

Does Ketamine-Mediated N-methyl-D-aspartate Receptor Antagonism Cause Schizophrenia-like Oculomotor Abnormalities?

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Evidence from histological and pharmacological challenge studies indicates that N-methyl-D-aspartate (NMDA) receptor hypofunction may play an important role in the pathophysiology of schizophrenia. Our goal was to characterize effects of NMDA hypofunction further, as related to schizophrenia-associated neuropsychological impairment. We administered progressively higher doses of ketamine (target plasma concentrations of 50, 100, 150, and 200 ng/ml) to 10 psychiatrically healthy young men in a randomized, single-blind, placebo-controlled design and assessed oculomotor, cognitive, and symptomatic changes. Mean ketamine plasma concentrations approximated target plasma concentrations at each infusion step. Verbal recall, recognition memory, verbal fluency, pursuit tracking,

visually guided saccades, and fixation all deteriorated significantly during ketamine infusion; lateral gaze nystagmus explained some, but not all, of the smooth pursuit abnormalities. We concluded that ketamine induces changes in recall and recognition memory and verbal fluency reminiscent of schizophreniform psychosis. During smooth pursuit eye tracking, ketamine induces nystagmus as well as abnormalities characteristic of schizophrenia. These findings help delineate the similarities and differences between schizophreniform and NMDA-blockade-induced cognitive and oculomotor abnormalities.

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The noncompetitive N-methyl-D-aspartate (NMDA) antagonists, phencyclidine (PCP) and ketamine, cause dissociative, cognitive, and perceptual phenomena similar to those observed in schizophreniform psychoses

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(Lear et al. 1959; Luby et al. 1959; Corssen and Domino 1966). Despite the activity of PCP and ketamine at other receptors, NMDA receptor antagonism is probably responsible for these effects. For example, naloxone fails to reverse ketamine-induced psychosis (Byrd et al. 1987), suggesting that the μ -binding properties of ketamine are not responsible for the psychotomimetic effects. Involvement of sigma receptors in the action of ketamine is unlikely, because the behavioral effects of ketamine correlate with NMDA, but not sigma, receptor binding affinity (Ginski and Witkin 1994). The presence of glutamatergically mediated psychotomimetic effects of ketamine is also congruent with histological (Benes et al. 1991; Benes et al. 1992; Benes 1995; Simpson

et al. 1991; Ishimaru et al. 1994; Akbarian et al. 1996) and neuroimaging (Bartha et al. 1997) evidence for glutamatergic abnormalities in schizophrenia (see also Olney and Farber 1995).

Detailed description of the psychological, cognitive, and neurological effects of experimental NMDA receptor blockade will help to define the roles of these receptors in normal and abnormal brain function. In pursuit of this goal, Krystal et al. (1994), Malhotra et al. (1996) and Hartvig et al. (1995) all found that intravenous administration of ketamine induces positive and negative symptoms of schizophrenia in a dose-dependent manner. These investigators also found that intravenous ketamine caused cognitive impairments similar to those noted among schizophrenia patients. Lahti et al. (1995) found that intravenous ketamine caused dose-dependent increases in psychosis among agitated schizophrenia patients. Finally, Vollenweider et al. (1997) demonstrated that subanesthetic doses of (S)-ketamine caused increased metabolism in a variety of cortical and subcortical areas and that some of these increases were associated with psychotic symptoms.

In addition to the cognitive and symptomatic domains addressed by these studies, oculomotor abnormalities are a widely employed method of assessing the pathophysiology (Ross et al. 1995; Schreiber et al. 1995; Grawe and Levander, 1995), familial pattern (Clementz et al. 1994), and genetics (Holzman et al. 1988; Grove et al. 1992) of schizophrenia and other neurological conditions. A detailed description of the oculomotor effects of ketamine infusion will further define the role of NMDA receptors in normal and abnormal brain function.

The goal of the present study was to determine the pattern of oculomotor deficits resulting from noncompetitive antagonism of NMDA receptors with subanesthetic doses of ketamine. We hypothesized that ketamine will cause decreased gain and increased catch up saccade frequency during eye tracking, slowed open-loop gain during a step ramp task, increased frequency of saccades during fixation, decrements in antisaccade performance, but no change in visually guided saccade parameters. We also concurrently assessed the cognitive (verbal fluency and verbal memory) and psychological effects of the ketamine infusion. We assessed all the measures at baseline and at four progressively increasing plasma levels of ketamine.

METHODS

Subjects

Ten normal male volunteers (aged 21–25) who had previously participated in another study in our laboratory were recruited through word of mouth. All subjects received a Structured Clinical Interview for *DSM-III-R*,

performed by a board certified psychiatrist (DSC), that demonstrated absence of all axis I disorders, including substance abuse. All subjects provided written informed consent after study procedures were explained to them and were paid \$100 for participation in the study. Subjects refrained from the use of alcohol the evening prior to the study and had no oral intake beginning at midnight prior to study days. Although we did not obtain urine toxicology screens, subjects were observed and interviewed in detail to verify absence of substance abuse.

Protocol

Because an anesthesiologist was not always available, but was deemed necessary for safety reasons during the ketamine (but not placebo) infusion, subjects, but not the investigators, were blinded. Intravenous catheters for the infusion and for obtaining blood for determination of ketamine concentrations were placed in the right and left arms, respectively, and the study began approximately 30 minutes later. Ketamine was administered by computer-assisted continuous infusion (CACI) with a Harvard Pump 22 (Harvard Apparatus) syringe pump controlled by a DOS-based computer and the Stanpump program (Steven L. Shafer, M.D., Department of Anesthesiology, Stanford University). The Stanpump program utilizes a "BET" (bolus-elimination-transfer) infusion scheme to attain a steady-state plasma concentration nearly instantaneously, by combining a bolus, a constant rate infusion to compensate for drug elimination, and an exponentially decreasing infusion to compensate for drug distribution or transfer (Kruger-Theimer 1968). Pharmacokinetic parameters for ketamine were taken from a previous study (Domino et al. 1984). The target concentrations were designed to approximate the range of concentrations hypothetically achieved by the low and high doses infused in the Krystal et al. (1994) and Malhotra et al. (1996) studies; the total dose of ketamine infused was 0.97 mg/kg over 2 h. Ketamine plasma concentrations were determined by gas chromatography mass spectrometry (Kharasch and Labroo 1992).

Identical series of measurements were made at ketamine target plasma concentrations of 0, 50, 100, 150, and 200 ng/ml in the following sequence. Four minutes after the CACI pump initiated the dosing step, a blood sample was obtained followed by the oculomotor (fixation, visually guided saccades, smooth pursuit eye tracking, and antisaccades), attention and recall memory tasks, self-ratings on a visual analog scale, recognition memory, and verbal fluency tasks. Subjects were monitored for vital sign and significant mental status changes. Two minutes prior to the end of the step, a blood sample was obtained again.

Eye Movement Recording and Initial Analysis

Our techniques for presentation of oculomotor stimuli, acquisition and recording of horizontal eye movements, and data analysis have been reported in detail in recent publications (Roy-Byrne et al. 1995; Radant and Homer 1992; Litman et al. 1994; Ross et al. 1994). Software-generated dependent measures for the smooth pursuit, visually guided saccade, antisaccade, and step ramp tasks have excellent test-retest reliability in our laboratory (Roy-Byrne et al. 1995).

Eye Movement Tasks

Visually guided saccades were elicited by presenting 37 pseudorandom targets, each of 2 s duration. Distance between successive targets varied from 3 to 27°, in 3° increments. The sequence was balanced so that each size jump in a given direction occurred twice.

The antisaccade task consisted of 20 repetitive pseudorandom cycles starting with central fixation (2,000 ms), an antisaccade cue (3, 6, 9, 12, or 15° to the left or right, 1,000 ms) and finally, the appearance of a target in the antisaccade location (800 ms).

The pursuit task consisted of a trapezoidal pattern with 10°/s constant velocity ramps (14 total, each lasting, 3,000 ms) and fixation epochs at the lateral extremes of the display (+/− 15°) of 1,400 ms. To quantify nystagmus during the smooth pursuit task, we determined the frequency of saccades (i.e., the fast component of nystagmus) that moved away from central fixation during the 1,400 ms lateral fixation periods.

To assess the smooth pursuit system better, a step ramp task (Rashbass 1961) was administered to six of the subjects during both drug and placebo. This task consisted of 2,000 ms of central fixation followed by a small step and then a ramp in the opposite direction (at 10 or 20°/s); the step prior to the ramp was constructed so that the target crossed the midline 100 ms after the step.

The fixation task consisted of an initial 30 s of simple fixation on a central target. After the initial 30 s, repetitive distractor stimuli, consisting of a 450 ms duration target at 2.5, 5, or 7.5° to the left or right of central fixation, were presented in a pseudorandom fashion. The central fixation target was turned off while each distractor stimulus was present and turned off while each distractor stimulus was present and turned back on during the 1,000 to 2,800 ms interval between each distractor stimulus. Subjects were instructed to “ignore any blinking dots you might see and just stare at the center of the screen.” Performance was quantified by determining the frequency of saccades during the distractor and nondistractor conditions.

Different versions of the fixation, visually guided saccade, antisaccade, and step ramp tasks were created

for each assessment point in the protocol to prevent subjects from learning the pseudorandom patterns.

Memory, Verbal Fluency, and Psychological Measures

A 12-word memory task was administered to assess attention, recall, and recognition (Roy-Byrne et al. 1987). Modified versions of Benton's controlled Oral Word Association Test (Benton et al. 1983) were used to assess verbal fluency. Because we needed to perform the test at each time point, 10 different letters were used (two at each time point). At each step, subjects were asked to rate the current level of 13 psychological symptoms on a 10-cm visual analog scale anchored with low, medium, and high.

Data Analysis

Standard dependent measures were obtained from all the oculomotor, verbal memory, and verbal fluency tasks. Visual analog scale ratings were converted to percentage (0–100%). A Bonferroni correction was applied to significance values from the analysis of the psychological symptoms. Data were analyzed with repeated measures within-subjects analyses of variance (ANOVAs). Smooth pursuit measures showing significance on the initial ANOVA, were further analyzed with a repeated measures, within-subjects analyses of covariance (ANCOVAs), using frequency of nystagmus as the covariate.

RESULTS

Plasma Ketamine Concentrations

One value from one subject at the highest dose of ketamine was missing because of failure of the blood drawing line. Plasma ketamine concentrations increased linearly with the infusion step (Figure 1; correlation between infusion step and blood concentration: $r = .97$; $n = 8$, $p < .001$). Plasma ketamine concentrations also rose from the beginning to the end of each step, especially during the first step. The main effect of infusion step was highly significant ($F[3,71] = 98.38$, $p < 10^{-15}$), and the main effect of time of blood draw within step was slightly less significant ($F[1,71] = 16.44$, $p < .0001$). The interaction between step and time of blood draw within the step was not significant ($p > .10$).

All but one subject spontaneously reported feelings of intoxication and perceptual distortion during the ketamine infusion, but no subject complained of oversedation and ratings of “feeling drowsy” were not significantly higher with ketamine than with placebo (repeated measures ANOVA, $F[4,36] = 2.46$, $p > .05$). Three sub-

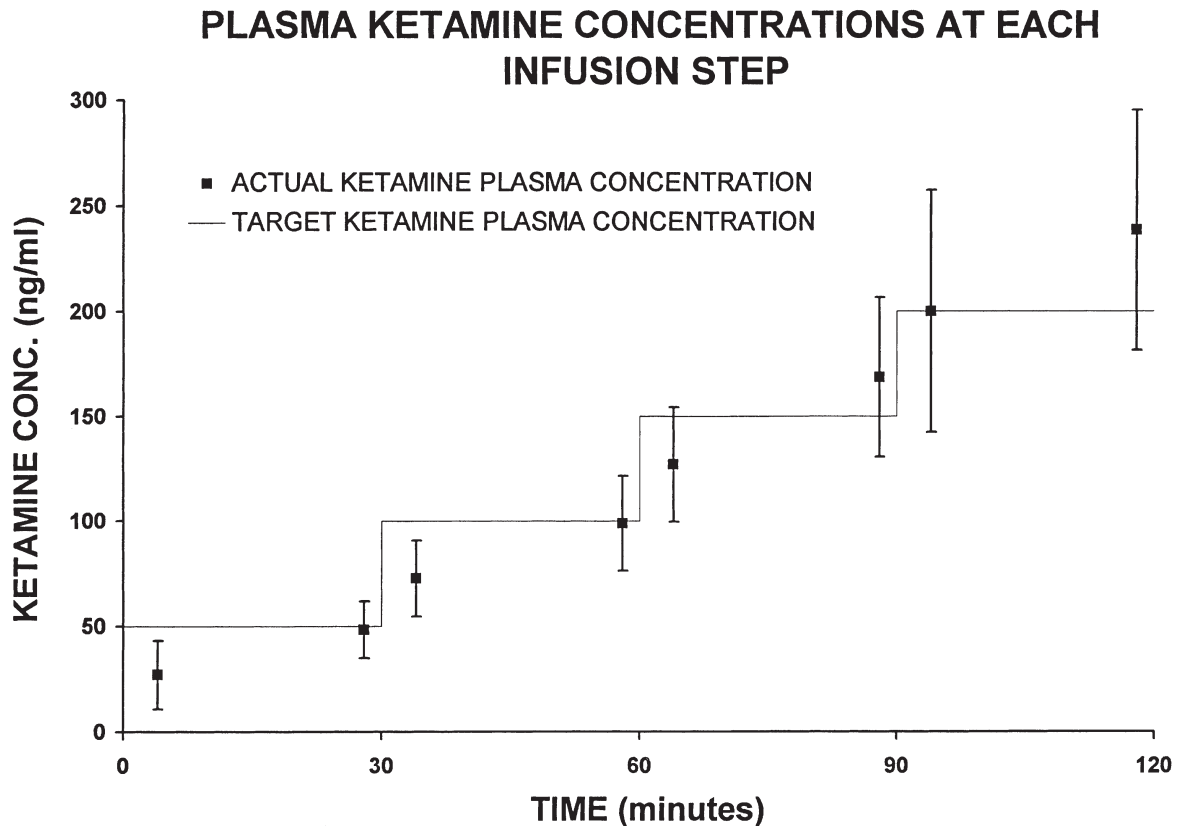


Figure 1. Plasma ketamine concentrations at each infusion step, mean (+/- SC) plasma ketamine concentrations at each infusion step. A two-by-four ANOVA showed a significant main effects of infusion step ($F(3,71) = 98.38, p < 10^{-5}$) and beginning vs. end of each step ($F(1,71) = 16.44, p < .0001$) but no significant interaction between the two ($F(3,71) = 1.99, p > .10$).

jects became moderately dysphoric, and one subject developed nausea and vomited after termination of the ketamine infusion. All subjects had clinically observable lateral gaze nystagmus at the two highest doses of ketamine. Despite these effects of ketamine, all subjects held their heads still and generally approximated the target during all the eye-tracking tasks, indicating the absence of gross sedation or inability to cooperate.

Memory, Verbal Fluency, and Self-Ratings

Ketamine caused dose-dependent impairment in delayed recall and dose-independent impairment in recognition memory, but had no effect on attention (Table 1). Except for suspiciousness and drowsiness, all self-ratings increased significantly more during the ketamine as opposed to the placebo infusion (Figure 2). Statistically, ketamine caused dose-dependent changes in verbal fluency; however, inspection of the data revealed that this was primarily because of poor verbal fluency during the fourth step of the ketamine infusion combined with exceptional verbal fluency during the

last placebo step. There was no sustained, recognizable pattern of ketamine-induced changes in verbal fluency.

Oculomotor Function

Visually Guided Saccades. Ketamine infusion caused a dose-dependent decrease in peak velocity and a dose-independent increase in latency of visually guided saccades (Table 2).

Fixation. Although baseline saccadic frequencies were higher on ketamine infusion days for both fixation with and without distraction, these differences did not reach statistical significance. During fixation with no distractor, there was significantly decreased saccadic frequency with step, but no effect of ketamine infusion. Ketamine also caused a dose-independent increase in saccadic frequency during the fixation with distractor task (Table 2); however, after correction for the higher baseline value on the ketamine day, there was no significant difference.

Antisaccade Task. Initial inspection of the data showed a steady decrease in performance with ket-

Table 1. Cognitive Measures During Ketamine and Placebo Infusions

Task		Step					ANOVA		
		1	2	3	4	5	Step F(4,36)	Plac/Ketam. F(1,9)	Interaction F(4,36)
Attention	K	7.4 (0.4)	8.6 (0.6)	8.3 (0.6)	7.6 (0.8)	6.9 (0.8)	0.58	0.59	1.20
	P	8.4 (0.7)	8.1 (0.6)	7.3 (0.5)	8.2 (0.6)	8.7 (0.6)	ns	ns	ns
Recall Memory	K	8.0 (0.5)	6.4 (0.6)	4.6 (0.5)	4.6 (0.9)	4.5 (0.5)	16.34	4.23	7.60
	P	6.1 (0.8)	7.5 (0.6)	6.4 (0.5)	7.1 (0.6)	7.1 (0.6)	$p < .003$	$p < .007$	$p < .0001$
Recognition Memory	K	10.0 (0.5)	8.9 (0.6)	8.3 (0.8)	7.4 (0.6)	7.8 (0.8)	5.48	23.67	1.97
	P	10.8 (0.4)	10.3 (0.4)	9.9 (0.4)	9.4 (0.4)	11.0 (0.3)	$p < .001$	$p < .0001$	ns
Verbal Fluency	K	13.7 (1.5)	13.4 (1.4)	13.5 (1.0)	10.9 (0.7)	13.6 (1.3)	1.06	10.18	4.91
	P	13.4 (1.0)	12.8 (0.90)	13.3 (1.0)	12.7 (0.7)	16.1 (0.9)	ns	$p < .0001$	$p < .003$

Means (with standard errors in parentheses) of the four cognitive measures at each step during ketamine and placebo infusion. The upper row (K) next to each test shows measures during the ketamine infusion, the lower row (P) shows measures during the placebo infusion. The last three columns show the results of 2 × 5 repeated measures ANOVAs. All of the verbal memory tasks involved a list of 12 words. Verbal fluency is number of words produced in 1 min starting with a given letter.

amine. However, the number of incorrect saccades did not change significantly with step or type of infusion or the interaction between the two (Table 2), indicating that this was a spurious phenomenon. There was no global change in performance on this task with ketamine infusion, because the total number of identifiable saccades (both correct, away from the stimulus, and in-

correct, toward the stimulus) did not vary significantly with step, ketamine vs. placebo infusion, or the interaction between the two ($p < .10$ for all ANOVAs).

Smooth Pursuit Eye Tracking. Ketamine infusion resulted in dose-dependent decreases in smooth pursuit gain and dose-dependent increases in catch-up saccade

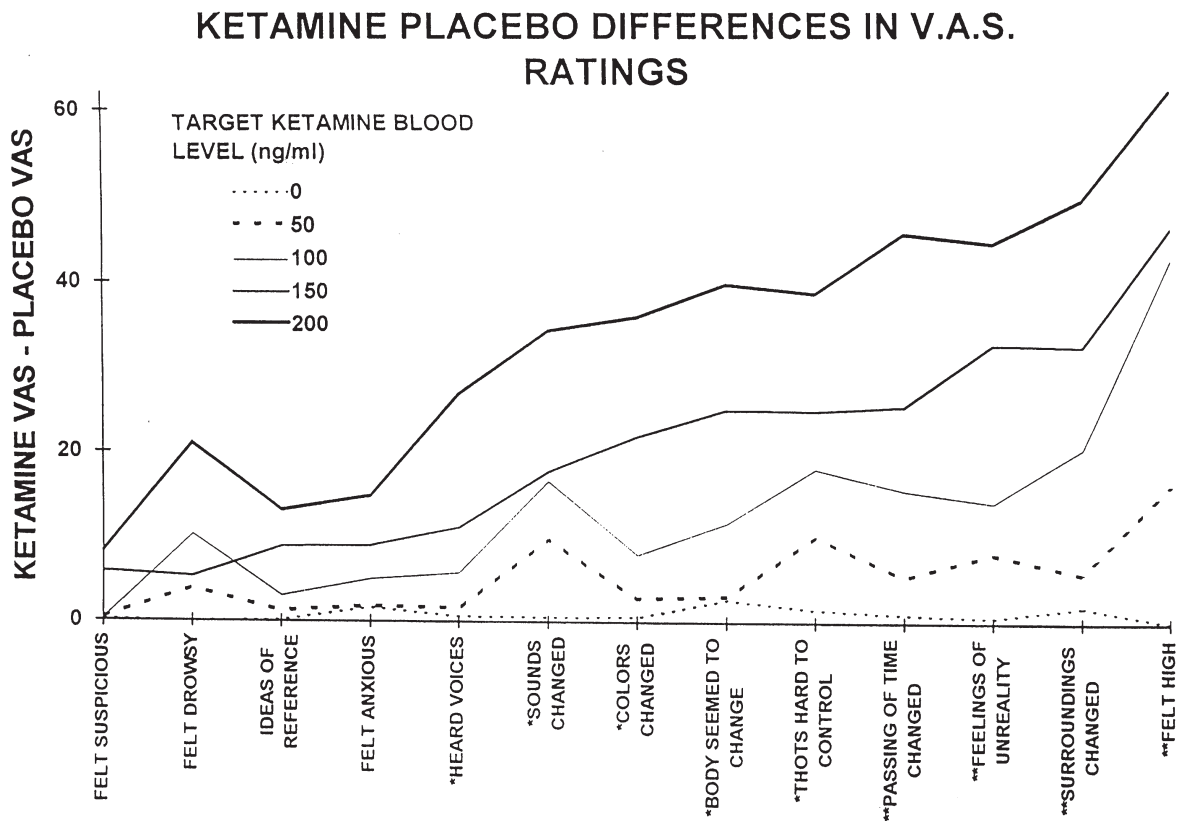


Figure 2. Ketamine placebo differences in V.A.S. ratings; each point represents the self-rating during the ketamine infusion at the given target plasma concentration minus the rating during the corresponding step of the placebo infusion. Statistical significance was determined with a 2 × 5 repeated measures ANOVA with Bonferroni correction. * $p < .05$, ** $p < .01$.

Table 2. Oculomotor Measures During Each Step of the Ketamine and Placebo Infusions

Task/Measure		Step					ANOVA		
		1	2	3	4	5	Step F(4,36)	Plac/Ketam. F(1,9)	Interaction F(4,36)
Eye track Gain	K	.973 (.015)	.891 (.019)	.803 (.030)	.735 (.038)	.676 (.024)	40.13	15.30	28.87
	P	.944 (.036)	.919 (.032)	.917 (.022)	.920 (.020)	.933 (.022)	$p < .0001$	$p < .004$	$p < .0001$
Eye track cus fq (/s)	K	0.48 (.04)	0.77 (.06)	1.00 (.09)	1.14 (.12)	1.25 (.12)	29.52	20.78	9.09
	P	0.38 (.03)	0.52 (.06)	0.57 (.07)	0.53 (.08)	0.52 (.06)	$p < .0001$	$p < .0001$	$p < .0001$
Eye track cus-amp (°)	K	1.08 (.06)	1.26 (.10)	1.30 (.07)	1.50 (.15)	1.76 (.25)	2.51	4.67	2.84
	P	1.15 (.07)	1.08 (.09)	1.21 (.12)	1.31 (.14)	1.19 (.06)	(ns)	$p < .004$	$p < .04$
Eye track as fq (/s)	K	0.21 (.03)	0.33 (.05)	0.41 (.06)	0.31 (.05)	0.21 (.07)	2.50	1.33	1.50
	P	0.26 (.05)	0.26 (.05)	0.25 (.03)	0.30 (.05)	0.21 (.43)	(ns)	(ns)	(ns)
Eye track nyst (/s)	K	0.35 (.06)	0.65 (.16)	0.85 (.11)	1.15 (.17)	1.25 (.20)	17.46	11.27	4.88
	P	0.41 (.10)	0.47 (.06)	0.57 (.11)	0.61 (.13)	0.50 (.09)	$p < .0001$	$p < .008$	$p < .003$
Antisaccade percentage	K	17.0 (5.5)	20.3 (8.0)	21.0 (5.5)	22.8 (6.3)	25.3 (4.5)	0.58	2.55	1.10
	P	14.7 (4.8)	15.3 (3.8)	15.5 (4.0)	16.5 (4.8)	16.8 (6.0)	(ns)	(ns)	(ns)
VG Saccades latency (ms)	K	167 (1.9)	165 (3.9)	172 (4.3)	181 (7.2)	181 (6.6)	1.05	3.95	1.99
	P	165 (3.6)	166 (3.9)	172 (4.3)	174 (4.9)	167 (4.1)	(ns)	$p < .009$	(ns)
VG Saccades velocity (°/s)	K	487 (11.5)	479 (16.5)	453 (11.7)	425 (11.5)	415 (14.4)	1.72	24.92	9.96
	P	489 (12.5)	480 (11.4)	459 (18.9)	473 (13.6)	469 (13.3)	(ns)	$p < .0001$	$p < .0001$
Fix. sac. fq - distr. (/s)	K	0.27 (.05)	0.64 (.16)	0.26 (.05)	0.30 (.08)	0.29 (.09)	2.92	2.95	2.62
	P	0.48 (.10)	0.46 (.11)	0.47 (.09)	0.48 (.12)	0.38 (.08)	$p < .05$	(ns)	(ns)
Fix. sac. fq + distr. (/s)	K	0.42 (.05)	0.40 (.09)	0.34 (.07)	0.30 (.08)	0.48 (.15)	1.35	11.80	0.15
	P	0.60 (.15)	0.60 (.11)	0.65 (.09)	0.54 (.09)	0.72 (.13)	(ns)	$p < .007$	(ns)
10° SR velocity (°/s)	K	8.78 (1.03)	6.30 (0.58)	6.70 (0.85)	5.56 (0.46)	5.64 (0.54)	F(4,20) = 2.96	F(1,5) = 22.21	F(4,20) = 1.75
	P	8.74 (0.79)	8.56 (0.71)	8.94 (0.33)	8.42 (0.47)	8.29 (0.73)	$p < .05$	$p < .01$	(ns)
20° SR velocity (°/s)	K	8.20 (1.10)	8.09 (1.27)	6.91 (1.23)	5.92 (0.65)	5.95 (0.91)	F(4,20) = 1.56	F(1,5) = 9.39	F(4,20) = 1.34
	P	9.12 (0.84)	9.54 (0.84)	9.02 (0.81)	9.17 (1.13)	9.87 (1.32)	(ns)	$p < .05$	(ns)

Means (with standard errors in parentheses) of the major oculomotor measures at each step during ketamine and placebo infusion. The upper row next to each test shows measures during ketamine infusion (K), the lower row shows measures during placebo infusion (P). Two × five repeated measures ANOVAs were used to assess significance. CUS = catch-up saccades during eye-tracking task; AS = anticipatory saccades during eye tracking task; NYST = frequency of nystagmus during eye tracking task. ANTISACCADE PERCENTAGE = number wrong way antisaccades/total trials (×100). VG saccades = visually guided saccades; FIX SAC. FQ. = fixation saccade frequency with and without distractor; SR = step ramp task.

frequency and amplitude (Table 2). The frequency of anticipatory saccades did not change significantly during ketamine infusion. Ketamine infusion also caused a dose-dependent increase in nystagmus at the lateral fixation points during the smooth pursuit eye-tracking task (Table 2; Figures 3 and 4). After covarying for nystagmus, the interaction between ketamine infusion and step remained significant for gain and catch-up saccade frequency and amplitude, although the main effects of ketamine (vs. placebo) were no longer significant for gain and catch-up saccade amplitude (Table 3).

Step Ramp Task. Six subjects completed the step ramp task; 10°/s and 20°/s ramps were analyzed separately. Ketamine caused a dose-independent decrease in initial velocity for both ramp speeds (Table 2). Ketamine did not cause any significant changes in initial acceleration or latency to onset of pursuit.

DISCUSSION

Plasma ketamine concentrations were reasonably close to target concentrations at each infusion step. The infusion algorithm is based on average pharmacokinetic parameters from a study of a relatively small number of subjects. Any randomly selected subject is likely to deviate somewhat from the average. Therefore, target concentrations will not be precisely attained in each subject. A mean variation of measured to target concentration of 20 to 30% is expected with a CACI system (Glass et al. 1990; Shafer et al. 1990; Schuttler et al. 1988). The mean performance error and the mean absolute performance error in this study were less than 30%. The relationship between the target concentration and the measured concentration was highly linear, but the slope was slightly greater than unity, resulting in a trend for plasma ketamine concentrations during the

EYE TRACKING AT BASELINE AND TWO KETAMINE DOSES

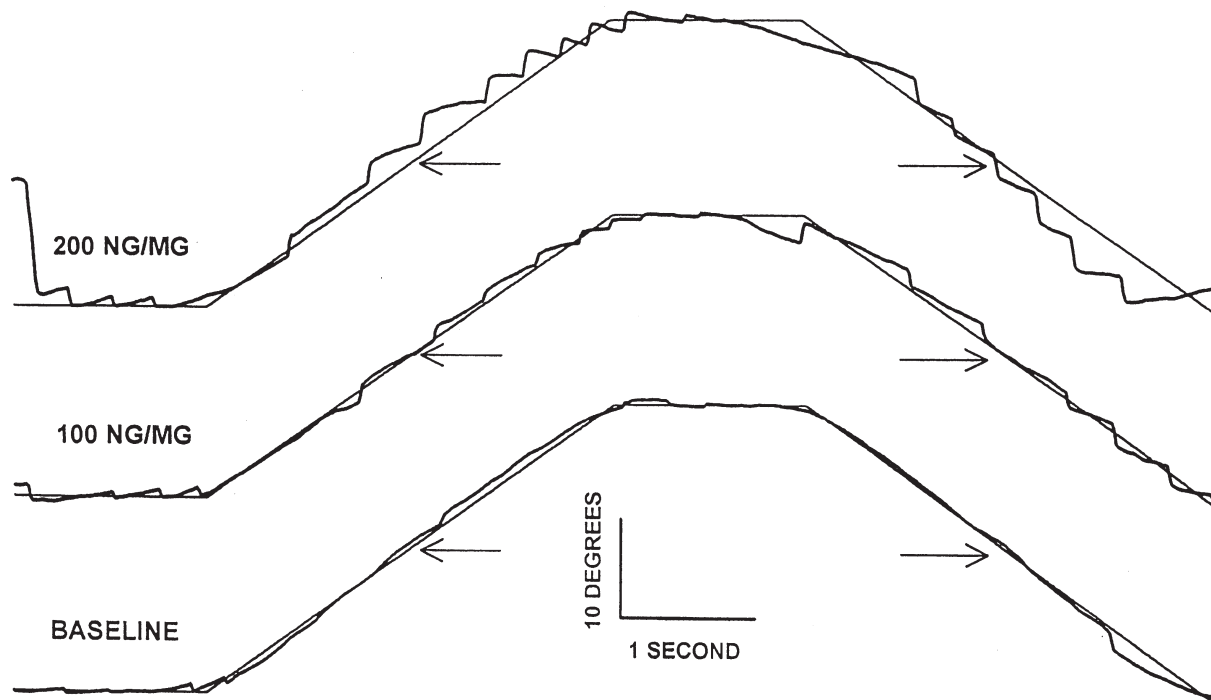


Figure 3. Eye tracking at baseline and two ketamine doses; eye-tracking records of the same subject showing gaze-evoked nystagmus (both during fixation and superimposed on smooth pursuit) with increasing doses of ketamine. Arrows represent the midline of the visual field.

last two steps (150 and 200 ng/kg) to exceed the target. The cause for this overshooting of the target concentrations is unknown; presumably there was a discrepancy between the pharmacokinetic parameters used in the CACI system and the actual pharmacokinetic behavior of the subjects (Hartvig et al. 1994).

The dose-dependent induction of nystagmus by ketamine was probably caused by NMDA receptor blockade in brain stem oculomotor nuclei. NMDA receptors are important components of brain stem oculomotor nuclei (Bosco et al. 1994; Watanabe et al. 1994), and their peripheral or direct blockade with NMDA antagonists results in nystagmus in the cat (Godaux et al. 1990; Mettens et al. 1994). Also, ketamine often induces nystagmus during routine clinical use.

Smooth pursuit gain and catch-up saccade frequency and amplitude were all significantly impaired by ketamine in a dose-dependent manner. After covariance for nystagmus, ketamine had significant effects on catch-up saccade frequency and nonsignificant trend effects on catch-up saccade amplitude and gain (interaction significant but not main effects), suggesting that some of ketamine's impact on smooth pursuit function is independent of its propensity to cause nystagmus. Because of the substantial variance in the data, reliable

quantification of the relative contributions of nystagmus vs. other mechanisms of ketamine-induced smooth pursuit impairment was not possible. Collection of substantially more smooth pursuit data would be necessary to describe better the portion of the ketamine-induced smooth pursuit impairment that is unrelated to nystagmus. Ketamine also caused impairment of open-loop gain during the step ramp task, a phenomenon recently reported among schizophrenia patients (Clementz and McDowell 1994). This task was less likely to be influenced by failure of gaze holding, because the pursuit began at the central fixation point.

NMDA receptors located in human cortical (Conti et al. 1997), striatal (Ulas et al. 1994), and cerebellar (Jansen et al. 1991) regions might be functionally important for smooth pursuit. Ketamine antagonism of NMDA receptors in any of these areas may have been responsible for the portion of the smooth pursuit impairment not attributable to frank nystagmus. The pattern of ketamine-induced smooth pursuit impairment, decreased gain, and increased catch-up saccade frequency is similar to that found in schizophrenia. Although our results are consistent with the hypothesis that schizophrenia-related eye-tracking dysfunction is caused by NMDA receptor hypofunction in frontal cortical, striatal, or cer-

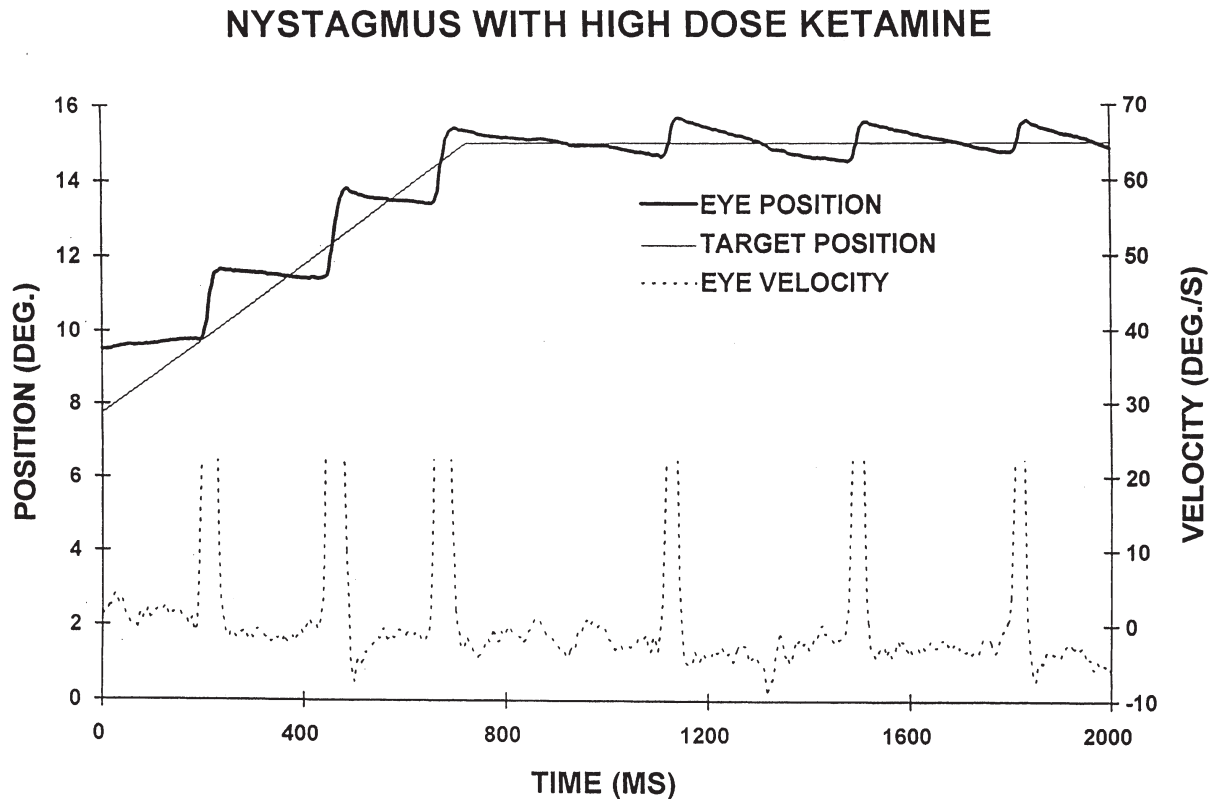


Figure 4. Nystagmus with high dose ketamine; detailed illustration of nystagmus at the 200 ng/ml target concentration of ketamine. Note the rhythmic nature of the saccades and the higher amplitude of the saccades during centrifugal, as opposed to centripetal, pursuit.

ebellar regions, the data do not allow us to exclude the possibility that different mechanisms cause ketamine-induced and schizophrenia-related eye-tracking dysfunction.

Ketamine might be expected to interfere with anti-saccade performance, because this type of eye movement partially depends upon intact function of prefrontal cortex (Funahashi et al. 1993) and the frontal eye fields (O’Driscoll et al. 1995), where NMDA receptors are functionally important (Verma and Moghaddam 1996). Brier et al. (1997) have demonstrated that ketamine causes prefrontal metabolic changes that are correlated with schizophrenia-related symptoms. There was a nonsignificant trend toward increased incorrect antisaccades during the ketamine infusion. It is possible that ketamine impairs antisaccade performance but that the low number of subjects and limited number of trials in our study made it impossible to detect this effect. Another possibility is that ketamine-impaired antisaccade performance but that acute tolerance developed, thus diminishing the magnitude of the impairment and making it harder to detect.

Ketamine also caused dose-independent increased latency and dose-dependent decreased peak velocity of visually guided saccades, a type of oculomotor function

that seems normal in schizophrenia (Fukushima et al. 1990). Although ketamine did not cause impaired verbal attention, these results are consistent with ketamine-induced impairment in visuospatial attention. The decreased peak velocity may be attributable to ketamine-induced impairment of subcortical oculomotor nuclei.

As with Malhotra et al. (1996) and Krystal et al. (1994), we also found that ketamine caused significant

Table 3. ANCOVA of Smooth Pursuit Measures Using Nystagmus Frequency as a Covariate

Eye-tracking measure	Step (F4,35)	Plac. vs. ket. F(1,8)	Interaction F(4,35)
Gain	11.37 <i>p</i> < .0001	3.35 ns	17.51 <i>p</i> < .0001
Catch-up saccade frequency (/s)	4.50 <i>p</i> < .005	9.03 <i>p</i> < .02	3.93 <i>p</i> < .01
Catch-up saccade amplitude (°)	4.07 <i>p</i> < .01	0.10 ns	2.68 <i>p</i> < .05

Smooth pursuit of eye-tracking measures that were significant on initial ANOVA were reanalyzed by ANCOVA using nystagmus (frequency of fast components) during the lateral fixation periods of the eye-tracking task as a covariate.

impairment in both delayed recall and recognition memory. As with Krystal et al. (1994), but unlike Malhotra et al. and Hartvig et al. (1995), we did not observe any significant changes in measures of verbal attention during ketamine infusion. Because the instruments used and doses of ketamine seem comparable between studies, we conclude that the effects of ketamine on verbal attention, although present, are not very robust. LaPorte et al. (1996) failed to find an effect of ketamine on verbal and visual-spatial memory among schizophrenia patients; their use of substantially different methodology than that used in the previously mentioned studies probably explains this result.

Unfortunately, the pattern of ketamine-induced changes in verbal fluency was uninterpretable, despite statistically significant ketamine-placebo differences. Krystal et al. (1994), using a different experimental design, found that ketamine induced a significant decline in verbal fluency; our results do not contradict those of Krystal et al.

Because we did not obtain measures of other cognitive functions, we cannot discriminate between generalized slowing of cognitive function vs. specific schizophrenia-like cognitive impairments resulting from blockade of NMDA receptors.

As expected, ketamine induced a number of psychological symptoms as measured by subject's self-ratings. The rating "Felt high" changed the most with ketamine infusion; in general, the size of the ketamine-induced changes was higher for dissociative symptoms, such as perceptual distortions, than it was for core psychotic symptoms. This pattern of results is consistent with multiple reports in the literature (Lear et al. 1959; Luby et al. 1959; Corssen and Domino 1966; Krystal et al. 1994; Malhotra et al. 1996; Hartvig et al. 1995).

Methodological limitations of our study, including absence of a double-blind design and the small number of subjects, may have influenced the results. Absence of a double-blind design probably did not substantially affect the results, because the oculomotor data were all analyzed by custom software, without experimenter input. It is possible that the experimenters might have influenced the visual analog scale ratings, but it seems unlikely that this could explain the magnitude of the ketamine-related effects. The small n employed in our study indicates that we may have had false negative results; for example, significant ketamine effects on verbal attention and antisaccade performance might have been apparent with a larger sample size.

Another limitation of the study is that total time of exposure to ketamine is confounded with dose level. Persistent exposure to constant plasma ketamine concentrations might result in progressive impairment in cognitive or oculomotor function. Krystal et al. (1994) shows a tendency for ketamine effects to increase with time; however, the authors used a constant infusion for

40 min, and did not determine plasma concentrations so that accumulation of ketamine may have occurred. Two studies (Lahti et al. 1995 and Hartvig et al. 1995) utilized different doses of ketamine on different days and found dose-dependent effects of ketamine similar in magnitude to the effects we found. Therefore, it is likely that the effects we found were attributable to increasing dose of ketamine, rather than total time exposed to ketamine.

Our study adds to an emerging picture of the cognitive and neurological consequences of acute NMDA receptor blockade. It seems that NMDA antagonism reliably induces impaired recognition and recall memory and a number of schizophrenia-like symptoms in a dose-dependent manner. Subanesthetic doses of ketamine cause nystagmus, but seem to cause schizophrenic-like smooth pursuit abnormalities independently. The preservation of antisaccade, and impairment of visually guided saccade, performance during ketamine infusion differs from the pattern found in schizophrenia. Our results are consistent with the hypothesis that abnormal function of cortical, striatal, or cerebellar NMDA receptors may contribute to smooth pursuit eye-tracking abnormalities resulting from either schizophrenia or ketamine infusion.

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