Clinical and Sensorimotor Gating Effects of Ketamine in Normals

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The clinical similarities between PCP psychosis and schizophrenia have contributed importantly to the development of the glutamate hypothesis of schizophrenia. Sensory gating, as measured by prepulse inhibition of the acoustic startle reflex (PPI), is impaired in patients with schizophrenia. In animals, the noncompetitive NMDA antagonists PCP and ketamine disrupt PPI in a way that resembles the defect seen in schizophrenia. The purpose of this work is to investigate the modulation of sensory gating in humans by subanaesthetic doses of ketamine. 16 healthy male subjects received a 60-min infusion of ketamine (0.5 mg/kg) or normal saline on two separate days in a randomized double-blind crossover design. Clinical ratings and PPI were done during the infusion on both days. Ketamine produced robust clinical effects. Dissociative symptoms as measured by the CADSS increased from 0 ± 0.0 to 29.3 ± 14.3; negative symptoms (Affect Rating Scale) increased from 17.2 ± 0.8 to 24.8 ± 3.1; and total BPRS scores increased from 18.3 ± 0.8 to 26.4 ± 5.1. ANOVAs for these ratings were all significant at the p < .000 level, although BPRS increases were not in the range seen in decompensated schizophrenic patients. The amplitudes of the startle responses to pulse-alone stimuli were not significantly different on ketamine and placebo days. Ketamine did not cause disruption in PPI as expected. On the contrary, in the first block of the PPI session ketamine significantly enhanced PPI (ANOVA; F =6.15, p = .026). These results indicate that the clinical effects of ketamine are not coupled with schizophrenic-like disruption of PPI in normal controls.

[Neuropsychopharmacology 25:72–83, 2001]
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The clinical similarities between PCP psychosis and schizophrenia have contributed importantly to the development of the glutamate hypothesis of schizophrenia. PCP and ketamine bind to the PCP site in the channel of the NMDA receptor complex, resulting in noncompetitive inhibition of NMDA type neurotransmission (Javitt and Zukin 1990). This induces a transient state in normals characterized by positive and negative symptoms and cognitive dysfunction which is similar to what is commonly observed in schizophrenics (Luby et al. 1959; Davies and Beech 1960; Bakker and Amini 1961; Allen and Young 1978; Krystal et al. 1994; Malhotra et al. 1996; Adler et al. 1999). Schizophrenics in remission experience a resurgence of symptoms characteristic of their decompensation when given ketamine (Ban et al. 1961; Itil et al. 1967; Lahti et al. 1995; Malhotra et al. 1997). The glutamate hypothesis of schizophrenia, which stems in part from the above findings, posits that a hypofunction of glutamatergic activ-

NEUROPSYCHOPHARMACOLOGY 2001–VOL. 25, NO. 1
© 2001 American College of Neuropsychopharmacology
Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/01/$–see front matter
PII S0893-133X(00)00240-2

ity contributes to the pathophysiology of this illness (Kim et al. 1980; Deutsch et al. 1989; Javitt and Zukin 1991; Olney and Farber 1995).

The acoustic startle response (ASR) is mediated by a simple three-synapse pathway (Davis 1997). The ASR is inhibited when the startling stimulus is preceded by a lower amplitude nonstartling prestimulus, a phenomenon termed prepulse inhibition (PPI)(Graham 1975). PPI is modulated by a number of sites, including the hippocampus (Swerdlow et al. 1993), which is heavily dependent on NMDA neurotransmission (Grunze et al. 1996).

Deficits in sensorimotor gating have been proposed to be linked to the symptoms of cognitive fragmentation, sensory flooding, and thought disorder (McGhie and Chapman 1961; Braff and Geyer 1990). Schizophrenics have impairments in PPI (Braff et al. 1978; Braff et al. 1992; Grillon et al. 1992; Bolino et al. 1994; Parwani et al. 2000). PPI is similarly impaired in animals following treatment with the NMDA antagonists PCP, MK-801, or ketamine (Mansbach and Geyer 1989; Mansbach 1991; Keith et al. 1991; Swerdlow et al. 1993; Johansson et al. 1995; al-Amin and Schwartzkopf 1996). However, PPI changes in animals treated with ketamine appear to be variable depending on timing and dose of ketamine administered (Mansbach and Geyer 1989; Mansbach 1991; Johansson et al. 1995; Swerdlow et al. 1998; de Bruin et al. 1999).

To date, there has been one published clinical study investigating the effects of ketamine on PPI in normals. van Berckel et al. (1998) found that low dose ketamine did not affect PPI. However, their PPI paradigm used a fixed interstimulus interval between prepulse and pulse stimuli.

We administered a ketamine challenge at a higher dose to normals, using a paradigm with varied interstimulus intervals, to investigate whether the resultant positive and negative symptoms would be accompanied by a gating deficit resembling that seen in schizophrenia.

METHODS

Subjects

Sixteen normal male volunteers (mean age = 33.3 ± 3.1) were recruited by means of local advertising at the Veterans Administration New York Harbor Medical Center (VAMC) and New York University Medical Center. The subjects signed informed consent forms which had been approved by the University IRB and the VAMC. All subjects were screened using the SCID -NP for Axis I and Axis II to rule out any psychiatric disorder. Additionally, the Wisconsin Psychosis Proneness Scale (Chapman et al. 1978) was administered to rule out any

schizotypal personality traits. The exclusion criteria also included screening for psychiatric disorders in the subjects' first degree relatives, history of any medical or neurological illness, history of loss of consciousness, and history of any drug or alcohol dependence. All subjects were screened for intact hearing using an audiometer (Grason-Stadler, Model GS1710). Subjects were right-handed as determined by the Handedness Inventory.

Ketamine Administration

The study followed a double-blind cross-over design, with each subject receiving both a ketamine infusion and a placebo (saline) infusion on two separate days. The order of placebo and ketamine days was randomized with a mean interval of eight days between testing (range 4-21 days). Seven subjects received ketamine on Day 1 and saline on Day 2; nine subjects were randomized to the opposite medication order. The subjects were instructed to abstain from alcohol and other drug use for 24 hours preceding the study. Subjects reported to the startle laboratory at 8AM after an overnight fast.

Thirty minutes prior to infusion, an indwelling venous catheter was placed in the right forearm. Subjects received either saline (0.9% sodium chloride) or ketamine hydrochloride (0.5 mg/kg) infused over a 60 minute period. Blood pressure and pulse were measured 30 min prior to infusion, and again at the 20, 50, 90, and 120 minute timepoints after the beginning of the infusion.

Behavioral Ratings

Behavioral changes were assessed with the Brief Psychiatric Rating Scale (BPRS)(Guy 1976), the Abrams and Taylor Rating Scale for Emotional Blunting (Abrams and Taylor 1978), and the Affect Rating Scale (Andreasen 1979). Perceptual changes were assessed with the Clinican-Administered Dissociative States Scale (CADSS), a 27-item scale designed to assesses five symptom domains: body perception, time perception, environmental perception, feelings of unreality, and memory impairment (Bremner et al. 1998). Anger, anxiety, drowsiness, highness, sadness, and feelings of interpersonal closeness were assessed by using subject rated 100 mm line visual analog scales. Subjects were evaluated using all the above scales 15 min before ketamine/placebo administration, 20 and 50 minutes into the infusion, and 30 min following the termination of the infusion (90- minute time point). Mental status ratings were conducted in a double-blind fashion by a single research clinician (AP, ED, SM, or BA). All ratings

on both study days for a given subject were carried out by a single rater.

Startle Response Measurement

The methodology for startle response measurement follows that of Braff et al. (1992), and is similar to the methods reported in Parwani et al. (2000). Immediately after catheter insertion, each subject's right eye was prepped and two disc electrodes (Ag-AgCl; impedance less than 6 Kohm) were positioned over the orbicularis oculi muscle, approximately 5 mm below the right eyelid, one directly below the pupil and the second approximately 5 mm lateral to the first. A third electrode was placed behind the right ear over the mastoid to serve as a ground. The acoustic startle session was administered starting 20 minutes after the beginning of the ketamine/placebo infusion and continued for 15 minutes. Subjects were seated comfortably in a chair and asked to gaze straight ahead at a picture positioned on a wall facing the subject. They were told that they could think of whatever they wished and did not have to attend specifically to the acoustic stimuli.

All acoustic stimuli were delivered binaurally through headphones (Maico,TDH-39-P). The startle session began with a three minute acclimation period consisting of 70 dB(A) broadband noise, which continued as the background noise throughout the session. The pulse-alone stimulus was a 116 dB(A), 40 msec duration burst of 1000 Hz pure tone with a near instantaneous rise time. The prepulse stimuli were 85 dB(A) 20 msec bursts of pure tone, also at 1000 Hz, presented 30, 60, and 120 msec prior to the startle stimulus. The startle session consisted of 36 startle stimuli comprised of three blocks of 12 trials each. Each block consisted of three pulse-alone trials plus three trials of pulse with prepulse at each of the three designated prepulse intervals(30, 60, and 120 msec), presented in a pseudorandom order. Each session began with an initial pulse-alone trial. Inter-trial intervals were 11–45 sec (average 26 sec) occurring in randomized order.

The eyeblink component of the acoustic startle response was measured via EMG of the right orbicularis oculi muscle. EMG activity was filtered (1-500 Hz), amplified, digitized by using a computerized EMG startle response monitoring system (SR-LAB, San Diego Instruments) and recorded in 250 1-msec readings from pulse onset. Digital signals were smoothed by an averaging paradigm that calculates a rolling average of the digital signals whereby the number of digital signals averaged is 10. Startle amplitude was recorded in terms of digital units, where each digital unit equals 1.221 microvolts. Latencies are reported in milliseconds. The onset latency is defined by a shift of 6-digit units from the baseline value, occurring 21 to 120 milliseconds after the pulse-alone stimulus. Peak latency is defined as the

point of maximal amplitude occurring within 150 milliseconds from the pulse-alone stimulus. Trials were rejected because of unstable EMG activity during the first 20 msec or failure to reach peak amplitude within 95 msec of onset latency.

Statistical Analysis

Behavioral data were analyzed by using repeated measures analyses of variance (ANOVAs) with time and drug condition as within subjects factors. When the ANOVA drug × time interactions were significant, *post hoc* multiple comparisons of post-infusion time points to placebo/baseline were conducted by using Student Neuman-Keuls t-tests. Dependent measures for the startle reflex included startle amplitude, onset and peak startle latency, reflex habituation, and PPI. The latter was examined using both difference scores (amplitude difference between pulse-alone and prepulse+pulse trials) and percentage scores (calculated as the difference between the average pulse-alone and prepulse amplitudes, divided by the average pulse-alone amplitude for each block and multiplied by 100). Various ANOVA models were used to examine differences in startle amplitude, percent inhibition, and onset and peak latency with respect to the factors of drug (2 levels: placebo vs. ketamine), block (3 levels), and prepulse condition (4 levels: pulse-alone, 30 msec prepulse, 60 msec prepulse, and 120 msec prepulse). Correlations between the changes in behavioral measures and the changes in startle data at the time of peak drug effect (+50 minutes) as well as between startle amplitude and prepulse inhibition were conducted using Spearman Rank Correlations. One subject was classified as a nonstartler (mean startle amplitude on the pulse-alone trials in block 1 (saline infusion day) was below 25 units) and was therefore excluded from the subsequent analyses.

RESULTS

Behavioral Effects

Pulse and Blood Pressure. Pulse rate as well as systolic and diastolic blood pressure increased during ketamine infusion but not during saline (ANOVA, pulse, Drug: $p = .002$; ANOVA, systolic blood pressure, Drug: $p < .0001$; ANOVA, diastolic blood pressure, Drug: $p < .0001$) (see Table 1). None of these changes were clinically significant.

Brief Psychiatric Rating Scale. Ketamine produced highly significant increases in total BPRS score (Table 1). (ANOVA, Drug: $p < .0001$). There were no significant differences in baseline scores between test days. BPRS scores returned to baseline within 30 minutes following the termination of ketamine infusion.

Table 1. Mean Pre- and Post-Treatment Subjective and Objective Clinical Ratings Scales

Clinical Rating	Ketamine				Saline				ANOVA F(1,15) Values and Results[6]			
									Main Effects		Interaction	
	Baseline	+20	+50	+90	Baseline	+20	+50	+90	Drug	Time	Drug × Time	Result
Pulse	66.9 ± 6.1	70.8 ± 8.0	71.0 ± 5.9	69.0 ± 6.2	68.0 ± 6.6	66.6 ± 7.2	65.8 ± 7.2	60.8 ± 3.7	13.48‡	6.2‡	7.74‡	Ket > Saline
Systolic BP	117.5 ± 9.0	130.8 ± 14.2	129.1 ± 11.9	126.0 ± 12.0	115.8 ± 10.3	112.8 ± 11.5	114.9 ± 11.1	117.6 ± 13.8	25.44‡	3.82*	8.19‡	Ket > Saline
Diastolic BP	78.1 ± 7.0	85.3 ± 11.2	85.4 ± 10.7	80.3 ± 8.5	75.7 ± 8.1	72.1 ± 9.0	74.5 ± 9.5	76.5 ± 11.8	29.86‡	1.93	10.32‡	Ket > Saline
BPRS Total	18.3 ± 0.8	23.6 ± 5.7	26.4 ± 5.1	19.8 ± 3.1	18.0 ± 2.0	18.1 ± 0.3	18.0 ± 0.6	18.1 ± 0.4	47.11‡	11.82‡	12.29‡	Ket > Saline
BPRS Factor I[1]	4.2 ± 0.5	4.8 ± 1.2	5.3 ± 2.0	4.6 ± 1.3	4.3 ± 0.8	4.1 ± 0.3	4.1 ± 0.4	4.1 ± 0.4	4.15	1.43	3.29*	Ket = Saline
BPRS Factor II[2]	3.0 ± 0.0	5.6 ± 2.5	5.8 ± 3.0	3.4 ± 1.0	2.8 ± 0.4	3.0 ± 0.0	2.9 ± 0.5	3.0 ± 0.0	27.15‡	9.25‡	9.40‡	Ket > Saline
BPRS Factor III[3]	4.0 ± 0.0	5.7 ± 2.2	6.9 ± 2.3	4.5 ± 1.1	3.9 ± 0.3	4.0 ± 0.0	3.9 ± 0.5	4.0 ± 0.0	25.54‡	0.88	2.67	Ket > Saline
BPRS Factor IV[4]	3.1 ± 0.3	3.4 ± 1.0	3.8 ± 1.4	3.3 ± 0.7	3.1 ± 0.4	3.0 ± 0.0	2.9 ± 0.3	3.0 ± 0.0	12.79‡	10.26‡	9.80‡	Ket > Saline
BPRS Factor V[5]	3.0 ± 0.0	3.2 ± 0.8	3.6 ± 1.1	3.1 ± 0.3	2.9 ± 0.3	3.0 ± 0.1	2.9 ± 0.5	3.0 ± 0.0	5.71*	2.94*	2.73	Ket > Saline
Abrams & Taylor	0.0	6.69 ± 5.82	9.50 ± 4.91	0.73 ± 2.09	0.0	0.0	0.0	0.000	42.81‡	26.06‡	26.06‡	Ket > Saline
Affect Rating												
Scale	17.2 ± 0.8	23.1 ± 5.2	24.8 ± 3.1	17.1 ± 0.3	17.2 ± 0.8	17.0 ± 0.0	17.2 ± 0.8	17.2 ± 0.8	44.43‡	34.40‡	38.41‡	Ket > Saline
CADSS	0.0	17.1 ± 10.1	29.3 ± 14.3	2.2 ± 4.1	0.1 ± 0.3	0.1 ± 0.3	0.0	0.000	72.45‡	49.61‡	50.32‡	Ket > Saline
Anger	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	Ket = Saline
Anxiety	6.9 ± 10.6	13.1 ± 14.5	15.6 ± 17.9	2.8 ± 5.8	5.7 ± 7.8	3.6 ± 5.9	1.9 ± 4.4	1.9 ± 4.4	5.76*	3.05*	3.95†	Ket > Saline
Drowsiness	7.2 ± 10.8	22.9 ± 28.8	31.3 ± 35.1	11.3 ± 11.9	2.3 ± 5.4	1.7 ± 3.5	4.4 ± 7.2	1.4 ± 2.9	15.34‡	5.15‡	4.01†	Ket > Saline
Highness	0.3 ± 1.3	56.4 ± 25.8	69.7 ± 18.7	11.9 ± 11.7	2.5 ± 5.8	2.5 ± 5.8	2.5 ± 5.5	2.5 ± 4.5	133.04‡	104.52‡	105.96‡	Ket > Saline
Sadness	0.0	2.1 ± 8.3	1.9 ± 5.4	0.0	0.0	0.0	0.0	0.0	2.77	0.83	0.83	Ket = Saline
Interpersonal closeness	70.3 ± 23.4	60.6 ± 27.3	58.8 ± 31.1	72.5 ± 15.5	72.5 ± 16.0	73.8 ± 14.9	73.1 ± 16.1	72.5 ± 15.3	3.42	1.34	1.5	Ket = Saline

Values are reported as Mean ± SD
*p < .05 †p < .01 ‡p < .001
[1] Anxiety/depression subscale: BPRS #1(Somatic concern), 2(Anxiety), 5(Guilt), 9(Depressed mood)
[2] Withdrawal/retardation subscale: BPRS #3(Emotional withdrawal), 13(Motor retardation), 16(Blunted affect)
[3] Thought disturbance subscale: BPRS #4(Conceptual disorganization), 8(Grandiosity), 12(Hallucinations), 15(Unusual thought)
[4] Activation subscale: BPRS #6(Tension), 7(Mannerisms/posturing), 17(Excitement)
[5] Hostile/suspicious subscale: BPRS #10(Hostility), 11(Suspiciousness), 14(Uncooperativeness)
[6] ANOVAs calculated with mean substitution for missing values for 1 subject for T+90 timepoint on both days.
Results were unchanged without mean substitution, using an N of 15.

Some BPRS subfactors also showed robust increases on the ketamine day (Table 1). The Thought Disturbance subfactor showed highly significant increases on ketamine (ANOVA, Drug: $p < .0001$), as did the Withdrawal Retardation subfactor (ANOVA, Drug: $p < .001$) and the Hostility/suspiciousness subscale (ANOVA, Drug: $p < .03$). *Post hoc* Neuman-Keuls t-tests of both the total BPRS score and the subscales revealed significant increases from baseline ($p < .001$) at 20 and 50 min following the initiation of ketamine infusion. Placebo treatment did not result in significant increases in BPRS scores from baseline. Individual data on the ketamine day showed that 13 out of the 16 subjects (81%) had increases from baseline in the Thought Disturbance subscale, 12 of 16 (75%) had increases in the Withdrawal-Retardation subscale; 10 of 16 (63%) had increases in the Anxiety-Depression subscale, 6 of 16 (38%) had increases in the Hostility-Suspiciousness subscale, and 5 of 16 (31%) had increases in the Activation subscale. There were no increases in these subscales on the saline day.

Negative symptoms scales.   Ketamine significantly increased affective flattening as measured by the Affect Rating Scale (Table 1). (ANOVA, Drug: $p < .0001$). There were no changes in the items in this scale measuring affective overreactivity for any subject. Ketamine significantly increased negative symptoms from baseline both at the 20 and 50 min timepoints. Placebo did not elicit significant increases from baseline at any time point. Emotional blunting as measured by the Abrams and Taylor Scale was similarly increased by ketamine (ANOVA, Drug: $p < .0001$).

Perceptual Alterations.   Perceptual alterations, as measured by the CADSS, were robustly increased by ketamine at the 20 and 50 min infusion points as revealed by ANOVA ($p < .0001$)(Table 1).

Visual Analog Scales of Mood States.   Ketamine significantly increased anxiety, highness, and drowsiness as assessed by the 100 mm line visual analog scales of mood states. There were no significant changes in anger or sadness (Table 1). (ANOVA, anxiety: $p < .05$; highness: $p < .0001$); drowsiness: $p < .001$); anger: $p = 1.0$; sadness: $p = .12$). The visual analog scale assessing interpersonal closeness showed a trend level decrease of $p = .08$.

Description of ketamine phenomenology.   Ketamine produced very robust clinical effects, some of which were most fully elicited during a debriefing interview after the effects of the drug had waned. Visual perceptual distortions were the most frequently reported, with subjects describing moving images or objects (the rocks in the picture [on the wall] "seem to be breathing," the mountains "look like faces"). Examiners were often perceived as being "robots" or "cartoon-like." Some subjects described a sensation of visual field narrowing ("tunnel vision") and others had a feeling that everything was in slow motion. Subjects described things in the environment as being "in and out of focus…like being on a merry-go-round, not dizzy but disoriented." Colors and lights appeared intensified and space and depth were "distorted," "seen in 2-D." Changes in the tones of people's voices and hypersensitivity to the startle stimuli were also described by some subjects. One subject perceived the background noise of the startle apparatus as "music coming from a stereo system." Two subjects became suspicious of being overmedicated with ketamine. Two others had hyperacusis which led to paranoia with referential thinking about the conversations of people in the adjoining room.

During ketamine infusion, subjects appeared muted and withdrawn. In the debriefing interview they subsequently described feeling that it took "too much effort" to sustain interpersonal interactions. They felt it was difficult to do things, as though they had to "think about moving or talking." Mood states were described as "profoundly neutral." One subject described feeling "introverted" while many subjects reported a lack of motivation, or a sense of indifference to things happening around them. Subjects often described experiencing "some kind of barrier" ("styrofoam", "a thick haze") between themselves and the examiner. Several of the subjects commented that they would not care about seeing their loved ones in their current state or would not care if they heard their favorite music while under the effects of ketamine.

During ketamine infusion subjects frequently reported an increased disorganization of thinking. One subject described this as "my thoughts are like holding a garden hose in the middle and it's spewing everywhere out of control." Subjects consistently had difficulty putting thoughts into words, and ketamine treated subjects appeared to be struggling to describe the feeling states induced by ketamine: "I'm trying to talk but nothing comes out of my mind." The thinking disturbance induced by ketamine was characterized both by poverty of content and concreteness. Many subjects demonstrated an inability to respond to proverbs with meaningful associations. For example, in response to the proverb "the tongue is the enemy of the neck" one subject commented "the tongue might hurt you, I just keep thinking of the tongue moving… it can't go any farther around."

Abnormal bodily sensations were commonly reported: "feels like I'm moving through a gel," in "viscous fluid." Feelings that the extremities did not belong to the body or to the subject himself were commonly described, and subjects were frequently observed moving their fingers, looking at their hands, touching their legs, etc. Other subjects reported that their bodies felt strange and distorted ("my head is a giant balloon"),

and these feelings were usually coupled with changes in tactile sensations (i.e. heaviness of the limbs, paresthesias). Many subjects experienced numbness of various parts of their bodies, which is consistent with the analgesic effects of ketamine.

Subjects frequently described themselves as being "detached," with feelings of depersonalization and a sense of unreality. At the time of peak drug effect, one subject stated, "it feels like I'm looking out through an armor suit visor....my soul has shrunk inward, farther away from my body." Somatic sensations of "floating" and "out of the body" feelings were frequently described. Other subjects in the study described these sensations as "a hollow feeling inside," and "my legs are far away...I feel dissociated...like I'm not really here." Of the two subjects that vomited during the infusion, one reported that he felt curiously detached from the sensation of nausea and physical discomfort experienced during the episode.

The ketamine-induced high was described as a sense of "giddiness" or feeling "spaced out" which some subjects described as being similar to but not identical with the intoxicating effects of marijuana and nitrous oxide. A few subjects partially likened the high to feeling "a little drunk."

Other clinical effects. One subject developed ataxia which became apparent when he tried to walk at the conclusion of the ketamine infusion. A decreased sense of subjective coordination and proprioception was frequently reported. Nausea/vomiting occurred in two subjects, and the ketamine-induced emesis in one subject was repeated and severe. For this latter subject, nausea persisted for approximately one hour post-infusion. For other subjects, aside from a sense of fatigue which was reported by a few subjects to last for several hours after the infusion, ketamine treatment did not have any prolonged adverse effects. By 30 minutes post-infusion (+90 minute timepoint), all subjects had returned to their baseline mental status.

Acoustic Startle

Startle Amplitude. The mean amplitudes of the acoustic startle responses elicited by the pulse-alone and prepulse+pulse trials in Block 1 are presented in Table 2.

Amplitude to pulse-alone trials was first analyzed separately. The initial reactivity to the first pulse-alone stimulus was not significantly different between the ketamine and saline days ($F(1,14) = .40, p = .54$). There were no significant differences in startle response amplitude between ketamine and saline across the three blocks of the session (ANOVA: $p = .32$). There was robust habituation to pulse-alone startle across the session with both drugs (ANOVA: $p = .003$). Ketamine

Table 2. Acoustic Startle Data for Ketamine vs Saline Days[1]

	Ketamine	Saline	ANOVA F Values and Results			
			Main Effects(1,14)		**Interaction**	
			Drug	Block	Drug × Block	Result
Pulse-alone startle						
Block 1	236.0 ± 170.3	220.0 ± 103.2	1.09	7.41[†]	6.41[†]	Ketamine = Saline Habituation
Block 2	166.0 ± 126.9	218.5 ± 119.1				
Block 3	159.4 ± 119.8	179.6 ± 74.9				
			Drug	**Trial Type**	**Drug × Trial Type**	
PPI—Block 1						
30msec	52.2 ± 36.8	37.0 ± 37.0	6.15*	6.52[†]	0.36	Ketamine > Saline
60msec	48.6 ± 36.8	43.7 ± 26.6				
120msec	48.5 ± 36.7	48.7 ± 33.0				
Onset Latency—Block 1						
Pulse alone	40.1 ± 7.3	36.5 ± 5.1	11.30[†]	10.92[‡]	1.41	Ketamine > Saline[2]
30msec	33.7 ± 8.5	30.3 ± 6.8				Latency facilitation
60msec	37.5 ± 8.8	34.5 ± 6.2				
120msec	41.2 ± 8.4	38.2 ± 5.7				
Peak Latency—Block 1						
Pulse alone	65.2 ± 6.4	66.1 ± 8.3	2.07	9.55[‡]	0.82	Ketamine = Saline[2]
30msec	51.4 ± 7.9	51.7 ± 4.3				Latency facilitation
60msec	56.5 ± 8.0	54.6 ± 7.4				
120msec	55.6 ± 5.4	57.1 ± 6.3				

[1]Values are reported as Mean ± SD
[2]ANOVA performed on data from Blocks 1–3 with d.f. of 1,8
*$p < .05$ [†]$p < .01$ [‡]$p < .001$

was associated with more rapid habituation (Drug $\times$ Block interaction: $p = .005$)(Table 2).

An ANOVA was performed on pulse-alone amplitude using Day rather than Drug as a factor to assess possible order effects. In this model there was no effect of Day ($F(1,14) = 1.07$, $p = .32$).

The data was next approached by means of a repeated measures ANOVA on raw amplitudes of all 36 trials, with drug (2 levels: ketamine and placebo), block (3 levels), and trial type (4 levels: pulse-alone, and 30, 60, or 120 msec interstimulus interval). Startle amplitude across all four trial types was lower on ketamine at a trend level ($F(1,14) = 3.81$, $p = .07$). PPI was confirmed as indicated by a significant main effect for Trial Type ($F(3,42) = 27.62$, $p < .0001$).

Prepulse Inhibition as Difference Score.   PPI as a difference score was computed as (pulse-alone amplitude) - (prepulse+pulse amplitude) for each of the prepulse trial types in each block. There were no differences between ketamine and saline when ANOVAs were performed on the three blocks together ($F(1,14) = .02$, $p = .9$) or on Block 1 alone ($F(1,14) = .84$, $p = .4$).

Percent Prepulse Inhibition.   Percent PPI was computed as $100 \times$ (pulse-alone amplitude - prepulse+pulse amplitude) / pulse-alone amplitude. When the three blocks and the three trial types of each session were analyzed together, there was a weak trend level difference in PPI between the two drugs ($F(1,14) = 3.21$, $p = .09$) in the direction of greater PPI on the ketamine day. As expected, PPI increased as the interstimulus interval between the prepulse and pulse increased from 30 to 60 to 120msec ($F(2,28) = 6.55$, $p < .005$). See Figure 1.

In order to minimize the effects of habituation, PPI was examined in Block 1 alone for the two test days. In this analysis, ketamine significantly increased PPI ($p = .026$). Again, PPI was greater in the trial types with longer interstimulus intervals ($p = .005$)(Table 2).
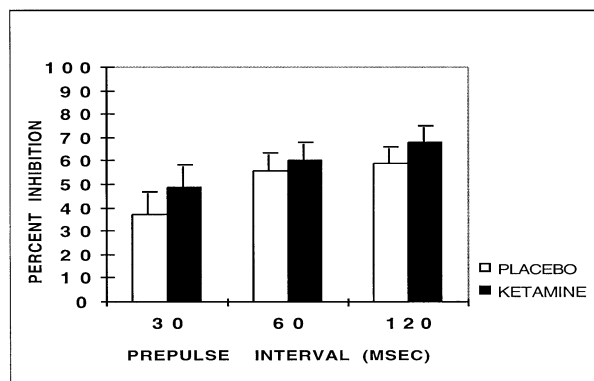

Figure 1.   PPI for Block 1, Saline vs Ketamine Days (Mean $\pm$ SEM). Prepulse interval refers to interstimulus intervals between prepulse and pulse-alone stimuli for the three trial types. ANOVA for Drug: $F(1,14) = 6.15$, $p < .026$.

In order to control for the possible confound which startle to pulse-alone may exert on PPI, a supplemental analysis by ANCOVA was performed. In this model, startle to pulse-alone amplitude for Block 1 was used as a covariate, with Condition (2 levels), and Trial Type (3 levels: 30, 60, and 120 msec trials), were entered as within subject factors. The results of this ANCOVA model remained significant for Condition.

In order to rule out order effects, a separate analysis substituting Day for Drug as a factor was performed. There was no significant effect of Day when an ANOVA was performed on the three prepulse+pulse trial types for all three blocks ($F(1,14) = .36$, $p = .56$) or for Block 1 alone ($F(1,14) = .01$, $p = .92$).

Startle Latencies.   Onset latency for all four trial types across the three blocks of each session was longer on ketamine than on saline, indicating that ketamine slowed the startle response (ANOVA: $p = .01$). On both drugs latency facilitation was apparent as expected, i.e. the 30msec prepulse trials shortened the onset latency compared to the latency to pulse-alone stimuli (ANOVA: $p = .0001$)(Table 2). There was a significant effect of block ($F(1,8) = 7.0$, $p = .001$) reflecting a relative lengthening of onset latency in blocks 2 and 3 in the 60msec and 120 msec trial types.

The ANOVA for peak latency showed no difference between the two drug conditions ($p = .19$). On both drugs peak latency showed latency facilitation (ANOVA: $p < .000$)(Table 2). There was no significant block effect ($F(1,8) = .33$, $p = .19$) indicating that peak latencies did not change significantly across blocks.

Clinical Correlations.   Ketamine's effects on total BPRS scores (at +50 min after the start of the infusion) correlated negatively with ketamine-induced changes in PPI for the 60 msec trial type ($r = -0.50$, $p < .05$). PPI at the 30 and 120 msec trial types varied negatively with total BPRS scores, although these relationships did not reach statistical significance. Ketamine-induced changes in total CADSS scores, as well as total scores on the Affect Rating Scale and the Abrams and Taylor Rating Scale, were not significantly related to ketamine's effects on PPI ($r = 0.42$ to -0.08, n.s. for all comparisons). There were no significant correlations between any of the behavioral measures and onset and peak startle latencies.

DISCUSSION

The principal finding of this study is that ketamine infusion produced quite profound dissociative and negative symptoms, and less profound positive symptoms. These behavioral effects were not accompanied by a disruption of PPI. Rather, an enhancement of PPI was noted in some conditions of the startle paradigm.

It is instructive to compare our clinical results with prior studies using comparable rating scales to document clinical effects of ketamine in normal controls. The study of Krystal et al. (1994) used modestly higher ketamine doses, and reported somewhat more robust positive and negative symptoms. Breier et al. (1997) also used a higher dosing schedule, and found somewhat more robust positive symptoms. Two additional studies (Malhotra et al. 1996; Krystal et al. 1999) used higher ketamine doses, although the resulting positive and negative symptom scores were very similar those of our study.

Ketamine infusion produced robust clinical effects which were reminiscent of but by no means identical to the symptoms commonly seen in schizophrenia. The subjects in our study experienced visual and auditory illusions rather than true hallucinations. Perceptual aberrations were more in the realm of visual, somatic, or proprioceptive distortions than is commonly seen in schizophrenics. There was a predominance of temporal and spatial distortions which, although not unheard of in schizophrenia, is not typical. Unlike what is commonly seen in schizophrenia, only a minority of our subjects (4 out of 16 or 25%) gave evidence of frank suspiciousness.

The heightened perceptual sensitivity produced by ketamine appeared more similar to the psychotomimetic effects of psychedelic drugs than to stimulant induced psychoses. The "highness" experienced by our subjects was quite distinct from the subjective state endured by most schizophrenics. A few subjects reported feeling "a little bit drunk," likening the effects of ketamine to those of alcohol. These comments are in accord with recent work showing that ketamine produces ethanol-like subjective effects in detoxified alcoholics (Krystal et al. 1998). While most subjects described the ketamine experience as affectively "pleasant" or neutral, a few subjects experienced the sense of derealization and loss of control over thought processes as anxiety-provoking or frightening.

In contrast to the above symptom domains, the negative symptoms induced by ketamine were a much closer match to the characteristic negative symptoms of schizophrenia. Each one of our subjects showed an increase in the Affect Rating Scale and in the Abrams and Taylor scale during ketamine infusion. We observed blunting of affect, emotional withdrawal and impoverishment of speech, all of which closely mimicked the negative symptoms of schizophrenia. Yet our debriefing interviews, conducted after the last clinical effects of the infusion had waned, provided an important perspective on these negative symptoms. The subjects reported that, during the peak of the experience, they were either unable or uninterested in describing the drug effects, but found the experience extremely engrossing and intense. This inner state is likely to be dissimilar to that experienced by many of our chronic schizophrenic patients with profound negative symptoms, particularly those who report sitting for hours each day with few specific things on their minds.

The thought disorder elicited by ketamine was somewhat subtle, but concreteness on proverb interpretation was striking in some subjects and quite like the poor abstraction seen in schizophrenics. Our rating instruments only captured thought disorder in the Conceptual Disorganization item of the BPRS, which increased from 1 ± 0 at baseline to 1.7 ± 1.0 at +50 minutes on the ketamine day. Adler et al. (1998) have quantified thought disturbance more thoroughly by means of more sensitive instruments and found significant increases. Furthermore, the ketamine-induced thought disorder scores did not differ from scores in stable schizophrenics (Adler et al. 1999).

The clinical effects we elicited were not accompanied by impairments in PPI such as are seen in schizophrenia (Braff et al. 1992; Grillon et al. 1992; Bolino et al. 1994; Parwani et al. 2000). On the contrary, ketamine produced a significant enhancement of gating as indicated by increases in percent prepulse inhibition in Block 1 of the startle session. This is contrary to the disruptions in gating which have been reported in animals treated with PCP, ketamine, and MK-801 (Mansbach and Geyer 1989; Mansbach 1991; Keith et al. 1991; Swerdlow et al. 1993; Johansson et al. 1995; al-Amin and Schwartzkopf 1996; Swerdlow et al. 1998; de Bruin et al. 1999).

We doubt that the difference between our finding and that of the preclinical studies is simply a function of the timing of the prepulse paradigm relative to ketamine administration. The infusion lasted 60 minutes; prepulse testing was done at 30–45 minutes into the infusion, by which time the subjective and rating effects of the drug had reached robust and near maximum levels. Likewise, we doubt that it is due to inadequate dosing. As is evident from Table 1, changes in positive, negative, and dissociative symptoms were quite robust, indicating that our subjects attained clinically relevant plasma levels of ketamine.

There are several possible explanations for the discrepancy between our results and the preclinical findings in the literature. Firstly, the doses used in animal studies are much larger than what we used. We used 0.5 mg/kg infused over 60 minutes; whereas preclinical doses of ketamine have ranged from 5.6 to 36 mg/kg (Mansbach 1991; Johansson et al. 1995). The plasticity of PPI is due in part to modulatory inputs from the hippocampus (see Swerdlow et al. 1993 for review). As Grunze et al. (1996) have pointed out, there is NMDA-dependent modulation of inhibitory intrinsic circuits in the CA1 region of the hippocampus. The sensitivity of these circuits to NMDA antagonism may be such that different doses of ketamine will result in a difference in

the valence of hippocampal output and its consequent modulation of the startle circuitry. Alternately, humans and rodents may simply differ with respect to sensitivity to NMDA antagonism in the circuits which mediate sensory gating. However, dose response studies of ketamine effects on PPI in humans would be extremely useful to clarify the discrepancy between our results and those of preclinical studies which found gating disruption after ketamine (Mansbach and Geyer 1989; Mansbach 1991; Johansson et al. 1995; Swerdlow et al. 1998; de Bruin et al. 1999).

By way of comparison, the preclinical literature indicates that amphetamine disrupts PPI under some conditions, although the effect is dependent on dose, timing, parameters of testing, and rat strain (Davis 1988; Ott and Mandel 1995; Druhan et al. 1998; Zhang et al. 1998; Sills 1999; Kinney et al. 1999; Lacroix et al. 2000; Zhang et al. 2000). There is one study in the literature demonstrating amphetamine-induced disruption of PPI in humans (Hutchison and Swift 1999).

There is one prior report in the literature concerning effects of ketamine on PPI in humans (van Berckel et al. 1998). This group found that ketamine did not alter pulse-alone startle or PPI. However, their dose was 0.3 mg/kg IV given over 135 minutes, whereas we gave 0.5 mg/kg over 60 minutes. The clinical effects we observed were somewhat more robust than in the van Berckel study. Their startle paradigm only included prepulse+pulse trials with an interstimulus interval of 120 msec. We found the greatest difference between ketamine and saline in the 30 msec prepulse trials. These methodological differences between our study and that of van Berckel et al. are possible explanations for our differing results.

Recent PET studies indicate that ketamine administration to normals increases metabolic activity in the frontal cortex, which increases correlate with ketamine-induced positive symptoms (Breier et al. 1997; Vollenweider et al. 1997a; Vollenweider et al. 1997b). Schizophrenia, and negative symptoms of schizophrenia in particular, have been associated with decreased frontal metabolic activity (Buchsbaum et al. 1982; Buchsbaum et al. 1990; Farkas et al. 1984; Wolkin et al. 1985; Cohen et al. 1987; Volkow et al. 1987; Wolkin et al. 1992; Siegel et al. 1993). However, this is not a consistent finding. In fact, studies in unmedicated acutely relapsed schizophrenics with robust positive symptoms have reported a hyperfrontal metabolic pattern (Volkow et al. 1986; Wiesel et al. 1987; Cleghorn et al. 1989; Ebmeier et al. 1993; Parellada et al. 1994). The extent to which ketamine administration is an accurate model of brain metabolic changes in schizophrenia needs further clarification.

Ketamine significantly prolonged onset latencies; peak latencies were nonsignificantly increased by ketamine. The significance of this finding is not clear, however, it does not seem surprising that an anesthetic agent should produce such a slowing of response. Clinical studies of PPI have demonstrated increases in onset and peak tactile startle latencies in schizophrenia (Braff et al. 1992). Hence, although our findings regarding PPI contrast with the findings of impaired gating in schizophrenia, the prolonged onset latency with ketamine resembled that seen in schizophrenia.

The glutamatergic modulation of PPI is complex, and is dependent on methods of drug administration. Local infusions of NMDA and NMDA antagonists into the nucleus accumbens decrease and increase PPI respectively (Reijmers et al. 1995). Intra-accumbens infusion of both competitive NMDA receptor antagonists and glycine site antagonists cause disruptions of PPI (Kretschmer and Koch 1997), while both classes of drugs have no effects on PPI when administered systemically (Mansbach 1991; Bristow et al. 1995). Glutamatergic NMDA effects on PPI are thought not to be mediated through mesolimbic dopamine receptors, since disruption of PPI by NMDA antagonists are not reversed by D2 antagonists (Keith et al. 1991; Wan et al. 1996).

Ketamine interacts at several non-NMDA sites (Cohen et al. 1974; Smith et al. 1980; Smith et al. 1981; Øye et al. 1991) and hence it is possible that the effects of ketamine we observed were not related to its NMDA receptor activity. However, ketamine has higher affinity for NMDA receptors than for other sites (Øye et al. 1991; Javitt and Zukin 1991), and its behavioral effects are not blocked by drugs acting at these other sites (Byrd et al. 1987). In drug discrimination studies, ketamine produces PCP-like discriminative stimulus effects (Browne 1986; Brady and Balster 1982). For these reasons it is likely that the effects we observed are in fact largely due to NMDA sites of action.

In conclusion, ketamine administration to normal controls induced positive symptoms which were only a rough approximation of the positive symptoms of schizophrenia. Ketamine was a much better model for the negative symptoms of schizophrenia and for some aspects of schizophrenic thought disorder (particularly impoverishment and concreteness). These clinical effects were not accompanied by impaired gating as is seen in schizophrenia. Rather, in some stimulus conditions, ketamine improved PPI.

ACKNOWLEDGMENTS

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