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Effects of the NMDA Antagonist Ketamine on Task-Switching Performance: Evidence for Specific Impairments of Executive Control

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In humans, the effects of subanesthetic doses of ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, substantially impair executive control functions. Here, we consider whether ketamine exposure can provide an animal model for the effects of ketamine on executive control. Two monkeys (*Macaca mulatta*) performed a cued task-switching paradigm. We studied their behavior before and after a range of ketamine doses. We found that ketamine slowed overall performance and decreased overall accuracy, strongly impaired the capacity to ignore task-irrelevant information and, to a lesser degree, decreased accuracy when a task switch was required. This pattern of results is very similar to that found in studies of schizophrenic patients performing task-switching paradigms or the Stroop task. We conclude that ketamine in monkeys provides a good animal model for exploring the relationship between the glutamate system, executive control, and the symptoms of schizophrenia.
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INTRODUCTION

Executive control, that is, the mental capacity to control and coordinate other mental processes (Atkinson and Shiffrin, 1968; Butterfield and Belmond, 1977), is crucial to normal function. Aspects of executive control are impaired in many disease processes. For example, schizophrenic patients show thought disorders and an impaired capability to plan (Evans *et al*, 1997; Royall *et al*, 2002; Kravariti *et al*, 2005). These impairments have not only been characterized in neuropsychological tests, but also in studies of daily life activities. For example, Semkovska *et al* (2004) studied schizophrenic patients and healthy control subjects during daily life tasks, such as shopping and cooking. They found that schizophrenic patients have difficulty performing such tasks, and are particularly prone to omissions, repetitions, inappropriate switching between subcomponents of tasks (eg inefficient switching between working on different dishes of a dinner), and have difficulty maintaining attention.

Task-switching paradigms have frequently been used to study human executive functions (for an overview, see Monsell, 2003). Each trial of a cued task-switching paradigm begins with the presentation of a task instruction cue. This cue instructs a rule, which must then be applied to a subsequent target stimulus. For example, in a switch paradigm in which the target stimulus is a number, one cue might instruct the subject to determine whether or not the number is even, while another cue might instruct the subject to determine whether or not the number is greater than five. Both cues are often interleaved within one run of trials, such that volunteers often have to switch from doing an odd/even task to a low/high task (or *vice versa*). This design provides two independent measures of executive control: switch costs and congruity costs. The ability to switch from one task to another is measured by subtracting the performance on repetition trials from the performance on switch trials. The ability to ignore irrelevant information is measured by subtracting the performance on trials using a stimulus that instructs the same response on each task (a congruent stimulus, eg the digit '7', which is both odd and greater than five, and both of these classifications would call for the same button to be pressed in the paradigm) from performance using a stimulus that instructs different responses (an incongruent stimulus, eg the digit '3', which is odd but not greater than five, and these classifications would thus require opposite responses).

We can formulate hypotheses about the neuropharmacology of executive control by considering a disease like schizophrenia, which profoundly affects executive control (Evans *et al*, 1997; Royall *et al*, 2002; Kravariti *et al*, 2005). A

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number of theories link schizophrenia to neurotransmitter abnormalities. The dopamine hypothesis states that the symptoms of schizophrenia result from increased levels of the neurotransmitter dopamine (Carlsson and Lindqvist, 1963). Many studies support this theory, and many schizophrenia medications directly affect dopamine transmission. The glutamate hypothesis links schizophrenia to low levels of glutamate (Olney *et al*, 1999). Medications that increase glutamate levels relieve schizophrenia symptoms (Goff, 2000). The dopamine and glutamate hypotheses are not incompatible with one another, and the effects may even be causally linked (Kegeles *et al*, 2000). Still other neurotransmitter pathways are important in the pathophysiology of schizophrenia; see Laruelle *et al* (2003) for an overview.

N-methyl-D-aspartate (NMDA) receptor antagonists, like ketamine, are model systems for the study of the role of the glutamate system in schizophrenia. NMDA antagonists are known to mimic the neurobehavioral correlates of schizophrenia in healthy humans. For example, Adler *et al* (1999) found thought disorders in ketamine-treated healthy individuals that were indistinguishable from those of schizophrenic patients (but see also Krystal *et al*, 1999; Morgan *et al*, 2004). Schizophrenia-like saccadic disturbances were also observed in healthy subjects (Radant *et al*, 1998; Avila *et al*, 2002) and in monkeys (Condy *et al*, 2005) following ketamine treatment. There are also reports of memory impairments similar to those found in schizophrenic patients, although it remains unclear whether these reflect deficits of memory acquisition or maintenance (Radant *et al*, 1998; Krystal *et al*, 2000; Umbricht *et al*, 2000; Morgan *et al*, 2004; Rowland *et al*, 2005).

Studies comparing the effects of systemically administered pharmacological agents with the symptoms of schizophrenia should be considered as one way of testing predictions logically deduced from neuropharmacological theories. Although these studies cannot reveal the cause of schizophrenia, they can help validate neuropharmacological models of schizophrenia. The resulting animal model could be used to test specific pharmacologic interventions.

In the current report, we test, for the first time, the effects of ketamine on executive control in monkeys. Previously, we developed a monkey model of executive control (Stoet and Snyder, 2003a). We trained monkeys on a task-switching paradigm to measure behavioral correlates of task preparation and task interference, and to compare these correlates with human performance and human brain activity as measured with brain imaging techniques. The paradigm consists of two randomly interleaved tasks (Figure 1). At the beginning of each trial, animals were informed by a yellow or blue screen which of the two tasks was to be performed. This was followed first by a delay and then the delay was followed by a colored square whose center was either brighter or darker than the outer border. In the color task, the monkeys had to judge whether the color of the square was closer to red or to green, and in the pattern task the monkeys had to judge whether the square was brighter on the inside or on the outside (Figure 1b). The animals pressed a left or right response button to indicate their judgment. To measure switch costs, we compared behavior in switch trials (trials in which the task changed) with behavior in repetition trials (in which the task did not change). To measure congruity costs, we compared responses to response-incongruent and response-congruent stimuli.

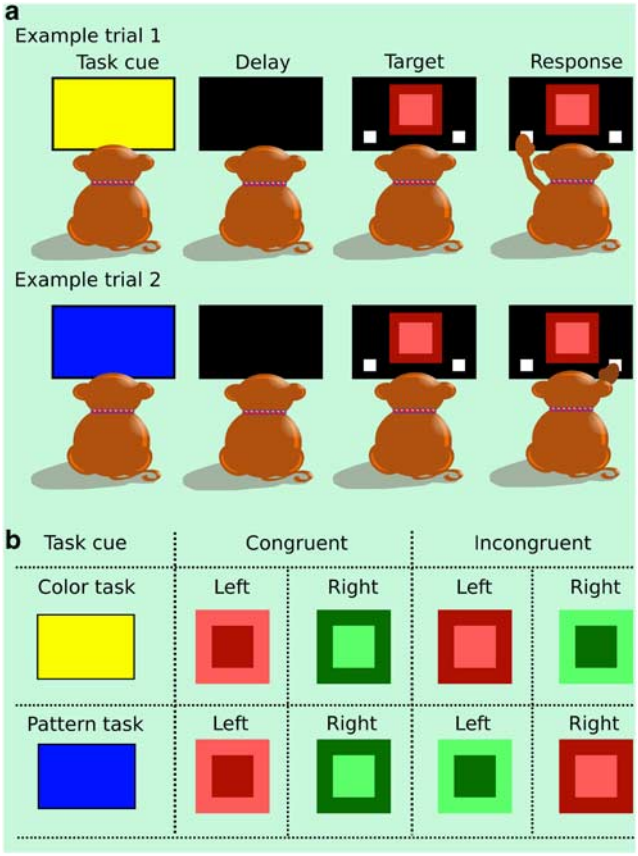

Figure 1 Experimental paradigm. (a) Every trial started with a task cue, which was either yellow or blue. Yellow indicated the color task and blue the pattern task. The task cue was followed by a delay period, followed by the target stimulus. Depending on the task cue and target stimulus, monkeys moved their left hand from the resting position (ie home key) to either the left or rightward-positioned response button on the touch-sensitive screen. The two example trials illustrate that identical incongruent target stimuli require different responses depending on the task. (b) Task cues, examples of target stimuli and their associated responses.

Using the task-switching paradigm, we found that monkeys and humans have a similar level of accuracy. Monkey switch costs were smaller than human switch costs, whereas costs of congruity were larger in monkeys (Stoet and Snyder, 2003a). Furthermore, we demonstrated that monkeys prepare the upcoming task prior to the appearance of the target stimulus, which suggests that monkeys are capable of representing abstract task information (Stoet and Snyder, 2003b). Using electrophysiological extracellular recordings from single neurons in the posterior parietal cortex, we identified a population of neurons which represents this abstract task information prior to and following stimulus appearance (Stoet and Snyder, 2004).

Here, we employ the same task-switching paradigm to test how two executive functions, the capacity to switch and the capacity to ignore irrelevant information, are affected by subanesthetic doses of ketamine in the monkey. While the typical neuropsychological tests of cognitive functions are extremely valuable in clinical settings, the major advantage

of our paradigm is that it measures executive control more precisely. A more precise measurement of executive control is necessary to resolve deficiencies and inconsistencies in the schizophrenia and ketamine data currently available.

We expected that ketamine would produce large congruity costs and little or no switch costs in monkeys. We based our expectations on studies of schizophrenia in humans. Patients show normal (Cools *et al*, 2000; Manoach *et al*, 2002; Turken *et al*, 2003) or nearly normal switch costs (Meiran *et al*, 2000). They also show increased congruity costs in saccade/anti-saccade paradigms (Manoach *et al*, 2002) and in Stroop tasks. However, it should be noted that the cost of making an antisaccade compared to a regular saccade may not reflect the same process as congruity costs in task-switching paradigms (see Discussion). In a Stroop task, subjects name the ink color of a word which is either congruent (eg 'red' printed in red ink) or incongruent (eg 'red' printed in green ink) with the meaning of the word. In healthy subjects, responses to incongruent stimuli are slower and less accurate than responses to congruent stimuli (Stroop, 1935). These congruity costs are even larger in schizophrenic patients (Abramczyk *et al*, 1983; Wysocki and Sweet, 1985; Everett *et al*, 1989; Hepp *et al*, 1996; Barch *et al*, 1999).

MATERIALS AND METHODS

Subjects

Two male rhesus monkeys (*Macaca mulatta*), weighing 6.0 and 6.3 kg, were tested (IDs: F & T). Monkey F was also used in three previous task-switching studies (Stoet and Snyder, 2003a, b, 2004).

Apparatus and Stimuli

Stimulus presentation, trial selection, and data collection were controlled by computers running custom software. During data collection, monkeys were seated in a sound-attenuating dark room.

Stimuli were projected onto a touch-sensitive rectangular screen (30×20 cm) positioned 25 cm in front of the animals. A touch-sensitive (capacitive) button (*home key*, Efector, Inc.) was positioned 2 cm below the screen. The animals could freely move their arms and easily touch the screen.

Response buttons were white squares (4.6° of visual angle on a side) at the left and right bottom of the screen. The distance between the two squares was 15.5 cm (33.3°). Task cues were presented by setting the color of the entire screen to yellow or blue. Targets were squares (13.6°) presented near the center of the screen. The outer border of these squares, which comprised one-half of the total surface area, was either more or less luminant than the inside of the square (Figure 1a, b). Target color was randomly chosen from a large number of different shades of red and green. The different combinations of color and luminance contrasts yielded 18 144 different target stimuli. A large range of color and luminance was chosen to encourage the use of general rules rather than 'lookup tables' for solving the tasks. Every color and luminance combination that was used could be easily distinguished by a human observer.

Procedure

Each trial started with the task cue, which stayed on screen for 250 ms, followed by a blank screen for 400 ms. Premature removal of the paw from the home key resulted in immediate termination of the trial. The delay was followed by a target, which disappeared as soon as the monkey initiated his response. The monkeys only used their left hand to make a response. The monkey had 2000 ms to touch within ~6 cm of the left or right response button. We used this very large window in order to encourage a rapid response rather than a precise touch. Reaction time (RT) was measured as the interval between target onset and home key release. Monkeys were rewarded for correct responses with a drop of water (0.05–0.33 ml). Incorrect trials were not rewarded and were followed by a 1 s wait period. The intertrial interval was 350 ms.

Based on other monkey studies of ketamine, we used a range of doses at which monkey behavior would be only minimally affected. At doses of 10–25 mg/kg, ketamine produces anesthesia. At doses of 5–10 mg/kg, ketamine acts as a dissociative agent. Subcutaneous doses of 1 mg/kg but not 0.5 mg/kg produce signs of dystonia, bradykinesia, and impaired locomotor activity (Shiigi and Casey, 1999). Taffe *et al* (2002) found impaired performance in monkeys trained on a neuropsychological test battery at ketamine doses of 1 mg/kg but not at 0.3 mg/kg. In humans, the threshold for cognitive effects is similar, at around 0.3–1.0 mg/kg (Ghoneim *et al*, 1985; Morgan *et al*, 2004). For comparison, neuronal damage and death (apoptosis) have been reported in rats after a cumulative dose of 140 mg/kg (Ikonomidou *et al*, 1999).

Ketamine (Ketaset, Fort Dodge, IA) doses were diluted in saline so that the volume of the injection was fixed at 0.3 ml, independent of the dose. Dosages were 0.07 (monkey T only), 0.18, 0.32, 0.57, 0.75 (monkey T only), and 1.0 mg/kg. Only one dosage was used in each experiment, and experiments were separated in time by at least 1 day. Dosages were randomly ordered. In each experiment, monkeys first performed 240 baseline trials. The ketamine was then injected intramuscularly over a period of ~2 s in order to minimize any painful or distracting sensation. Animals generally did not react to the injection. We recorded the time of the injection, and the start time of each trial was logged automatically with the data. Following the ketamine injection, monkeys performed on average 1159 trials.

RESULTS

We analyzed RT and error rate (PE) as a function of trial type (switch or repetition; congruent or incongruent), ketamine dose, and elapsed time since the injection in each of the two monkeys. Switch trials are trials following a correct trial of the alternate task. Repetition trials are trials following a correct trial of the same task.

Behavior before ketamine injection (baseline) was similar to previously reported studies (Stoet and Snyder, 2003a, b). Baseline RT $\pm$ SD was 288 ± 38 ms in monkey T and 251 ± 23 ms in monkey F. Baseline error rates were 3.0 and 4.3%, respectively.

We analyzed the effect of dose and elapsed time since the injection on the mean reaction time (Figure 2). We found a dose-dependent effect of ketamine, with a peak RT across conditions and monkeys occurring between 5 and 15 min following each injection.

To further characterize the behavioral effects of ketamine, we plotted the mean RT during the time interval from 5 to 15 min against the dosage on a semilogarithmic scale (Figure 3, top). An increasing effect on RT following increasing ketamine doses can be recognized for doses higher than 0.3 mg/kg. A similar trend can be seen in the error rates (Figure 3, bottom).

To test our hypothesis regarding ketamine and executive control, we analyzed the costs of switching and the costs of a response-incongruent stimulus. Switch costs were calculated by subtracting the average RT or PE in incongruent repetition trials from the average RT or PE in the incongruent switch trials. Similarly, congruity costs were calculated by subtracting scores on trials with response-congruent stimuli from scores on trials with response-incongruent stimuli. In the RT data, we excluded error trials and trials that immediately followed an error trial. In the error data, we analyzed only errors that followed a correctly performed trial. We included trials that occurred in the interval between 5 and 15 min following injection.

At baseline, congruity costs in the two animals were 28 and 2 ms, respectively (Figure 4, dashed blue lines). At the highest dose of ketamine used (1 mg/kg), these costs increased by 189 and 112 ms, respectively (Figure 4, solid blue lines). The effect on error rates was similarly dramatic (from 7 to 43% in monkey T, and from 8 to 45% in monkey F). Even at a dose of 0.57 mg/kg, which increased mean RT by only 70 and 68 ms, respectively, and increased the overall error rate by only 9.8 percentage points and 6.9 percentage

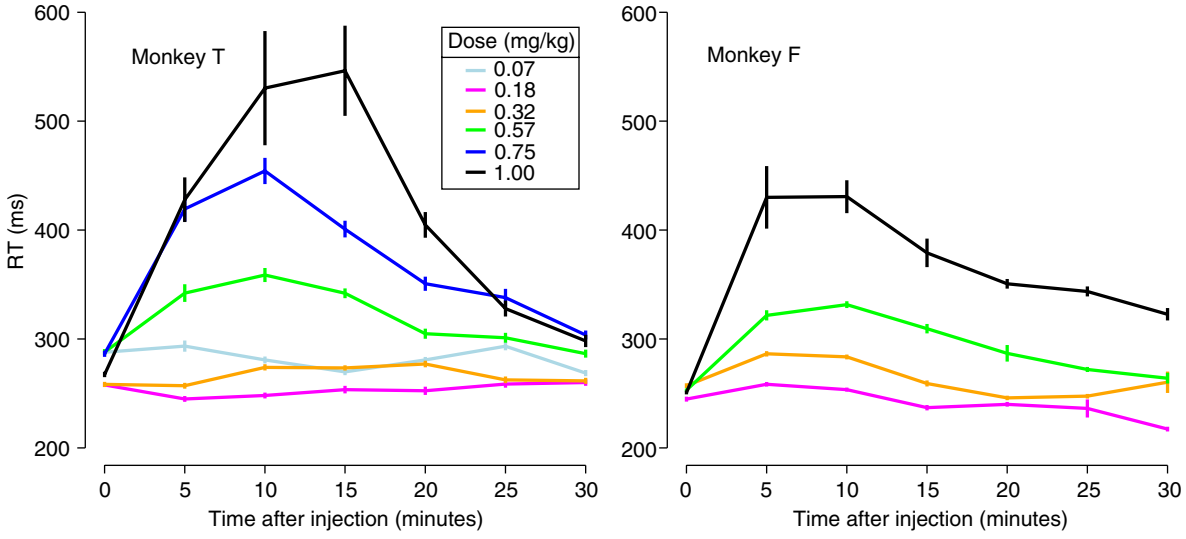

Figure 2 Response time as a function of elapsed time (in bins of 5 min) since injection time for monkey T (left panel) and monkey F (right panel). The curve color indicates the dose (see legend). Error bars indicate standard error of the mean.

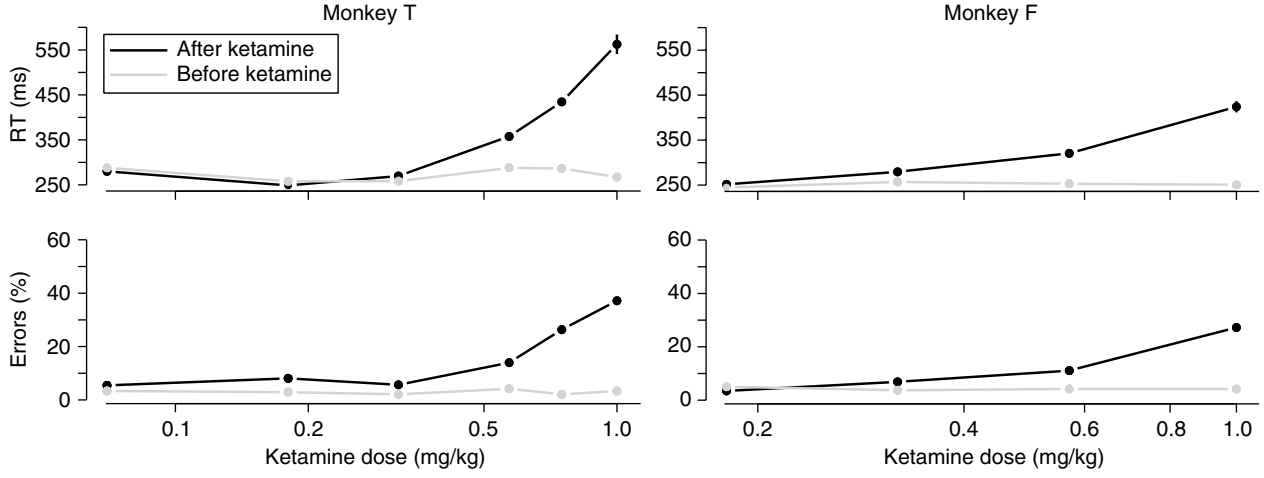

Figure 3 Mean response time (RT) (top panels) and error rate (bottom panels) as a function of dose during the 5–15 min interval following ketamine injection for monkey T (left panels) and monkey F (right panel). Black lines indicate measurements following ketamine and gray lines indicate measurement during the baseline condition (ie measured in the same experimental session before the ketamine injection).

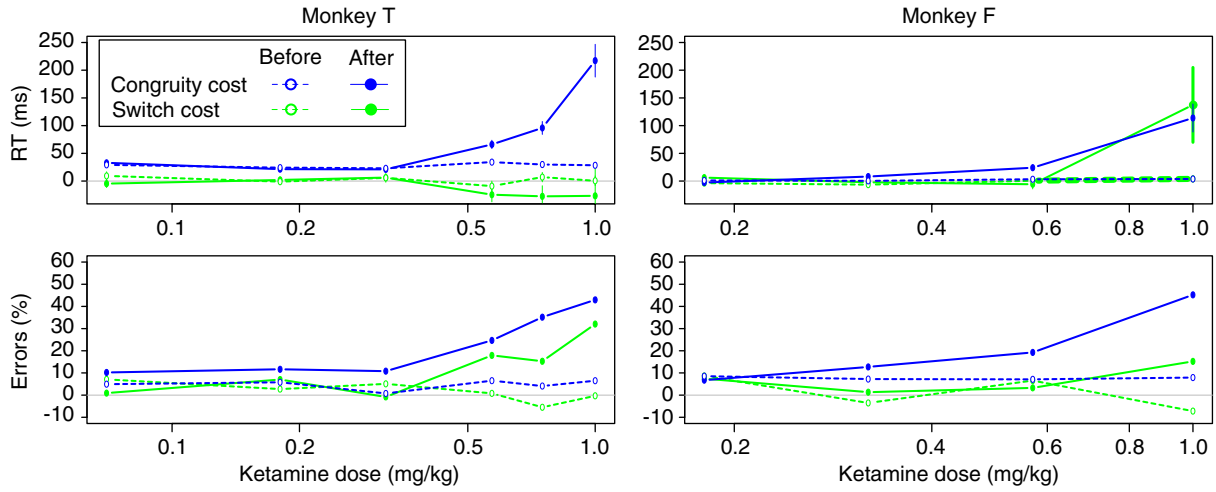

Figure 4 Switch and congruity costs in response time (top panels) and error rate (bottom panels) as a function of dose during the 5–15 min interval following ketamine injection for monkey T (left panels) and monkey F (right panels). Blue lines indicate the congruity costs, and green lines the switch costs. Solid lines indicate the effect measured in the 5–15 s interval following ketamine injection, whereas dashed lines indicate the effect measured in the same session before the ketamine injection was administered. For both monkeys, the congruity costs are higher in the post-ketamine condition (solid blue lines) than in the baseline conditions (dashed blue lines). This was the case for both reaction times (top panels) and error rates (bottom panels). In contrast, ketamine had little effect on switch costs when measured in response times (top panels), though there were effects on switch errors (bottom panel).

points, respectively, the congruity costs were increased by 66 and 24 ms, respectively, for RT, and by 25 and 19 percentage points for PE.

The current data set confirmed the previous report (Stoet and Snyder, 2003a) of no switch costs in either RT or PE in the baseline condition (Figure 4, dashed green lines). The effects of ketamine on switch costs were substantially smaller than the effects on congruity costs. Ketamine had no significant effect on switch costs (solid green lines) in RT at even high doses (−25 ms and −6 ms after 0.57 mg/kg; −27 and 137 ms after 1 mg/kg; all effects >0.05; −25 and 137 ms both $P<0.1$). These same doses of ketamine did, however, cause a small increase in error rate that was statistically significant in one animal (T: 18% after 0.57 mg/kg, $P<0.05$; 32% after 1 mg/kg, $P<0.05$) and showed a trend in the other at the highest dose (F: 3% after 0.57 mg/kg, $P>0.7$; 15% after 1 mg/kg, $P<0.2$).

DISCUSSION

We studied the behavioral effects of ketamine in a task-switching paradigm to test an animal model of executive control. Previous work has demonstrated that subanesthetic doses of ketamine impair cognition in monkeys (Shiigi and Casey, 1999; Taffe *et al*, 2002). We asked whether ketamine in monkeys might model some of the specific impairments of executive control observed in schizophrenia. As expected, performance was slower and less accurate following ketamine doses between 0.3 and 1 mg/kg. More importantly, we found that ketamine specifically impairs the capacity to respond to task-incongruent stimuli and, to a lesser extent, the capacity to switch between tasks. These impairments are similar to those described in patients with schizophrenia.

Our data suggest that ketamine acts differently on the capacities to switch tasks and to ignore irrelevant stimuli. In both monkeys, ketamine induced congruity costs of more than 100 ms in the latency and more than 30 percentage points in the error rates. However, ketamine had only a minor effect on switch costs, increasing error rates slightly but having no significant effect on switch latency. In normal monkeys, unlike normal humans, switch costs are not a ubiquitous finding across tasks and task conditions; they occur only with short intertrial intervals (Stoet and Snyder, 2003a). If the mechanism by which switch costs occur in the normal human is absent or substantially different in the monkey, then this might itself explain the fact that ketamine has only a small effect on monkey switch costs. This issue could be resolved by determining whether ketamine impairs switch costs in normal humans.

Might the fact that we observe only small and inconsistent effects of ketamine on monkey switch costs reflect a lack of statistical power? This is unlikely for several reasons. First, we obtained data from a very large number of trials (>1000 per animal per dosage level). Second, we are able to reliably resolve small effects on congruity costs using these same data. Finally, the results from the two animals are extremely similar. However, given that individual human responses to ketamine are variable and that we tested only two animals, we cannot rule out the possibility that our two monkeys represent outliers in the population.

The increased congruity costs that we found in the monkeys are similar to the well-documented difficulty of schizophrenic patients to ignore irrelevant stimulus features, as in the Stroop task (Abramczyk *et al*, 1983; Wysocki and Sweet, 1985; Everett *et al*, 1989; Hepp *et al*, 1996). However, when using just congruent and incongruent stimuli it cannot be determined whether congruity costs are due to facilitation in the congruent condition or to interference in the incongruent condition, or to both. To determine this, Barch *et al* (1999) performed a Stroop study including neutral stimuli. They found that both healthy subjects and schizophrenic patients show stronger facilitation than interference, and that this pattern was even more

pronounced in patients. As we did not have a neutral stimulus category, we could not determine whether the effect we observed in the animals reflected facilitation in the congruent condition or interference in the incongruent condition.

Our findings of increased congruity costs can be considered in relation to other tasks in which a stimulus can instruct more than one response. In the prosaccade/antisaccade paradigm (Fischer and Weber, 1992), subjects make saccades either towards or away from a visual target. Response times are slower in the antisaccade condition. These slowed responses may be similar to congruity costs, inasmuch as they arise from the inherent conflict between two possible responses. Of course, antisaccade effects and switch paradigm congruity costs, though related, are not identical. Nonetheless, it is interesting to note that, in an antisaccade/prosaccade task-switching paradigm, schizophrenic patients show intact switch capabilities combined with an increased difficulty to suppress the default prosaccade (Levy *et al*, 1998; Barton *et al*, 2002; Manoach *et al*, 2002; Reuter and Kathmann, 2004).

Our finding of weak effects of ketamine on switch costs are also matched by studies of schizophrenia in humans. In cued task-switching paradigms, task switching is intact (Cools *et al*, 2000; Manoach *et al*, 2002; Turken *et al*, 2003) or only slightly impaired (Meiran *et al*, 2000). Yet, on the basis of the (uncued) Wisconsin Card Sorting Task (WCST), schizophrenic patients are often characterized as having significant difficulty switching their attention from one task to another (Franke *et al*, 1992; Pantelis *et al*, 1999). However, the WCST is multidimensional and failure can represent one of many potential deficits in these patients. Therefore, it is incorrect to conclude, on the basis of WCST results, that there are switch defects in schizophrenia. In fact, when explicit task-switching cues are provided, patients show marked improvement on the WCST (Goldman *et al*, 1992). One possible explanation for the difference in performance is that the noncued WCST draws more on working memory than the cued version of the task. Several studies have suggested that it is the working memory load that determines the ability of schizophrenic patients to switch between tasks (Meiran *et al*, 2000; Manoach *et al*, 2002). Finally, Li (2004) has challenged the notion that schizophrenic patients have difficulty switching tasks even in the uncued WCST by showing that, across many studies, the ratio of perseverative errors (which are analogous to switch errors) to nonperseverative errors in patients is only slightly increased.

In summary, the current data suggest that the dose-related impact of the NMDA receptor antagonist ketamine on executive control functions in non-human primates resembles the impact of NMDA receptor antagonists on executive control functions in humans. In particular, both monkeys exposed to low-dose ketamine and human patients with schizophrenia show significant impairments in generating task-specific responses to stimuli, but show little impairment in switching from one task to another. These findings support the use of ketamine exposure in monkeys as a model system for studying schizophrenia, and more generally, support the use of the task-switching paradigm as a model system for investigating different aspects of executive function in the non-human primate.

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