasks; the effects of each dose were determined twice. Animals completed one of three memory tasks (vsPAL, DMS, SOSS), and either PR or RT on alternating days. The BMS task was completed at the end of each session. The behavioral schedule repeated every 3 weeks. Drug challenges were performed Tue and Fri in an ascending-descending order for each memory task combination. DMS, Delayed Match-to-sample; RT, Reaction Time; BMS, Bimanual Motor Skill; vsPAL, visuo-spatial Paired Associates Learning; SOSS, Self-Ordered Spatial Search.