Ketamine-Induced Deficits in Auditory and Visual Context-Dependent Processing in Healthy Volunteers

Implications for Models of Cognitive Deficits in Schizophrenia

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Background: In patients with schizophrenia, deficient generation of mismatch negativity (MMN)—an event-related potential (ERP) indexing auditory sensory (“echoic”) memory—and a selective increase of “context dependent” (“BX”) errors in the “A-X” version of the Continuous Performance Test (AX-CPT) indicate an impaired ability to form and use transient memory traces. Animal and human studies implicate deficient N-methyl-D-aspartate receptor (NMDAR) functioning in such abnormalities. In this study, effects of the NMDAR antagonists ketamine on MMN generation and AX-CPT performance were investigated in healthy volunteers to test the hypothesis that NMDARs are critically involved in human MMN generation, and to assess the nature of ketamine-induced deficits in AX-CPT performance.

Methods: In a single-blind placebo-controlled study, 20 healthy volunteers underwent an infusion with subanesthetic doses of ketamine. The MMN-to-pitch and MMN-to-duration deviants were obtained while subjects performed an AX-CPT.

Results: Ketamine significantly decreased the peak amplitudes of the MMN-to-pitch and MMN-to-duration deviants by 27% and 21%, respectively. It induced performance deficits in the AX-CPT characterized by decreased hit rates and specific increases of errors (BX errors), reflecting a failure to form and use transient memory traces of task relevant information.

Conclusions: The NMDARs are critically involved in human MMN generation. Deficient MMN in schizophrenia thus suggests deficits in NMDAR-related neurotransmission. N-methyl-d-aspartate receptor dysfunction may also contribute to the impairment of patients with schizophrenia in forming and using transient memory traces in more complex tasks, such as the AX-CPT. Thus, NMDAR-related dysfunction may underlie deficits in transient memory at different levels of information processing in schizophrenia.

Arch Gen Psychiatry. 2000;57:1139-1147

EUROCOGNITIVE deficits represent a significant feature of schizophrenia1-7 and an important limiting factor for functional outcome.8-10 They include a deficient ability to form and use transient memory traces of task relevant information. For example, patients with schizophrenia show deficits in auditory sensory (“echoic”) memory, which encodes and maintains representations of simple physical features of auditory stimuli (eg, pitch, intensity) for up to 30 seconds after stimulus presentation.11 These deficits are manifested in an impaired ability to match tones after a brief delay12-14 and in deficient generation of an event-related potential (ERP) component that is termed mismatch negativity (MMN) and represents an index of echoic memory.5,15-21 Similarly, patients with schizophrenia perform poorly in more complex attention-dependent tasks—such as a modified version of the “A-X” Continuous Performance Test (AX-CPT)—that require the successful formation and transient maintenance of a representation of task relevant information for correct task performance.22,23

See also pages 1131 and 1149

Deficient N-methyl-D-aspartate (NMDAR)–dependent neurotransmission has been implicated in neurocognitive deficits of schizophrenia24,25 by similarities of cognitive deficits26-31 and abnormal brain activation patterns32-34 that are induced by NMDAR antagonists with abnormalities in schizophrenia. Deficient NMDAR functioning may specifically contribute to failures in transient memory, since NMDAR antagonists impair performance in tasks that tax transient maintenance of information.28,35-39 Furthermore, in nonhuman primates,

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SUBJECTS AND METHODS

The study was approved by the ethics committee of the Psychiatric University Hospital Zurich and conducted in the Research Department of the Psychiatric University Hospital.

SUBJECTS

Normal subjects were recruited in the local university and technical college through advertisement. During the initial screening interview by the principal investigator (D.U.), the rationale and the goal of the study were explained in lay terms to the subjects. In addition, the expected psychotomimetic and dissociative effects were reviewed in detail and described as accurately as possible. Potential physical adverse effects of low-dose ketamine, such as nausea, vomiting, and dizziness, were discussed with all subjects. Subjects were informed that they would be under constant supervision during the whole session and that the experiment would be stopped at any time if they wished or if adverse effects occurred. All potential study candidates were thus fully informed about the goal and the risks of the study orally and in writing, and signed informed consent. After signing informed consent, subjects underwent a screening that included a structured clinical interview (Composite International Clinical Interview) assessing present and past personal psychiatric history, a semistructured interview covering family psychiatric history, a physical examination, and laboratory tests that included a complete blood cell count, routine blood chemistry, and an electrocardiogram. Exclusion criteria were a history of Axis I disorders, a history of drug dependence or present drug abuse, a psychiatric family history of Axis I disorders extending to second-degree relatives, and the presence of any medical disorders. None of the female subjects was pregnant. Intelligence was assessed using the Hamburg-Wechsler Intelligence Scale, Revised Version. Handedness was determined using the handedness scale by Chapman and Chapman. Twenty-one subjects were enrolled in the study. They received a financial remuneration for participation in this study. One female subject was dropped from the study after she developed nausea and vomiting during the ketamine infusion, which necessitated a premature stop of test procedures. Thus, 20 subjects (14 men and 6 women) were included in the final analysis. Their mean ± SD age was 24.6 ± 2.9 years. Eighteen were university students; 2 had completed an apprenticeship and were employed at the time of the study. Nineteen of the subjects were right-handed; the mean ± SD verbal and performance IQ scores were 114 ± 11 and 117 ± 9, respectively.

PROCEDURES

Ketamine/Placebo Infusion

Each subject underwent both a placebo and ketamine infusion on 2 separate days in a randomized and counterbalanced order. Subjects were blind to infusion order. On both infusion days, subjects arrived in the laboratory around 9 AM after an overnight fast. An indwelling catheter was placed in the antecubital vein of the nondominant arm and an infusion of physiological sodium chloride solution and 5% glucose was started and kept at a flow of 20 mL/h. Then, a baseline ERP recording was acquired using the test paradigms described below. After the baseline phase, a bolus of ketamine, 0.24 mg/kg, was given intravenously over 5 minutes, followed by a 5-minute pause. Then, a maintenance infusion of ketamine, 0.9 mg/kg per hour, was started. Previous research has demonstrated that ketamine blood levels slowly increase during a constant ketamine infusion. Thus, to keep ketamine levels fairly constant, the dose was reduced by 10% every 15 minutes. In the placebo session, the same schedule (bolus, pause, and maintenance) was followed. Instead of ketamine, an infusion of physiological sodium chloride solution and 5% glucose was given. Twenty minutes after the start of the ketamine or placebo bolus the second ERP recording began. On completion of the second ERP recording, the ketamine or placebo infusion was stopped. Subjects were given 30 minutes to recover from the ketamine or placebo infusion; then a third ERP recording was acquired. During the entire session, subjects were under the constant supervision of study personnel.

Behavioral Ratings

At the end of each ERP recording session, behavioral effects were assessed using the Brief Psychiatric Rating Scale (BPRS) (scale points, 1-7). In 1 subject, several items could not be reliably assessed during ketamine administration; therefore, for some analyses, only data from 19 subjects were available. Orientation to person, place, and time were assessed with 3 items from the Modified Mini-Mental State Examination (date and place of birth, temporal orientation, and spatial orientation) that yield a maximum score of 25 indicating full orientation. This measure was obtained in 18 subjects.

Auditory Test Paradigm

The ERP recordings were acquired during the presentation of auditory stimuli, consisting of 100-millisecond, 1000-Hz standard intermixed with 100-millisecond, 1500-Hz pitch deviants and 250-millisecond, 1000-Hz duration deviants. Stimuli were presented in a fixed order (9 standard, 1 pitch deviant, 9 standard, and 1 duration deviant) with an stimulus onset asynchrony of 300 milliseconds and presented through foam insert earphones at nominal intensity of 75-dB sound pressure level. Stimuli were presented in 4 blocks with 1317 stimuli each. During presentation of the auditory test paradigm, subjects performed a visual AX-CPT to minimize their attention to the auditory stimuli.

The AX-CPT

Visual stimuli consisted of individual letters and were presented sequentially on a computer screen for 250 milliseconds.

NMDAR antagonists selectively abolish MMN, indicating a crucial role of NMDARs in MMN generation and echoic memory. These results suggest that deficient NMDAR-dependent neurotransmission may underlie deficits in MMN generation and echoic memory in schizophrenia and possibly contribute to impaired performance in tasks in which transient maintenance of information is crucial, such as the AX-CPT.
This study tested the hypothesis that in healthy volunteers NMDAR blockade—induced by low-dose ketamine—results in a selective deficit in MMN generation to provide supporting or refuting evidence for the as-

sumption that MMN deficits in schizophrenia may indeed reflect abnormal NMDAR functioning. In addition, ketamine-induced deficits in the performance of the AX-CPT were explored. Specifically, we were interested
in their resemblance to the deficits observed in schizophrenia.21 We hypothesized that ketamine would significantly decrease MMN without reducing sensory event-related potentials (ERPs), such as N1, and specifically increase those errors in the AX-CPT that are indicative of deficient formation and use of transient memory traces.

Ketamine—a so-called dissociative anesthetic—is a noncompetitive NMDAR antagonist binding to the phencyclidine site within the ion channel of the NMDAR complex.25 Its well-documented psychotomimetic effects at subanesthetic doses26,42-45 are short-lived because of its short half-life.46 Ketamine anesthesia produces minimal cardiac and respiratory effects, is not associated with any long-term psychological effects,47 and shows an excellent safety record.48 The minimal risks associated with low-dose ketamine justify its use as a pharmacological probe in healthy volunteers if important questions concerning the basis of neurocognitive deficits in schizophrenia are addressed that cannot be answered by studies in animals. That is the case in this study.

**RESULTS**

**EFFECTS OF KETAMINE ON BEHAVIOR AND ORIENTATION**

During ketamine administration, the expected behavioral changes were observed. The mean ± SD BPRS total score increased from 19.1 ± 1.3 to 33.3 ± 8.2 (infusion × time interaction: F2,18 = 31.32, P<.001). In addition, significant increases of the mean ± SD BPRS psychosis factor scores (baseline: 4.0 ± 0.0; ketamine administration: 9.8 ± 3.8; and infusion × time interaction: F2,18 = 22.72, P<.001) and the mean ± SD BPRS anergia factor scores (baseline: 3.5 ± 0.8; ketamine administration: 8.5 ± 3.7; and infusion × time interaction: F2,18 = 18.37, P<.001) were observed. There were also significant, but less pronounced, increases of the mean ± SD BPRS anxiety/depression factor (baseline: 4.3 ± 0.7; ketamine administration: 5.7 ± 2.5; and infusion × time interaction: F2,18 = 4.00, P = .04) and activation factor scores (baseline: 3.2 ± 0.6; ketamine administration: 4.3 ± 2.5, and infusion × time interaction: F2,18 = 3.61, P = .05) during ketamine administration. Ketamine did not affect autobiographic, temporal, or spatial orientation of subjects (repeated-measures ANOVA for ketamine infusion: F1,17 = 1.76, P = .20). In 1 subject, there was a decrease by 6 points, and in 2 subjects, a decrease by 1 point of the total score were noted. In all other subjects, orientation scores remained unchanged.

**EFFECTS OF KETAMINE ON AUDITORY ERPs**

Mismatch Negativity

In both baseline sessions, robust MMN amplitudes to pitch and duration deviants were recorded with MMN maxima at Fz. As expected, MMN latency to pitch-duration-deviant stimuli were approximately 100 milliseconds longer than to pitch-deviant stimuli in the baseline phases of both the placebo and ketamine session (Table 1) (Figure 1).

Ketamine administration was associated with a significant reduction of MMN peak amplitudes in the pitch and duration-deviance condition (Table 2) (Figure 2). During ketamine administration, the mean peak amplitude of MMN-to-pitch deviants decreased by 1.47 µV, or 27%; the mean peak amplitude of MMN-to-duration deviants decreased by 0.9 µV, or 21%, from the corresponding baseline values of that session. A repeated-measures ANOVA demonstrated a significant infusion × time interaction (F2,18 = 4.57, P = .03). The infusion × time × MMN-

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**Table 1. Peak Amplitudes and Latencies of Mismatch Negativity (MMN) to Pitch and Duration Deviants (N = 20)**

<table>
<thead>
<tr>
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<th>Placebo Session</th>
<th>Ketamine Session</th>
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<tbody>
<tr>
<td><strong>MMN-to-Pitch Deviants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>−5.42 ± 2.07</td>
<td>124 ± 15</td>
</tr>
<tr>
<td>Placebo/ketamine</td>
<td>−4.96 ± 1.99</td>
<td>127 ± 18</td>
</tr>
<tr>
<td>Infusion</td>
<td>−4.09 ± 2.08</td>
<td>127 ± 18</td>
</tr>
<tr>
<td>Postinfusion</td>
<td>−3.93 ± 1.22</td>
<td>232 ± 20</td>
</tr>
<tr>
<td><strong>MMN-to-Duration Deviants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>−6.05 ± 2.07</td>
<td>124 ± 16</td>
</tr>
<tr>
<td>Placebo/ketamine</td>
<td>−6.70 ± 2.07</td>
<td>129 ± 20</td>
</tr>
<tr>
<td>Infusion</td>
<td>−4.96 ± 1.99</td>
<td>127 ± 18</td>
</tr>
<tr>
<td>Postinfusion</td>
<td>−3.75 ± 1.15</td>
<td>233 ± 22</td>
</tr>
</tbody>
</table>

*Post hoc P = .002 compared with placebo administration.
†Post hoc P = .001 compared with session baseline.
‡Post hoc P = .006 compared with session baseline.
§Post hoc P = .003 compared with session baseline.
¶Post hoc P = .001 compared with session baseline.
||Post hoc P = .03 compared with postinfusion placebo phase.

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**Figure 1. Effects of ketamine administration on mismatch negativity (MMN) (difference wave) in the pitch (A) and duration (B) deviance condition (N=20). The gray lines represent the MMN wave during the baseline recording before ketamine administration; the black line, the MMN wave during infusion of ketamine; and the dark area, the difference between the 2 curves (ie, the reduction of MMN during ketamine administration).**

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Ketamine Session

but significant increase of MMN peak latencies in comparison for the placebo session were not significant. The increase of N1 amplitude during ketamine administration from the session baseline failed to reach significance (post hoc paired t test: $t_{18} = 1.88, P = .07$). Ketamine administration did not affect N1 peak latency.

The P2 amplitude increased slightly, but significantly, throughout both recording sessions (effect of time: $F_{2,18} = 16.01, P < .001$). Ketamine administration was not associated with any particular effect on peak amplitude (infusion × time interaction: $F_{2,18} = 0.89, P = .40$). There was no significant effect on peak latency of P2.

**EFFECTS OF KETAMINE ON AX-CPT PERFORMANCE**

During the collection of MMN data, subjects performed the AX-CPT (1 subject completely stopped performing the task during ketamine administration; thus, data of 19 subjects were included in the analysis). Ketamine administration was associated with a significant decline of the correct detection of the AX-sequence (hit rate) at both ISIs (Figure 2 and Figure 3). A repeated-measures ANOVA demonstrated a significant infusion × time interaction ($F_{2,18} = 10.02, P = .001$). The infusion × time × ISI interaction was not significant, indicating no differential impairment of performance at the 2 ISIs ($F_{2,18} = 2.19, P = .14$). Post hoc paired t tests confirmed significantly lower hit rates during ketamine administration than during the baseline of the ketamine infusion (short ISI: $t_{18} = -4.63, P < .001$; long ISI: $t_{18} = -4.60, P < .001$). Ketamine administration was associated with an increase of false alarms that was most pronounced for false alarms to BX sequences at both short and long ISI. A repeated-measures ANOVA demonstrated a significant 3-way interaction of infusion × time × false-alarm type ($F_{2,18} = 3.33, P = .04$). The degree of false-alarm increases were similar at short and long ISI, so that the infusion type × false-alarm type × ISI effect was nonsignificant ($F_{2,18} = 1.61, P = .37$). Contrasting BX error rates with rates of AV and BY errors, a significantly greater increase of BX errors than both AV and BY errors, was observed during ketamine administration as compared with baseline and placebo administration (contrasts: ketamine vs placebo session, baseline vs infusion phase, and BX vs AV error rates: $F_{1,18} = 3.54, P = .03$; contrasts: ketamine vs placebo session, baseline vs infusion phase, and BX vs BY error rates: $F_{1,18} = 12.14, P = .003$). The BX error rates were not significantly different than AV or BY error rates during the postinfusion phase as compared with the baseline phase (contrasts: ketamine vs placebo session, baseline vs postinfusion phase, BX vs AV error rates: $F_{1,18} = 0.22, P = .60$; contrasts: ketamine vs placebo session, baseline vs postinfusion phase, BX vs BY error rates: $F_{1,18} = 0.05, P = .80$). Paired t tests confirmed significantly higher BX error rates during ketamine administration than during baseline of the ketamine session for both ISIs (short ISI: $t_{18} = -4.08, P = .001$; long ISI: $t_{18} = -3.55, P = .005$).

### Table 2. Peak Amplitudes and Latencies of Sensory Event-Related Potentials (ERPs) N1 and P2 (N = 20)

<table>
<thead>
<tr>
<th></th>
<th>Placebo Session</th>
<th>Ketamine Session</th>
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<tbody>
<tr>
<td></td>
<td>Peak Amplitude, µV</td>
<td>Peak Amplitude, µV</td>
</tr>
<tr>
<td>N1 to Standards</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>$-0.49 ± 0.89$</td>
<td>$33 ± 8$</td>
</tr>
<tr>
<td>Placebo/ketamine</td>
<td>$-0.39 ± 0.98$</td>
<td>$133 ± 8$</td>
</tr>
<tr>
<td>Postinfusion</td>
<td>$-0.42 ± 0.94$</td>
<td>$128 ± 21$</td>
</tr>
<tr>
<td>P2 to Standards</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>$0.88 ± 0.57$</td>
<td>$171 ± 19$</td>
</tr>
<tr>
<td>Placebo/ketamine</td>
<td>$0.98 ± 0.62$</td>
<td>$169 ± 16$</td>
</tr>
<tr>
<td>Postinfusion</td>
<td>$1.19 ± 0.60$</td>
<td>$167 ± 9$</td>
</tr>
</tbody>
</table>

*Post hoc $P = .002$ compared with placebo administration.
†Post hoc $P = .07$ compared with session baseline.

Type interaction was not significant, indicating that the effect of ketamine on MMN-to-pitch and MMN-to-duration deviants was of similar magnitude. After ketamine administration, MMN in the pitch condition recovered partially to the session baseline value; in the duration condition, MMN remained reduced. Repeated-measures ANOVAs of MMN performed separately for each condition confirmed significant infusion × time interactions (pitch condition: $F_{2,18} = 4.42, P = .03$; duration condition: $F_{2,18} = 4.86, P = .02$). Post hoc paired t tests confirmed a significantly smaller MMN during ketamine administration than during the session baseline (pitch condition: $t_{18} = -4.82, P < .001$; duration condition: $t_{18} = -2.19, P = .04$). The corresponding comparisons for the placebo session were not significant.

Ketamine administration was associated with a slight, but significant increase of MMN peak latencies (infusion × time interaction: $F_{2,18} = 9.96, P < .001$) mainly as a result of an increase of the peak latency of MMN in the duration condition. Post hoc paired t tests demonstrated significantly longer MMN peak latency-to-duration deviants during ketamine administration than at session baseline ($t_{18} = 2.41, P = .03$) and than during placebo administration ($t_{18} = 3.56, P = .002$).

**MMN Topography**

Further analyses investigated effects of ketamine administration on MMN at specific electrode pairs (C3/C4, T3/T4, and P3/P4) that have been reported to be associated with lateralized dysfunction in schizophrenia. For each electrode pair, infusion × time × hemisphere interactions were not significant, indicating that the ketamine administration was not associated with a different left-right topography.

**N1/P2 Amplitudes and Latencies**

During the baseline of both sessions, subjects showed amplitudes and latencies of N1 and P2 in the range expected for an stimulus onset asynchrony of 300 milliseconds (Table 2). Ketamine administration was associated with a small, but significant, increase of N1 peak amplitude, resulting in a significant infusion × time interaction ($F_{2,18} = 4.70, P = .02$). Post hoc paired t tests demonstrated a significantly larger N1 peak amplitude during ketamine than placebo administration ($t_{18} = 3.69, P = .002$). The increase of N1 amplitude during ketamine administration from the session baseline failed to reach significance (post hoc paired t test: $t_{18} = 1.88, P = .07$). Ketamine administration did not affect N1 peak latency.

During the baseline of both sessions, subjects showed amplitudes and latencies of N1 and P2 in the range expected for an stimulus onset asynchrony of 300 milliseconds (Table 2). Ketamine administration was associated with a small, but significant, increase of N1 peak amplitude, resulting in a significant infusion × time interaction ($F_{2,18} = 4.70, P = .02$). Post hoc paired t tests demonstrated a significantly larger N1 peak amplitude during ketamine than placebo administration ($t_{18} = 3.69, P = .002$). The increase of N1 amplitude during ketamine administration from the session baseline failed to reach significance (post hoc paired t test: $t_{18} = 1.88, P = .07$). Ketamine administration did not affect N1 peak latency.

The P2 amplitude increased slightly, but significantly, throughout both recording sessions (effect of time: $F_{2,18} = 16.01, P < .001$). Ketamine administration was not associated with any particular effect on peak amplitude (infusion × time interaction: $F_{2,18} = 0.89, P = .40$). There was no significant effect on peak latency of P2.
Similar results were obtained, when a’ measures obtained from signal-detection analyses and calculated separately for both ISIs, were used in place of BX false-alarm rates. There was a significant infusion \times time interaction: $F_{2,17}=21.14, P<.001$, but a nonsignificant infusion \times time \times ISI interaction: $F_{2,17}=1.21, P=.30$, again indicating a significantly worse performance during ketamine administration irrespective of ISI. Paired $t$ tests demonstrated a significant decline of a’ at short and long ISI during ketamine administration as compared with baseline values (short ISI: $t_{18}=-6.24, P<.001$; long ISI: $t_{18}=-6.18, P<.001$).

**COMMENT**

This study evaluated the hypothesis that NMDARs are critically involved in formation and use of transient memory traces, both at the auditory sensory level and in a task engaging prefrontal circuitry. Specifically, the hypothesis was tested that, in humans, MMN generation—an index of the auditory sensory memory—depends on intact NMDAR functioning. The results support this hypothesis: In healthy volunteers, subanesthetic doses of the NMDA antagonist ketamine significantly diminished MMN generation, both in a pitch and duration deviance condition in patients with recent-onset and chronic schizophrenia, confirming previous reports of MMN deficits in schizophrenia. Our findings thus suggest that these deficits may be direct manifestations of deficient NMDAR-dependent neurotransmission. Reduced glutamate release, abnormal expression of specific subunits of the NMDAR, reduced messenger RNA for specific subunits of the NMDAR, and evidence for altered connectivity have been described in schizophrenia and could possibly lead or contribute to NMDA/glutamatergic hypofunction. Our results thus provide indirect evidence in support of the glutamate/NMDA hypothesis of schizophrenia.

In our study, generally greater MMN amplitudes and larger MMN-to-pitch than MMN-to-duration deviants were observed compared with the study by Javitt et al. These differences are consistent with an association of

Figure 2. Effects of ketamine infusion on performance on the “A-X” version of the Continuous Performance Test at the short interstimulus interval (n=19). Error bar values are mean±SEM. In the 4 panels, the hit and alarm rates, respectively, to the 4 possible combinations of cue and target stimuli, are presented.
greater MMN with a lower probability of the deviant stimuli and a larger difference between pitch deviant and standard stimulus, respectively, as used in our study.65 Also, ketamine increased the latency of MMN-to-duration deviants, while this latency was not abnormal in patients with schizophrenia in the study by Javitt et al. This disparity may be related to the lower deviant probability in our study, but may also point to real differences between ketamine-induced MMN deficits and those observed in schizophrenia.

Our results are at odds with a recent study in which ketamine reduced ERP measures of selective attention, but not MMN.66 However, this study used a much smaller dose of ketamine. Second, the paradigm used in this study is suited for investigating ERP indices of selective attention, but not MMN. In addition, low numbers of deviant stimuli as used in the paradigm of that study result in a poor signal-to-noise ratio, further obscuring subtle but potentially significant changes.

Generators for MMN have been localized to primary auditory cortex.57,67,68 Consistently, infusion of NMDA antagonists into primary auditory cortex of monkeys abolishes MMN.40 Thus, it is parsimonious to assume that ketamine exerted its main effect on MMN generation locally in these cortical areas. However, in humans prefrontal lesions are also associated with deficits in MMN generation and, interestingly, slight increases of N1,69,70 similar to the ketamine-induced effects in the present study. Thus, early sensory processing failures may be caused, in part, by a loss of top-down control. Ketamine induces a marked increase of metabolic activity in prefrontal areas.32,34 Therefore, it is conceivable that a loss of this top-down control secondary to ketamine-induced prefrontal dysfunction exerted an additional reducing effect on MMN generation and was responsible for the slight increase of N1.

This study also investigated ketamine-induced performance deficits in a modified AX-CPT. Ketamine administration not only decreased hit rates significantly, but was associated with a specific and significant increase of those errors that are assumed to reflect a failure to form and use a transient representation of a cue stimulus (BX errors). In contrast, ketamine did not significantly increase the rates of other possible errors where such a transient memory is not tapped (AY and BY errors). Thus, higher BX errors cannot be ascribed to an indiscriminate increase in errors by subjects. This deficit did not disproportionately worsen at the long ISI, indicating that ketamine did not impair the maintenance of the memory trace (ie, result in a faster decay of information). Rather, the profile of deficits is consistent with an impairment of processes that may involve or affect the initial formation and/or utilization of such a memory trace. This specific pattern closely resembles the pattern of deficient performance that schizophrenic patients show in this task: the accompanying publication by Javitt et al,21 and other studies of patients with schizophrenia using almost identical versions of the AX-CPT, similarly reported specific increases of context-dependent BX
higher than their respective affinities for sigma, opioid, and NMDA receptors. The similarity of ketamine-induced deficits thus suggests that NMDA-related dysfunction may contribute to the observed deficits in schizophrenia.

Are the effects of ketamine observed in this study specifically caused by its NMDA antagonist properties or would other agents affecting attention but not active at NMDA exert similar effects? The available evidence argues against the latter: administration of a fragment of the adrenocorticotropic hormone resulted in a significant reduction of an ERP measure of selective attention without affecting MMN.71,72 Also, the stimulant methylphenidate did not affect MMN generation in hyperactive children despite a significant enhancement of attention-dependent ERPs.73 Furthermore, both subanesthetic doses of nitrous oxide—recently shown to be an NMDA antagonist74,75—and ethanol, which possesses NMDA antagonistic properties76—significantly reduce MMN without affecting ERP measures of selective attention.77,80 Ketamine used in this study is a racemic mixture of the enantiomers S- and R-ketamine, with S-ketamine binding with a 4 to 5 times higher affinity to the phencyclidine-binding site of the NMDAR complex than R-ketamine.81 However, the affinity of both enantiomers to the NMDAR is several-fold higher than their respective affinities for sigma, opioid, and muscarinic receptors.81,82 It is thus unlikely that direct actions at other receptors contributed substantially to the observed effects.

The NMDA antagonists induce excessive glutamate release—an effect shared by 5-HT2A agonists; thus, the reduction of MMN could have been the result of such an effect. However, in a recently completed study of 18 healthy volunteers the psychotomimetic psilocybin, a 5-HT2A agonist, did not significantly reduce MMN despite a comparable magnitude of behavioral effects. However, psilocybin induced similar deficits in AX-CPT performance.86,87 It is thus likely that ketamine-induced excessive glutamate release contributed substantially to the specific performance deficits in the AX-CPT.

This study demonstrated that the NMDAR antagonist ketamine induces deficits in MMN generation and performance of the AX-CPT that closely resemble deficits observed in schizophrenia. In both paradigms, the effects of NMDA blockade are consistent with impairments in the formation and use of transient memory traces. Deficient NMDAR-dependent neurotransmission may contribute to such deficits in schizophrenia. This study thus supports the glutamatergic/NMDA model of schizophrenia.

Accepted for publication September 30, 1999.

Supported by grant SNF 32-50957.97 from the Swiss National Science Foundation, Berne, Switzerland (Dr Umbricht).

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