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Dissociation of Ketamine Effects on Rule Acquisition and Rule Implementation: Possible Relevance to NMDA Receptor Contributions to Executive Cognitive Functions

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Abstract

Background: The demands of the Wisconsin Card Sorting Test (WCST) change with experience. This report contains two studies designed to examine *N*-methyl-D-aspartate (NMDA) receptor contributions to the executive components of WCST performance. These aspects of WCST performance figure more prominently in the initial completion of this task than in subsequent task repetitions in healthy populations.

Methods: In the first study, healthy subjects ($n = 15$) completed the WCST on two occasions separated by 1 week. In the second study, healthy subjects ($n = 22$) completed two test days spaced by approximately 1 week, during which, they completed the WCST and other assessments after administration of the NMDA antagonist ketamine (intravenous bolus 0.26 mg/kg followed by infusion of 0.65 mg/kg/hour) or matched placebo.

Results: In the first study, subjects reduced the number of total and perseverative errors with a single repetition of the WCST. In the second study, ketamine significantly increased the number of total errors and the number and percent of perseverative errors on the first, but not the second test day. Similarly, it reduced the number of category criteria met on the first, but not second test day. Ketamine also increased distractibility, impaired recall, produced psychosis, altered

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perception, and had effects resembling the negative symptoms of schizophrenia. However, only WCST performance showed order dependency.

Conclusions: This order dependency further implicates NMDA receptors in executive cognitive functions associated with the frontal cortex.

Keywords

Wisconsin Card Sorting Test; frontal cortex; ketamine; glutamate; learning and memory; schizophrenia; executive function

Introduction

The Wisconsin Card Sorting Test (WCST) grew out of sorting test methods developed by Goldstein and colleagues to assess patients with cortical injury (Grant and Berg 1948; Wiegl 1941). Goldstein (1949) suggested that frontal cortical injury impaired a group of related voluntary functions including the capacity to withdraw and focus attention, shift mental set, store information in a readily accessible form, shift between holistic and detail-oriented analyses, abstract common properties, engage in conceptual planning, and think symbolically. Subsequent studies suggest that the WCST is a complex task sensitive to many of the component functions described above (Dehaene and Changeux 1991; Heaton 1981). An extensive body of research confirmed that frontal cortical injury impaired WCST performance (Drewe 1974; Milner 1964; Robinson et al 1980) and indicated that WCST performance activated the dorsolateral prefrontal cortex in healthy individuals (Catafau et al 1994; Weinberger et al 1986). However, WCST performance was also impaired by diffuse disturbances in cortical function or lesions outside of the frontal cortex (Anderson et al 1991). Also, it is likely that WCST performance is differentially sensitive to regional lesions within the frontal cortex (Anderson et al 1991; Drewe 1974).

A great deal of recent interest in the WCST developed from its utility for assessing deficits attributable to the frontal cortex in patients with schizophrenia (Hoff et al 1992; Kolb and Whishaw 1983; Malmo 1974; Weinberger et al 1994). During the WCST, schizophrenic patients have reduced regional cerebral flood flow (rCBF), increases in the dorsolateral prefrontal cortex, and enhanced hippocampal activation relative to matched control groups (Berman et al 1986, 1992; Weinberger et al 1986, 1994). In schizophrenic patients, WCST performance deficits correlated with the presence of other cognitive impairments, negative symptoms, insight deficits, refractoriness to vocational rehabilitation, and poor social relationships (Braff et al 1991; Breier et al 1991; Lysaker and Bell 1994, 1995).

Ketamine produces symptoms associated with schizophrenia, including psychosis, blunted affect, thought disorganization, reduced capacity for abstract thought, learning deficits, and WCST impairments in a dose-related fashion in healthy subjects (Krystal et al 1994, in press-a). The behavioral effects at subanesthetic doses appear to result primarily from noncompetitive blockade of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor (Anis et al 1983). However, it has other sites of action at lower affinity (c.f., Krystal et al 1994). In healthy subjects performing the WCST, ketamine increases the percent of perseverative errors and the number of non-perseverative errors, decreases the number of

categories achieved, and to a lesser extent, increases the number of trials to the successful completion of the first category (Krystal et al 1994, 1998).

The current report contains findings from two studies designed to further explore ketamine effects on WCST performance. In the first study, we compared WCST performance in healthy subjects who completed the test two times separated by 1 week in order to characterize practice effects on this test. In the second study, we contrasted ketamine effects on WCST performance when administered on the first of two test days and its effects when administered on the second test day. The initial performance of the WCST involves many aspects of executive function. However, performance of this task, once matching rules are learned, places little demand on problem solving skills, although most other aspects of the sorting task remain unchanged. Thus, comparison of ketamine effects on the first and second exposure to the WCST provide insights into components of this task that are impaired by administration of subanesthetic ketamine.

Methods and Materials

Subjects

The studies described in this paper were approved by the VA Connecticut Healthcare System Human Subjects Subcommittee. Subjects were recruited for participation through public advertisement and they were paid for their participation. Healthy subjects were selected to enter these studies after obtaining written informed consent and following a two-step process to exclude individuals with a history of psychiatric illness, substance abuse disorders, or significant current life stress. The first step involved a structured psychiatric interview that excluded subjects who gave evidence of a psychiatric or substance abuse disorder, history of consultation for an emotional difficulty, psychiatric illness in a first-degree relative, or clinically significant current life stress defined operationally as 3 or greater on the Severity of Psychosocial Stressors Scale for Adults employed in Axis IV of DSM-III-R. The second step was a telephone interview conducted with an individual identified by the subject to confirm the information collected in the first stage of screening. No subject was excluded due to information obtained during the informant interview. Subjects were instructed to abstain from consuming psychoactive medications for the 4 weeks before testing. Compliance with this request was supported with urine toxicology screens at initial screening and on selected test days. None of the subjects reported a history of serious medical illness.

STUDY 1.—Eight male [mean age 32.2 ± 3.6 years (SEM)] and 7 female [mean age 42.6 ± 1.4 years (SEM)] subjects performed the WCST once per day on test sessions separated by 7 days. The mean education was 17.6 ± 0.6 (SEM). The racial composition was 11 Caucasian subjects, 2 Hispanic subjects, one African-American subject and one Asian subject.

STUDY 2.—In addition to the screening procedures described, all of the subjects had normal results on physical examination and laboratory testing, including liver and thyroid function tests. Thirteen male [mean age 31.5 ± 8.7 year (SEM); mean weight 85.6 ± 23.8 kg (SEM)] and 9 female [mean age 31.4 ± 10.5 year (SEM); mean weight 68.4 ± 22.8 kg (SEM)] subjects completed ketamine hydrochloride and placebo testing. The mean Slossen

IQ score (Slossen 1963) was 132.3 ± 28.2. The racial composition of the subject group was 19 Caucasian subjects, 2 African-American subjects, and 1 Hispanic subject.

Ketamine Administration

This study reports on the first two test days from subjects who completed larger studies involving four test days that were conducted in a randomized and balanced order under double-blind conditions (Krystal et al 1998, in press-b; Lipschitz et al 1997). This report is limited to test days in which ketamine hydrochloride (0.26 mg/kg over 2 min followed by 0.65 mg/kg/hr; Parke-Davis, Kalamazoo, MI) or placebo (Krystal et al 1998, in press-b). Thus, each subject received ketamine on only one of the two test days reported here. The mean number of days between tests was 8.3 ± 1.6 (SEM). Analyses were limited to those subjects who received ketamine and placebo on their first two test days. Analysis of lorazepam (Krystal et al 1998), haloperidol (Krystal et al, in press-b), and clozapine (Lipschitz et al 1997) responses will be reported elsewhere. While data related to WCST performance on the first days is included in the other reports, the WCST data collected on the second test days is reported here for the first time.

Behavioral Ratings

The WCST is a task in which cards are sorted by the color, shape, and number of objects depicted on the card. This task requires the subject to determine the rule governing the matching of cards and to change their sorting strategy in response to feedback when these rules shift during the task. Subjects completed up to six categories involving each matching condition presented twice in a fixed order feedback; the percent perseverative error was calculated as the ratio of perseverative errors to the total number of errors. Patients with frontal lobe lesions (Milner 1964) exhibit increased perseverative errors and fewer categories successfully completed on this task. Computerized versions of the WCST activated the frontal cortex in healthy subjects in a previous study (Weinberger et al 1986). The current study utilized a computerized version of the WCST. WCST administration began 40 min after initiation of ketamine infusion. Subjects in this study received identical instructions regarding the WCST on each test day.

Vigilance to visual stimuli was measured using a continuous performance task (Gordon 1983) in which subjects attended to numbers presented sequentially on a screen. The subject pushed a button to signal when a “9” was preceded by a “1”. The distractibility task was identical to the vigilance task with the exception that numbers were presented sequentially in three contiguous columns. Subjects had to attend to the numbers in the middle column and ignore the numbers presented in the outer two columns. Each task lasted for 8 min. The outcome measure analyzed for both vigilance and distractibility was A', a perceptual sensitivity measure derived from signal detection theory (Green and Swets 1966) that reflects the impact of both omission and commission errors (Nestor et al 1991): $A' = .5 + (\text{probability of a hit} - \text{probability of a false alarm})(1 + \text{probability of a hit} - \text{probability of a false alarm})(4 \times \text{probability of a hit})^{-1}(1 - \text{probability of a false alarm})^{-1}$.

Learning was assessed using items from the Mini-Mental Status Examination (MMSE; Folstein et al 1975). This study slightly modified this examination to add an assessment of

word recall following a 10 min delay. For the memory assessment, separate sets of three words each, selected on the basis of their comparable frequency of use in the English language (Kucera and Francis 1967) were presented at each time point. The three words were presented following the one min bolus infusion of ketamine or placebo. Care was taken to ensure that the subject was able to recall the three words correctly before moving on to the next task, but only the initial immediate recall was recorded. Thus, each set of words was presented once, but recall was assessed three times: immediately following presentation, following a distracting task, and following a 10-min delay. The MMSE was presented −150 minutes prior to ketamine infusion and at the 5, 90, 120, and 180 minute time points.

Symptoms and behaviors characteristic of schizophrenia were assessed on each test day using the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962). The BPRS previously was sensitive to ketamine effects in humans (Krystal et al 1994). Four key BPRS items were selected as an index of the positive symptoms of schizophrenia based on previous reports indicating their utility and validity (Bowers et al 1980; Kane et al 1988; Krystal et al 1993) and inclusion within the empirically derived thought disorder factor of the BPRS (Hedlund and Vieweg 1980). These four key positive symptoms were conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content. In evaluating hallucinatory behavior, bizarre perceptual experiences associated with an identifiable sensory reference were rated as illusory perceptual alterations rather than hallucinations. This definition was more conservative than that employed in a previous report (Krystal et al 1994), and selected to provide greater clarity in data interpretation. Three key BPRS items, blunted affect, emotional withdrawal, and motor retardation were selected as a measure of the negative symptoms of schizophrenia based on a report of their reliability and validity (Thiemann et al 1987) and their inclusion within the empirically derived withdrawal-retardation factor of the BPRS (Hedlund and Vieweg 1980). The BPRS and analog scales were administered prior to placebo (−120 min and ketamine (−15 min) administration, 5 min into the ketamine administration, and 60, 90, 120, and 180 min following the termination of ketamine infusion. For the two subjects from the clozapine study, the initial rating was performed at −150 min.

The Clinician-Administered Dissociative States Scale (CADSS; Bremner et al 1998; Krystal et al 1994) was a clinician-administered measure of perceptual, behavioral, and attentional alterations occurring during dissociative experiences, which had been validated in healthy subjects, schizophrenic patients, and patients with post-traumatic stress disorder. This measure was included in the test battery, in part, to ensure that perceptual distortions (illusions) that were not rated under the BPRS hallucinatory behavior item could be rigorously assessed. This scale involved 19 self-report questions and 8 observer ratings scored from 0 (not at all) to 4 (extremely). The CADSS was administered at the −150, 5, 60, 90, 120, and 180 min time points. For the two subjects from the clozapine study, the initial rating was performed at −180 min.

Data Analyses

STUDY 1.—Performance on the first and second test days were compared by paired *t* tests.

STUDY 2.—WCST variables and continuous performance task data were initially analyzed employing a repeated measures analysis of variance (RMANOVA) with within subjects factors of order (placebo first vs. ketamine first), drug (placebo vs. ketamine test days), and time (if multiple time points were assessed). Huynh-Feldt adjustments to the degrees of freedom were applied when indicated by sphericity tests. When both the main effects (drug, time) and interaction effects (drug by time) were significant, only the interaction effect is reported in the text in order to focus the presentation. Post-hoc comparisons were conducted using the Student's *t* tests with Bonferroni adjustments. No gender effects were observed in the data analyses and therefore the reported analyses are collapsed by gender.

Results

Study 1

As indicated in Table 1, paired *t* test comparisons showed a significant decrease in the number of perseverative errors on day 2 ($t = 2.2$, df = 14, $p = .04$) as well as in the total number of errors ($t = 2.9$, df = 14, $p = .01$) on that day. No significant practice effects were seen in the analysis of the percent perseverative errors, loss of set, criteria met, or trials to first criteria.

Study 2, WCST Results

Prominent order effects emerged for ketamine effects on most aspects of WCST performance. As outlined in Table 2, ketamine significantly reduced the number of matching criteria met when administered on the first, but not the second test day. The RMANOVA performed on the number of category criteria successfully met data revealed a significant drug by order interaction ($F[1,20] = 10.9$, $p = .004$) effects. The RMANOVA performed on percent perseverative error data revealed a significant drug by order interaction ($F[1,20] = 5.9$, $p = .02$). Post-hoc analyses of these data were suggestive of ketamine effects on the first, but not second test day (Table 2). The number of perseverative errors was significantly increased by ketamine only on the first test day (drug by order interaction: $F[1,20] = 11.8$, $p = .003$) effects. Similarly, the RMANOVA performed on the number of total errors data revealed a significant drug by order interaction ($F[1,20] = .006$) effects. The RMANOVA performed on the number of trials to competition of first criteria showed a nonsignificant drug by order interaction ($F[1,20] = 3.3$, $p = .08$). In contrast, no significant drug by order effects emerged on loss of set.

Other Cognitive and Behavioral Outcomes

No other cognitive or behavioral outcome showed order-dependent ketamine effects. Ketamine did not significantly impair vigilance. However, as shown in Table 3, it increased distractibility, as assessed by perceptual sensitivity (A′). It also produced a delay-dependent recall impairment (drug by delay by time interaction: $F[8,152] = 7.1$, $p = .0001$), BPRS 4 key positive symptoms associated with schizophrenia (drug by time interaction: $F[6,120] = 28.4$, $p = .0001$), BPRS 3 key negative symptoms associated with schizophrenia (drug by time interaction: $F[6,120] = 20.8$, $p = .0001$), and perceptual effects (CADSS, drug by time interaction: $F[6,120] = 54.5$, $p = .0001$).

Evaluation of Ketamine Effects on Subsequent WCST Performance

The outcome measures from the first study show that there was an improvement in the total number of perseverative error and total number of errors. As a result, we compared perseverative error data from study 1 to the group who received ketamine on the first day in order to examine the possibility that ketamine reduced the improvement shown on the second test day. Although the group by day interaction was significant ($F[1,23] = 11.9$, $p = .002$), this was attributable to the ketamine effect on their first test day. Post-hoc comparisons of the second test days of both groups did not reveal a significant difference.

Discussion

Ketamine effects on WCST performance showed a high degree of order dependency. It impaired WCST completion on the first test day, when the task required subjects to both learn matching rules and to implement these rules. However, ketamine did not significantly worsen WCST performance on the second test day, when subjects had previously learned the matching rules and had only to implement them again. Thus, ketamine appeared to interfere with the acquisition, but not the expression of functions related to abstract procedural learning. On the first test day, ketamine increased the number and percent of perseverative errors and it reduced the number of matching criteria achieved on the WCST. These impairments in WCST performance have been associated with frontal cortical dysfunction (Milner 1964; Weinberger et al 1994). The number of trials needed to complete the first matching criterion has shown variable sensitivity to ketamine (Krystal et al. 1994, 1998). In this study, the ketamine effect on this variable did not reach significance ($p = .08$). However, as before, (Krystal et al 1994), ketamine did not produce loss of set.

The order-dependency of ketamine effects on the WCST could not be accounted for by its effects on other measures in this study because no other measure was differentially sensitive to ketamine administered on the first as opposed to the second test day. The current findings replicated previous studies of ketamine effects on cognitive functions and behavior (Domino et al 1965; Ghoneim et al 1985; Krystal et al 1994, 1998; Malhotra et al 1996; Øye et al 1992). Among these measures, the absence of order-dependency in the amnestic effects of ketamine may imply that the disruptive effects of NMDA antagonism on learning do not contribute significantly to the impairments in cognitive functions, such as shifting of mental set, required for successful performance of the WCST. However, one must be cautious in making this interpretation due to the absence of a pure procedural learning test for comparison to the WCST in the current design. Because of its capacity to disrupt encoding, one might have expected that ketamine would have interfered with the improvement in WCST performance that would have been expected with repetition of this task. For example, healthy subjects showed a small, but consistent, reductions in perseverative and total errors with a single exposure to this test. However, this study was unable to demonstrate that ketamine exposure during the initial test day influenced performance on the subsequent placebo test day due to the modest statistical power of this analysis.

Ketamine effects on executive components of attention may have contributed to the order-dependence of ketamine effects on the WCST. Ketamine produced similar increases in distractibility on the first and second test days without significantly impairing vigilance.

Resource allocation theory would predict that more difficult tasks, i.e., those that make greater demands on the control of attention, are more susceptible than are easier tasks to disruption by a specified reduction in attention function (Norman and Bobrow 1975; Wickens 1984). Because the first attempt at completing the WCST is more "difficult" than subsequent exposures, it may have been more vulnerable to disruption by increased distractibility.

The current study has several limitations in addition to those cited. First, it describes a single dose of ketamine and it is likely that the order-dependence of ketamine effects on the WCST is dose-dependent. Second, although ketamine blood levels are not reported here, ketamine blood levels measured in the subjects participating in this study were relatively stable over the testing period and are reported elsewhere (Krystal et al 1998). Third, the addition of a control group receiving ketamine on both test days may have permitted a more complete evaluation of order-related effects of ketamine. Lastly, the population studied had higher levels of intelligence than the surrounding population, a factor that may limit the generalizability of the current findings.

The current data may suggest that deficits in NMDA receptor function, modeled by ketamine, preferentially disrupt procedural learning relative to procedural implementation. As reviewed in the introduction, executive cognitive deficits in schizophrenic patients are persisting features of the disorder, resistant to treatment, and predictive of poor response to rehabilitation. A growing body of literature implicates NMDA receptor abnormalities in deficits in frontal cortical function in schizophrenia (Ishimaru et al 1994; Javitt and Zukin 1991; Kornhuber et al 1989; Krystal et al, in press-a; Lahti et al 1995; Sherman et al 1991). The disruption of executive cognitive function by ketamine may be a preferential, rather than nonspecific consequence of reduction in NMDA receptor function. As a result, further exploration of pharmacologic strategies for ameliorating ketamine effects on cognitive function may have clinical importance.

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References

Anderson SW, Demasio H, Jones RD, Tranel D (1991): Wisconsin Card Sorting Test performance as a measure of frontal lobe damage. J Clin Exp Neuropsychol 13:909–922. [PubMed: 1779030]

Anis NA, Berry SC, Burton NR, Lodge D (1983): The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. Br J Pharmacol 79:565–575. [PubMed: 6317114]

Berman KF, Torrey EF, Daniel DG, Weinberger DR (1992): Regional cerebral blood flow in monozygotic twins discordant and concordant for schizophrenia. Arch Gen Psychiatry 49:927–934. [PubMed: 1360197]

Berman KF, Zec RF, Weinberger DR (1986): Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia, II: role of neuroleptic treatment, attention, and mental effort. Arch Gen Psychiatry 43:126–135. [PubMed: 2868701]

Bowers MB, Heninger GR, Sternberg D, Meltzer HY (1980): Clinical processes and central dopaminergic activity in psychotic disorders. Comm Psychopharmacol 4:177–188.

Braff DL, Heaton R, Kuck J, Cullum M, Moranville J, Grant I, et al. (1991): The generalized pattern of neuropsychological deficits in outpatients with chronic schizophrenia with heterogeneous Wisconsin Card Sorting Test results. Arch Gen Psychiatry 48:891–898. [PubMed: 1929758]

Breier A, Schreiber JL, Dyre J, Pickar D (1991): National Institute of Mental Health longitudinal study of chronic schizophrenia: Prognosis and predictors of outcome. Arch Gen Psychiatry 48:239–246. [PubMed: 1671741]

Bremner JD, Mazure CM, Putnam FW, Southwick SM, Marmar C, Hansen C, et al. (1998): Measurement of dissociative states with the Clinician Administered Dissociative States Scale (CADSS). J Traum Stress 11:125–136.

Catafau AM, Parellada E, Lomeña FJ, Bernardo M, Pavía J, Ros D, et al. (1994): Prefrontal and temporal blood flow in schizophrenia: Resting and activation technetium-99m-HMPAO SPECT patterns in young neuroleptic-naive patients with acute disease. J Nucl Med 35:935–941. [PubMed: 8195878]

Dehaene S, Changeux J-P (1991): The Wisconsin Card Sorting Test: Theoretical analysis and modeling in a neuronal network. Cereb Cortex 1:62–79. [PubMed: 1822726]

Domino EF, Chodoff P, Corssen G (1965): Pharmacologic effects of CI-581, a new dissociative anesthetic, in man. Clin Pharmacol Ther 6:279–291. [PubMed: 14296024]

Drewe EA (1974): The effect of type and area of brain lesion on Wisconsin Card Sorting Test performance. Cortex 10:159–170. [PubMed: 4844468]

Folstein MF, Folstein SE, McHugh PR (1975): “Mini-mental state”: A practical method of grading the cognitive state of patients for the clinician. J Psychiatry Res 12:189–198.

Ghoneim MM, Hinrichs JV, Mewaldt SP, Petersen RC (1985): Ketamine: Behavioral effects of subanesthetic doses. J Clin Psychopharmacology 5:70–77.

Goldstein K (1949): Frontal lobotomy and impairment of abstract attitude. J Nerv Ment Dis 110:93–111. [PubMed: 18136721]

Gordon M (1983): The Gordon Diagnostic System. DeWitt, New York: Gordon Systems.

Grant DA, Berg EA (1948): A behavioral analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card-sorting problem. J Exp Psychol 38:404–411. [PubMed: 18874598]

Green DM, Swets JA (1966): Signal Detection Theory and Psychophysics. New York: Wiley.

Heaton RK (1981): Wisconsin Card Sorting Test Manual. Odessa: Psychological Assessment Resources, Inc.

Hedlund JL, Vieweg BW (1980): The Brief Psychiatric Rating Scale (BPRS): A comprehensive review. J Op Psychiatry 11:48–64.

Hoff AL, Riordan H, O’Donnell DW, Morris L, DeLisi LE (1992): Neuropsychological functioning of first-episode schizophreniform patients. Am J Psychiatry 149:898–903. [PubMed: 1609868]

Ishimaru M, Kurumaji A, Toru M (1994): Increases in strychnine-insensitive glycine binding sites in cerebral cortex of chronic schizophrenics: Evidence for glutamate hypothesis. Biol Psychiatry 35:84–95. [PubMed: 7909453]

Javitt DC, Zukin SR (1991): Recent advances in the phencycli-dine model of schizophrenia. Am J Psychiatry 148:1301–1308. [PubMed: 1654746]

Kane J, Honigfeld G, Singer J, Meltzer H, and the Clozapine Collaborative Study Group (1988): Clozapine for the treatment-resistant schizophrenic: A double-blind comparison with chlorpromazine. Arch Gen Psychiatry 45:789–796. [PubMed: 3046553]

Kolb B, Whishaw IQ (1983): Performance of schizophrenic patients on tests sensitive to left or right frontal, temporal, or parietal function in neurological patients. J Nerv Ment Dis 171:435–443. [PubMed: 6864202]

Kornhuber J, Mack-Burkhardt F, Riederer P, Hebenstreit GF, Reynolds GP, Andrews HB, et al. (1989): [^{3}H]MK-801 binding sites in postmortem brain regions of schiozphrenic patients. J Neural Trans 77:231–236.

Krystal JH, Belger A, Abi-Saab W, et al. (in press-a): Glutamatergic contributions to cognitive dysfunction in schizophrenia. In: Harvey PD, Sharma T, editors. Cognitive Functioning in Schizophrenia. London: Oxford University Press.

Krystal JH, D'Souza DC, Karper LP, et al. (in press-b): Interactive effects of subanesthetic ketamine and haloperidol. Psychopharmacology.

Krystal JH, Karper LP, D'Souza DC, Bennett A, Abi-Dargham A, et al. (1998): Interactive effects of subanesthetic ketamine and subhypnotic lorazepam in humans: Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Psychopharmacology 135:213–229. [PubMed: 9498724]

Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, et al. (1994): Subanesthetic effects of the NMDA antagonist, ketamine, in humans: Psychotomimetic, perceptual, cognitive, and neuroendocrine effects. Arch Gen Psychiatry 51:199–214. [PubMed: 8122957]

Krystal JH, Seibyl JP, Price LH, Woods SW, Heninger GR, Aghajanian GK, et al. (1993): M-Chlorophenylpiperazine (MCPP) effects in neuroleptic-free schizophrenic patients: Evidence implicating serotonergic systems in the positive symptoms of schizophrenia. Arch Gen Psychiatry 50:624–635. [PubMed: 8102048]

Kucera H, Francis WN (1967): Computational Analysis of Present Day American English. Providence, RI: Brown University Press.

Lahti AC, Holcomb HH, Medoff DR, Tamminga CA (1995): Ketamine activates psychosis and alters limbic blood flow in schizophrenia. Neuroreport 6:869–872. [PubMed: 7612873]

Lipschitz DS, D'Souza DC, White JA, Charney DS, Krystal JH (1997): Clozapine blockade of ketamine effects in healthy subjects. Biol Psychiatry 41(S):23S(abstract#76).

Lysaker P, Bell M (1994): Insight and cognitive impairment in schizophrenia: Performance on repeated administrations of the Wisconsin Card Sorting Test. J Nerv Ment Dis 182:656–660. [PubMed: 7964675]

Lysaker P, Bell M (1995): Work rehabilitation and improvements in insight in schizophrenia. J Nerv Ment Dis 183:103–106. [PubMed: 7844571]

Malhotra AK, Pinals DA, Weingartner H, Sirocco K, Missar CD, Pickar D, et al. (1996): NMDA receptor function and human cognition: The effects of ketamine in healthy volunteers. Neuropsychopharmacology 14:301–307. [PubMed: 8703299]

Malmo HP (1974): On frontal lobe functions: Psychiatric patient controls. Cortex 10:231–237. [PubMed: 16295096]

Milner B (1964): Some effects of frontal lobectomy in man. In: The Frontal Granular Cortex and Behavior. Warrent JM, Akert K, editors. New York: McGraw-Hill, pp 313–334.

Nestor PG, Faux SJ, McCarley RW, Sands SF, Horvath TB, Peterson A (1991): Neuroleptics improve sustained attention in schizophrenia: A study using signal detection theory. Neuropsychopharmacology 4:145–149. [PubMed: 1673845]

Norman DA, Bobrow DG (1975): On data-limited and resource limited processes. Cog Psychol 7:44–64.

Overall JE, Gorham DR (1962): The Brief Psychiatric Rating Scale. Psychol Rep 10:799–812.

Øye N, Paulsen O, Maurset A (1992): Effects of ketamine on sensory perception: Evidence for a role of *N*-methyl-D-aspartate receptors. J Pharmacol Exp Ther 260:1209–1213. [PubMed: 1312163]

Robinson AL, Heaton RK, Lehman RAW, Stilson DW (1980): The utility of the Wisconsin Card Sorting Test in detecting and localizing frontal lobe lesions. J Consult Clin Psychol 48:605–614. [PubMed: 7410659]

Sherman AD, Hegwood TS, Baruah S, Waziri R (1991): Deficient NMDA-mediated glutamate release from synaptosomes of schiozphrenics. Biol Psychiatry 30:1191–1198. [PubMed: 1686412]

Slosson RL (1963): Slosson Intelligence Test (SIT) for Children and Adults. East Aurora, NY: Slosson Educational Publications.

Thiemann S, Csernansky JG, Berger PA (1987): Rating scales in research: The case of negative symptoms. Psychiatry Res 20:47–55. [PubMed: 3562690]

Weigl E (1941): On the psychology of so-called processes of abstraction. J Abnorm Soc Psychol 36:3–33.

Weinberger DR, Aloia MS, Goldberg TE, Berman KF (1994): The frontal lobes and schizophrenia. J Neuropsychiatr Clin Neurosci 6:419–427.

Weinberger DR, Berman KF, Zec RF (1986): Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. I. Regional cerebral blood flow evidence. Arch Gen Psychiatry 43:114–124. [PubMed: 3947207]

Wickens CD (1984): Processing resources in attention. In: Parasuraman R, Beatty J, Davies J, editors. Varieties of Attention. New York: Academic Press, pp 63–102.

Table 1.

Practice Effects on Wisconsin Card Sorting Test Performance in Healthy Subjects (n = 15)

Outcome Measure	First Day	Second Day
Category criteria met	4.8 ± .5	4.9 ± .5
Percent perseverative errors	51.2 ± 4.2	53.2 ± 2.2
Perservative errors	16.9 ± 3.5	12.7 ± 2.7[a]
Total errors	32.8 ± 6.2	25.1 ± 5.4[b]
Trials to first criteria	29.7 ± 8.3	27.9 ± 8.1
Loss of set	1.1 ± .3	1.6 ± .5

Data presented are mean ± SEM.

Two-tailed paired t tests:

[a] p = .04;

[b] p = .01.

Table 2.

Order-Dependency of Ketamine Effects on Wisconsin Card Sorting Test Performance

Outcome Measure	Order	Ketamine[a]	Placebo[a]	First vs. Second Day[d]	Drug by Order Effect[e]
Category criteria met	Ketamine first[b]	1.5 ± .7[f]	4.8 ± .6	$t_9 = 5.7$, $p = .0003$	$p = .003$
	Placebo first[c]	4.5 ± .7	5.1 ± .4	ns	
Percent perseverative errors	Ketamine first	69.2 ± 5.5[g]	53.1 ± 3.6	$t_9 = 3.3$, $p = .009$	$p = .03$
	Placebo first	49.2 ± 3.6	46.0 ± 3.6	ns	
Perseverative errors	Ketamine first	53.4 ± 8.6[h]	21.8 ± 5.9	$t_9 = 4.2$, $p = .002$	$p = .004$
	Placebo first	19.3 ± 3.8	13.8 ± 3.9	ns	
Total errors	Ketamine first	74.0 ± 8.1[f]	37.8 ± 7.4	$t_9 = 5.4$, $p = .0004$	$p = .005$
	Placebo first	42.8 ± 8.4	27.7 ± 6.5	ns	
Number of items	Ketamine first	124.6 ± 3.4[h]	110.0 ± 4.8	$t_9 = 3.3$, $p = .009$	$p = .04$
	Placebo first	112.4 ± 5.5	101.0 ± 7.9	ns	
Trials to first criterion	Ketamine first	21.9 ± 10.4	20.8 ± 3.3	ns	ns
	Placebo first	14.3 ± 3.2	23.4 ± 5.7	ns	
Loss of set	Ketamine first	1.2 ± .5	1.3 ± .6	ns	ns
	Placebo first	.9 ± .3	1.5 ± .6	ns	

[a] Data are presented as mean ± SEM.

[b] Ketamine first subjects received ketamine on the first test day and placebo on the second test day ($n = 10$).

[c] Placebo first subjects received placebo on the first test day and ketamine on the second test day ($n = 12$).

[d] Two-tailed post hoc paired *t* tests comparing subjects on their first and second test days. All post hoc tests underwent Bonferroni adjustments.

[e] Significance of the drug by time interaction effect in the repeated measures ANOVA, see text for other analyses. Two-tailed post hoc Student's *t* tests comparing groups of subjects on the same test day:

[f] $p \leq .005$;

[g] $p \leq .05$;

[h] $p \leq .01$.

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Table 3.

Ketamine Effects on Vigilance and Distractibility

Outcome Measure	Order	Ketamine[a]	Placebo[a]	Drug Effect[d]	Drug by Order Effect[d]
Vigilance	Ketamine first[b]	.98 ± .01	1.0 ± .002	$p \geq .1$	ns
	Placebo first[c]	.97 ± .02	.99 ± .004		
Distractibility	Ketamine first	.88 ± .05	.98 ± .003	$p = .006$	ns
	Placebo first	.98 ± .004	.91 ± .03		

The presented data refer to the perceptual sensitivity measure, A', defined in the text.

[a] Data are presented as mean ± SEM.

[b] Ketamine first subjects received ketamine on the first test day and placebo on the second test day ($n = 9$).

[c] Placebo first subjects received placebo on the first test day and ketamine on the second test day ($n = 12$ for vigilance; $n = 12$ for distractibility).

[d] Significance of the drug and drug by time interaction effect in the repeated measures ANOVA, see text for other information regarding these analyses.