Effects of the 5-HT$_{2A}$ Agonist Psilocybin on Mismatch Negativity Generation and AX-Continuous Performance Task: Implications for the Neuropharmacology of Cognitive Deficits in Schizophrenia

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Previously the NMDA (*N*-methyl-D-aspartate) receptor (NMDAR) antagonist ketamine was shown to disrupt generation of the auditory event-related potential (ERP) *mismatch negativity* (MMN) and the performance of an 'AX'-type continuous performance test (AX-CPT)—measures of auditory and visual context-dependent information processing—in a similar manner as observed in schizophrenia. This placebo-controlled study investigated effects of the 5-HT$_{2A}$ receptor agonist psilocybin on the same measures in 18 healthy volunteers. Psilocybin administration induced significant performance deficits in the AX-CPT, but failed to reduce MMN generation significantly. These results indirectly support evidence that deficient MMN generation in schizophrenia may be a relatively distinct manifestation of deficient NMDAR functioning. In contrast, secondary pharmacological effects shared by NMDAR antagonists and the 5-HT$_{2A}$ agonist (ie disruption of glutamatergic neurotransmission) may be the mechanism underlying impairments in AX-CPT performance observed during both psilocybin and ketamine administration. Comparable deficits in schizophrenia may result from independent dysfunctions of 5-HT$_{2A}$ and NMDAR-related neurotransmission.
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INTRODUCTION

Neurocognitive deficits represent an integral feature of schizophrenic pathology and include deficits in higher cognitive functions such as attention, executive functions, and memory (Bilder, 1998; Cornblatt and Keilp, 1994; Pantelis *et al*, 1998; Saykin *et al*, 1994). Patients are also impaired in simple tasks probing sensory memory across different modalities (Javitt *et al*, 1997, 1999; Strous *et al*, 1995). For example, schizophrenic patients 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 s following stimulus presentation (Lu *et al*, 1992). These deficits are manifested in an impaired ability to match tones following a brief delay (Javitt *et al*, 1997; Strous *et al*, 1995; Wexler *et al*, 1998) and most likely represent dysfunction at

the level of the auditory sensory cortex (Rabinowicz *et al*, 2000). Consequently, these deficits can also be demonstrated in an abnormal reduction of an event-related potential (ERP) component that is generated in auditory sensory areas (Alho, 1995; Frodl-Bauch *et al*, 1997; Korzyukov *et al*, 1999; Näätänen and Alho, 1995a; Tiitinen *et al*, 1993). This ERP component constitutes an index of echoic memory and is termed *mismatch negativity* (MMN) (Näätänen, 1995; Ritter *et al*, 1995). MMN is an auditory ERP that is automatically generated whenever features of a presented stimulus differ from features of previously presented standard stimuli (Näätänen, 1995; Näätänen *et al*, 1993; Ritter *et al*, 1995). MMN is thus the manifestation of a preattentive process that compares the deviant stimulus to the transient sensory memory trace of the standard stimulus (Näätänen, 1990; Novak *et al*, 1990; Ritter *et al*, 1995). In the absence of such a memory trace, a deviant stimulus does not elicit MMN (Näätänen, 1990). Furthermore, MMN is also generated when a stimulus violates a more abstract regularity that has been extracted from previously presented stimuli (Näätänen and Winkler, 1999; Schröger, 1997). For instance, in a series of stimuli of increasingly higher frequency, a stimulus of previously

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presented, but lower, frequency will elicit an MMN, because it violates the regularity of a stepwise increase in frequency (Schröger, 1997). Similarly, infrequent repetition of one tone in a regular alternation of two tones will elicit MMN (Alain et al, 1994). Thus, MMN is an electrophysiological index of context-sensitive information processing at the level of the auditory sensory memory (Dehaene-Lambertz, 1997; Näätänen, 1992; Näätänen and Alho, 1995b; Näätänen and Winkler, 1999).

Out of 15 studies in schizophrenia, deficits in MMN generation were found in 13 studies (Alain et al, 1998; Catts et al, 1995; Hirayasu et al, 1998; Javitt et al, 1993, 1995, 2000; Kreitschmann-Andermahr et al, 1999; Oades et al, 1997; Shelley et al, 1991; Shutara et al, 1996; Umbricht et al, 1998, 1999) demonstrating deficits in context-dependent information processing of auditory stimuli at a preattentive automatic level. Schizophrenic patients also exhibit deficient performance in complex tasks that engage the prefrontal cortex (Barch et al, 2001) and require utilization of contextual information for correct task performance (Cohen et al, 1999; Javitt et al, 2000; Servan-Schreiber et al, 1996). Such a task is a modified version of an 'AX'-type continuous performance task (AX-CPT), in which subjects are required to press a button whenever the letter X follows the letter A. The AX sequences are presented with a high probability, to set up a strong response bias in subjects. Thus, whenever a letter other than A (denoted as 'B') precedes an X, access to and use of this contextual information is required to inhibit the tendency to respond to the X. Schizophrenic patients specifically commit more BX errors, suggesting a deficient use of contextual information (Cohen et al, 1999; Javitt et al, 2000; Servan-Schreiber et al, 1996).

A growing body of evidence implicates deficient NMDA (N-methyl-D-aspartate) receptor (NMDAR)-dependent neurotransmission in these deficits. In nonhuman primates, NMDAR antagonists selectively abolish the generation of MMN without affecting sensory ERPs such as N1 (Javitt et al, 1992, 1994, 1996). Likewise, we recently demonstrated that the NMDAR antagonist ketamine induces a significant reduction of MMN, but not of N1, in healthy volunteers (Umbricht et al, 2000). Similarly, ketamine and other NMDAR antagonists significantly reduced MMNm (the magnetic counterpart of MMN) and MMN, respectively, in healthy volunteers (Jääskeläinen et al, 1995a, b, 1996; Kreitschmann-Andermahr et al, 2001; Pang and Fowler, 1999). In addition, subanesthetic doses of ketamine induce a pattern of deficits in AX-CPT performance in healthy volunteers that is characterized by a specific increase of context-dependent (BX) errors and closely resembles the deficits observed in schizophrenia (Umbricht et al, 2000). Thus, the available evidence suggests that in schizophrenia NMDAR-related dysfunction may contribute significantly to abnormalities in context-dependent information processing both at preattentive automatic and at attention-dependent controlled levels.

There is, however, evidence that abnormalities in 5-HT$_{2A}$ receptor-dependent neurotransmission may also play a role in some symptoms and cognitive deficits in schizophrenia. Some of this evidence comes from the observation that indoleamine hallucinogens such as LSD or psilocybin can induce—among a wide array of behavioral effects—psy-

chotic symptoms that resemble symptoms of schizophrenia (Vollenweider, 1998; Vollenweider et al, 1998). The affinity of indoleamine hallucinogens at the 5-HT$_{2A}$ receptor is highly correlated with their hallucinogenic potency in humans (Aghajanian and Marek, 1999a). A recent study demonstrated that psilocybin not only induced psychotic symptoms, but also impaired spatial working memory in a similar fashion as observed in schizophrenia (Geyer, 1998; Park and Holzman, 1992; Vollenweider et al, 1997, 1998). These cognitive and behavioral effects seem primarily mediated through the agonist action of psilocybin at the 5-HT$_{2A}$ receptor, in that they are blocked in a dose-dependent fashion by ketanserin and risperidone but not haloperidol (Vollenweider et al, 1998). Dysfunctional 5-HT$_{2A}$ receptors may also play a role in abnormal gating mechanisms in schizophrenia; in animals administration of 5-HT$_{2A}$ receptor agonists disrupts prepulse inhibition (PPI), a measure of gating mechanisms (Geyer, 1998). In healthy volunteers, however, psilocybin failed to reduce PPI (Gouzoulis-Mayfrank et al, 1998), possibly because doses were substantially lower than those used in rodents. Furthermore, the 5-HT$_{2A}$ antagonist effect shared by atypical antipsychotic drugs may play a role in their, albeit modest, ameliorative effects on certain cognitive deficits in schizophrenia that are not affected by classical D$_2$ receptor-blocking antipsychotics (Green et al, 1997; Meltzer and McGurk, 1999; Purdon et al, 2000; Stip and Lussier, 1996; Umbricht et al, 1998, 1999).

In humans, administration of psilocybin is, like ketamine, associated with increased dopamine release (Vollenweider et al, 1999), a putative model of dysfunctional dynamics of the dopaminergic system in schizophrenia. Recently, 5-HT$_{2A}$ agonists have also been reported to induce excessive release of glutamate that can be blocked by group II metabotropic receptor agonists (Aghajanian and Marek, 1999b). A similar excessive glutamate release has also been reported after administration of NMDAR antagonists (Moghaddam and Adams, 1998). Indeed, it has been suggested that this shared effect may be the mechanism mediating similar psychomimetic and cognitive effects of both NMDAR antagonists and 5-HT$_{2A}$ agonists, and that comparable disturbances in the dynamics of the glutamate system possibly due to dysfunction of NMDA and/or 5-HT$_{2A}$ receptor-dependent neurotransmission may be operative in schizophrenia (Aghajanian and Marek, 2000). In summary, there is evidence consistent with the hypothesis that dysfunctional 5-HT$_{2A}$ signaling may be an important factor in cognitive deficits in schizophrenia.

The primary aim of this study was to investigate the effects of a 5-HT$_{2A}$ agonist, psilocybin, on the generation of MMN and sensory ERPs and on AX-CPT performance in healthy volunteers using identical test procedures as used previously in our ketamine study (Umbricht et al, 2000) and to address the potential role of the 5-HT$_{2A}$ receptor in both these cognitive operations. We wanted to investigate if dysfunctional 5-HT$_{2A}$ receptor-dependent neurotransmission might also contribute to deficits in MMN generation and AX-CPT performance, and thus address the hypothesis that abnormalities of this receptor may play a role in comparable deficits in schizophrenia. Given both the direct action at distinct receptors and yet some overlap of secondary pharmacological effects of NMDAR antagonists

and 5-HT$_{2A}$ receptor agonists, we were also interested in addressing another question—whether such shared pharmacological effects indeed constitute an important mechanism by which these psychotomimetics achieve their effects at both the preattentive and attention-dependent level. We thus assumed that a similar pattern of deficits would point to shared pharmacological effects as an important mechanism, while different effects would indicate main mechanisms of action more closely related to the divergent pharmacological characteristics of ketamine and psilocybin.

Psilocybin (*O*-phosphoryl-4-hydroxy-*N,N*-dimethyltryptamine) is a naturally occurring indoleamine hallucinogen. After ingestion it is metabolized to psilocin (Hasler *et al*, 1997). In rats, psilocin has been demonstrated to bind with high affinity to the 5-HT$_{2A}$ ($K_i = 6.0$ nM) and with moderate affinity to the 5-HT$_{1A}$ receptor ($K_i = 190$ nM) (McKenna *et al*, 1990). Although indoleamine hallucinogens bind to various subtypes of serotonin receptors, the hallucinogenic and cognitive effects are primarily mediated through agonist action at the 5-HT$_{2A}$ receptor (Aghajanian and Marek, 1999a; Vollenweider *et al*, 1998). At the doses used, psilocybin has no medical side effects.

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 Zurich in accordance with the Helsinki declaration. The use of psilocybin was approved by the Swiss Federal Health Office (BAG), Department of Pharmacology and Narcotics (DPN), Bern, Switzerland. Psilocybin was obtained from the BAG–DPN and was prepared as capsules (1 and 5 mg) at the pharmacy of the Kantonsspital Luzern, Switzerland.

Subjects

Normal subjects were recruited from the local university and technical college through advertisement. The rationale and the goal of the study were explained in lay terms to the subjects during the initial screening interview by the principal investigator (DU). In addition, the expected psychotomimetic and hallucinogenic effects were reviewed in detail and described as accurately as possible. Subjects were informed that they would be under constant supervision during both sessions. All potential study candidates were thus fully informed about the goal and the risks of the study both orally and in writing, and all signed informed consent. After signing informed consent, subjects underwent a screening that included a structured clinical interview (Composite International Clinical Interview: CIDI) (Wittchen and Semler, 1996) 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 count, routine blood chemistry and an electrocardiogram. Exclusion criteria were (a) a history of present or past history of Axis I disorders, (b) a history of drug dependence or present drug abuse, (c) a family history of Axis I disorders extending to second-degree relatives, and (d) the presence of any medical disorder. Intelligence was assessed using the Hamburg-Wechsler Intelligence Scale, revised version

(Tewes, 1994). Handedness was determined using the handedness scale by Chapman and Chapman (1987). A total of 18 right-handed subjects (10 men/and eight women) were enrolled in the study. Their mean age was 25.1 ± 4.3 years. Of these, 16 were currently university students; two had completed an apprenticeship and were employed at the time of the study. Their mean verbal and performance IQs were 114 ± 11 and 117 ± 9, respectively. None of the female study subjects was pregnant. Study subjects received a financial remuneration for participation.

Procedures

Psilocybin/Placebo administration Each subject participated in both a psilocybin and a placebo session on two separate days in a randomized and counterbalanced order. Subjects were blind to drug order. On both days, subjects arrived in the laboratory around 0900 h after an overnight fast. After an initial baseline ERP recording, subjects were given psilocybin at a dose of 0.28 mg/kg in 1- and 5-mg capsules or an equal number of capsules containing placebo. A second ERP recording was obtained 70 min after ingestion of psilocybin or placebo. Afterwards subjects stayed under constant supervision until all drug effects had worn off. After an examination by the principal investigator, subjects were released into the custody of a partner or immediate relative.

Behavioral ratings At the end of each ERP recording session, behavioral effects were assessed using the Brief Psychiatric Rating Scale (scale points: 1–7) (Woerner *et al*, 1988). Orientation to person, place, and time were assessed with three items from the Modified Mini-Mental State interview (Teng and Chui, 1987): 'Date and Place of Birth', 'Temporal Orientation', and 'Spatial Orientation', with a maximum score of 25 indicating full orientation.

Auditory test paradigm ERP recordings were acquired during the presentation of auditory stimuli. Auditory stimuli consisted of 100-ms, 1000-Hz standard stimuli intermixed with 100-ms, 1500-Hz frequency deviants and 250-ms, 1000-Hz duration deviants. Stimuli were presented in a fixed order (nine standards, one frequency deviant, nine standards, one duration deviant) with a stimulus onset asynchrony (SOA) of 300 ms and presented through foam insert earphones at a nominal intensity of 75 dB sound pressure level (SPL). Rise–fall time was 5 ms for all stimuli. Stimuli were presented in four blocks, with a total of 1517 stimuli. Subjects performed the AX-CPT during presentation of the auditory test paradigm.

EEG recordings EEG recordings, acquired with a Neuroscan system (Neuroscan Labs, Sterling, VA, USA), were obtained from 28 scalp locations, consisting of standard 10/20 placements plus right and left mastoid placements, along with right vertical and horizontal electro-oculogram (EOG) electrodes. An electrode placed on the nose served as reference. Electrode impedance was kept below 5 kΩ. Activity was amplified with a band pass of 0.1–100 Hz (6 dB down) and digitized continuously at a sampling rate of 500 Hz. Digital tags were obtained to all auditory stimuli.

Epochs were constructed that consisted of a 100-ms prestimulus baseline and a 500-ms poststimulus interval. After correction for vertical eye movements and blinks using the algorithm provided by Neuroscan software, epochs with amplitudes exceeding $\pm 75\,\mu V$ at any electrode except the vertical eye leads were excluded from averaging. Following artifact rejection, epochs were averaged off-line for each subject, session, phase and stimulus type, and were digitally filtered with a low-pass filter of 15 Hz (24 dB down).

Analyses focused on the generation of N1 and P2 to the standard stimuli and MMN generation to frequency and duration deviant stimuli. MMN waveforms were obtained by subtracting waveforms elicited by standards from waveforms elicited by frequency- or duration-deviant stimuli. Waveforms were mathematically referenced to an average-mastoid reference prior to peak detection. For N1, amplitude was defined as peak negativity within the 50–150 ms latency; for P2, amplitude was defined as peak positivity within the 150–250 ms latency. For frequency MMN, amplitude was defined as the peak negativity within the 100–225 ms latency window. For duration MMN, amplitude was defined as the peak negativity within the 200–300 ms range.

In one subject, the number of sweeps available for computing the MMN average both in the frequency deviant and duration deviant condition during psilocybin administration was below the threshold of 100 (set because of signal-to-noise concerns). Thus, only 17 subjects were included in the analyses of MMN. The mean number of sweeps available for computing MMN to frequency deviants was not significantly lower during psilocybin administration (infusion $\times$ time interaction $F_{1,16} = 3.59$, $p = 0.08$). It was significantly lower for computing MMN to duration deviants (infusion $\times$ time interaction $F_{1,16} = 4.55$, $p = 0.05$) and the sensory ERPs N1 and P2 (infusion $\times$ time interaction $F_{1,17} = 5.78$, $p = 0.03$). In all instances, however, the mean number of sweeps was sufficiently high to ensure a satisfactory signal-to-noise ratio (see Table 1).

AX continuous performance test   Visual stimuli consisted of individual letters and were presented sequentially on a computer screen for 250 ms each. Subjects were instructed to press a button whenever the letter A (correct cue) was

followed by the letter X (correct target). All other sequences were to be ignored, including sequences in which an incorrect cue (designated 'B', but comprising all letters other than A or X) was followed by the target letter (X) or sequences in which a correct cue (A) was followed by an incorrect target (designated 'Y', but comprising all letters other than A or X). Stimuli were presented in four blocks of 280 stimuli (140 pairs) each. Within each block, 50% of the cue–target sequences were presented with short (0.8 s) interstimulus interval (ISI) and 50% with long ISI (4 s). Short and long ISIs were pseudorandomly intermixed. The time between stimulus pairs was constant at 0.8 s. Of the stimulus pairs, 70% were AX sequences; all other sequences (BX, AY, BY) occurred with a probability of 0.1 each.

One subject completely stopped performing the task during psilocybin administration; in another subject, registration of response codes during the psilocybin administration failed due to computer problems. Thus, data of 16 subjects were included in the analysis.

Statistical Analysis

For ERP analyses, the primary dependent measures consisted of (a) amplitude and latency of N1 and P2 at Fz to the standard stimulus, and (b) amplitude and latency of frequency and duration MMN at FCz. Effects of psilocybin were evaluated using repeated-measures ANOVAs with *session* (psilocybin *vs* placebo) and *time* (baseline *vs* psilocybin/placebo administration) as repeated measures. For the analysis of MMN, an additional within-subject two-level factor denoting *MMN type* (frequency *vs* duration condition) was included. Paired *t*-tests were performed for *post hoc* analysis if indicated.

For the analyses of performance of AX-CPT, dependent measures consisted of hit rate (correct detection of AX sequences) and false alarm rates to BX, AY, or BY sequences. Effects of psilocybin on hit rate were evaluated with $2 \times 3 \times 2$ factorial repeated-measures ANOVAs with *session* (psilocybin *vs* placebo), *time* (baseline *vs* psilocybin/ placebo administration), and *ISI* (short *vs* long) as repeated measures. For analyses of false alarm rates, an additional within-subject factor with three levels denoting *false alarm type* (BX *vs* AY *vs* BY) was included. Differences between

Table 1   Peak Amplitudes and Latencies of Sensory ERPs and MMN

	Placebo session			Psilocybin session		
	Peak amplitude	**Peak latency**	**Mean no. of averaged sweeps**	**Peak amplitude**	**Peak latency**	**Mean no. of averaged sweeps**
N1 to standards						
Baseline	−0.50 ± 83	132 ± 9	4002 ± 612	−0.60 ± 0.80	131 ± 9	3941 ± 542
Placebo/psilocybin administration	−0.58 ± 1.04	128 ± 21	3291 ± 767	−0.34 ± 0.61*	133 ± 9	2662 ± 930
P2 to standards						
Baseline	0.77 ± 0.56	186 ± 30	4002 ± 612	−0.85 ± 0.78	182 ± 18	3941 ± 542
Placebo/psilocybin administration	0.83 ± 0.59	186 ± 31	3291 ± 767	−0.77 ± 0.81	180 ± 27	2662 ± 930
MMN to frequency deviants						
Baseline	−5.36 ± 3.44	124 ± 10	252 ± 36	−5.23 ± 3.38	130 ± 16	247 ± 34
Placebo/psilocybin administration	−5.10 ± 2.56	124 ± 13	206 ± 53	−4.49 ± 2.88	126 ± 16	175 ± 49
MMN to duration deviants						
Baseline	−4.80 ± 3.90	233 ± 19.00	247 ± 40	−4.83 ± 2.37	228 ± 21	245 ± 34
Placebo/psilocybin administration	−4.10 ± 2.24	236 ± 22	206 ± 49	−3.83 ± 2.22	229 ± 31	176 ± 49

Peak amplitudes in μV; latencies in ms. *Post hoc* $p < 0.05$ compared with session baseline.

rates of BX errors and AY and BY errors, respectively, during the two phases of both sessions were evaluated with simple within-subject contrasts involving *session* (contrast: psilocybin *vs* placebo), *time* (contrast: baseline *vs* psilocybin/placebo administration), and *false alarm type* (contrast: BX *vs* AY; BX *vs* BY). *Post hoc* paired *t*-tests were used to assess specific differences if indicated. Furthermore, the discrimination index d' and response bias B_r were calculated using hit rates and total false alarm rates for the long and short ISI condition (Snodgrass and Corwin, 1988). Effects of psilocybin administration were evaluated with repeated-measures ANOVAs similarly as outlined above.

For behavioral analyses, we used the BPRS total score and five factors that can be derived from the BPRS items: (a) *psychosis factor*—conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content; (b) *activation factor*—tension, mannerism and posturing, excitement; (c) *anxiety/depression factor*—somatic concern, anxiety, guilt feelings, depressive mood; (d) *anergia factor*—emotional withdrawal, motor retardation, blunted affect; and (e) *hostility factor*—hostility, suspiciousness, uncooperativeness. Effects of psilocybin were evaluated with 2×3 factorial repeated-measures ANOVAs with *session* (psilocybin *vs* placebo) and *time* (baseline *vs* psilocybin/placebo administration) as repeated measures.

Alpha levels of 0.05 were considered significant throughout.

RESULTS

Effects of Psilocybin on Behavior and Orientation

The BPRS total score increased from 18.9 ± 1.5 to 28.1 ± 9.9 (infusion $\times$ time interaction: $F_{1,17} = 16.00$, $p = 0.001$). In addition, significant increases of the BPRS psychosis factor scores (baseline: 4.0 ± 0.0; psilocybin administration: 7.5 ± 2.9; infusion $\times$ time interaction: $F_{1,17} = 24.79$, $p < 0.001$) were observed. There were also significant, but less pronounced increases of the BPRS anergia factor score (baseline: 3.2 ± 0.5; psilocybin administration: 4.7 ± 2.7; infusion $\times$ time interaction: $F_{1,17} = 5.30$, $p < 0.05$), activation factor score (baseline: 3.2 ± 0.5; psilocybin administration: 4.7 ± 2.5; infusion $\times$ time interaction: $F_{1,17} = 6.82$, $p < 0.05$), and hostility factor score (baseline: 3.1 ± 0.5; psilocybin administration: 4.4 ± 1.9; infusion $\times$ time interaction: $F_{1,17} = 8.00$, $p < 0.05$) during psilocybin administration. In all subjects, psilocybin did not change autobiographic, temporal, or spatial orientation.

Effects of Psilocybin on Auditory ERPs

N1/P2 During the baseline of both sessions, mean amplitudes and latencies of N1 and P2 were in the range expected for an SOA of 300 ms (Table 1), with maxima at Fz. Psilocybin administration was associated with a significant decrease of N1 peak amplitude (session $\times$ time interaction: $F_{1,17} = 6.03$, $p < 0.05$) (Table 1 and Figure 1). *Post hoc* paired *t*-tests demonstrated a significantly smaller N1 peak amplitude during psilocybin than session baseline ($t = -2.09$, $df = 17$, $p = 0.05$). Psilocybin administration did not affect N1 peak latency. An analysis of the effects of psilocybin administration on N1 topography was performed with selected electrode sites (F3, F4, C3, C4, P3, P4) using a repeated-measures ANOVA with five within-subject factors: *left vs right location*, *anterior–posterior location* (frontal *vs* central *vs* parietal electrodes), *time* (baseline phase *vs* psilocybin/placebo administration) and *session* (psilocybin *vs* placebo). This analysis demonstrated a significant infusion $\times$ time interaction owing to the decrease of the mean N1 amplitude during psilocybin administration ($F_{1,17} = 6.14$, $p = 0.03$). The interactions
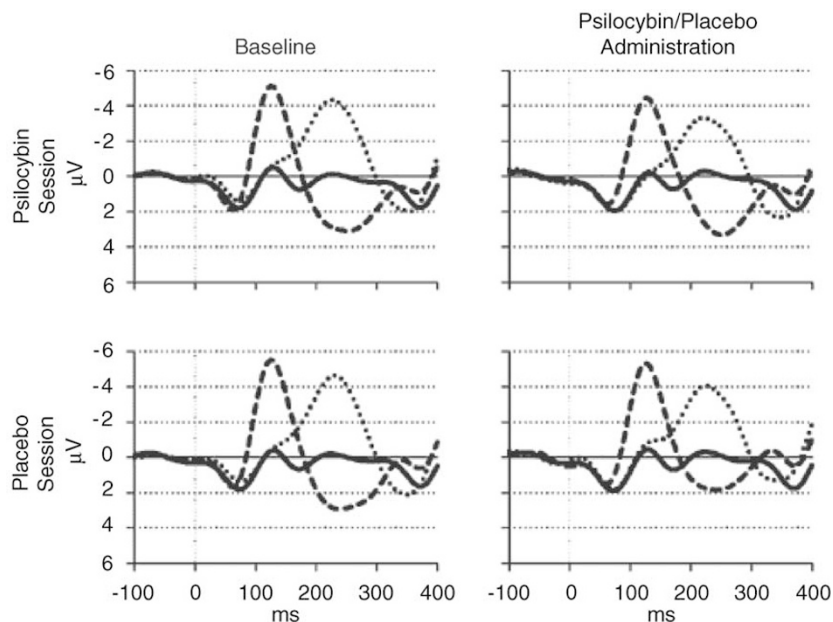
Figure 1 Grand average waves in response to standard stimuli (solid line), frequency deviants (dashed line), and duration deviants (dotted line).

involving the *left vs right location* or *anterior–posterior location* factors were not significant, indicating no change in topography of N1. Psilocybin did not affect the amplitude or latency of P2.

MMN In both baseline sessions, robust MMN amplitudes to frequency and duration deviants were recorded, with MMN maxima at FCz. MMN to frequency deviants was larger than MMN to duration deviants (see Table 1 and Figure 2). The MMN to frequency deviants peaked at 121 ± 9 and 128 ± 19 ms in the placebo and psilocybin baseline phases, respectively. As expected, the corresponding latencies for MMN to duration deviants occurred with a delay of approximately 100 ms at 234 ± 17 and 230 ± 21 ms in the placebo and psilocybin sessions, respectively. During both placebo and psilocybin administration, MMN amplitudes decreased slightly, and this decrease was more pronounced for the MMN to frequency deviants during psilocybin administration; however, repeated-measures ANOVA failed to demonstrated a significant effect of psilocybin administration on MMN peak amplitudes in the frequency and duration condition (session × time interaction: $F_{1,16} = 2.22$, $p = 0.16$; session × time × MMN type interaction: $F_{1,16} = 0.14$, $p = 0.7$) (Table 1 and Figure 2). In general, MMN to duration deviants was smaller than MMN to frequency deviants (main effect of MMN type: $F_{1,16} = 4.86$, $p < 0.1$). Repeated-measures ANOVAs of MMN performed separately for each condition demonstrated a stronger effect on MMN to frequency than MMN to duration deviants during psilocybin administration (session × time interaction: $F_{1,16} = 3.20$, $p = 0.09$ for frequency condition and $F_{1,16} = 0.36$, $p = 0.6$ for duration condition).

Psilocybin administration did not affect MMN peak latencies (session × time interaction: $F_{1,16} = 0.71$, $p = 0.4$). As expected, there was a highly significant effect of MMN type ($F_{1,16} = 452.96$, $p < 0.000$) due to the consistently longer peak latency of MMN to duration deviants.
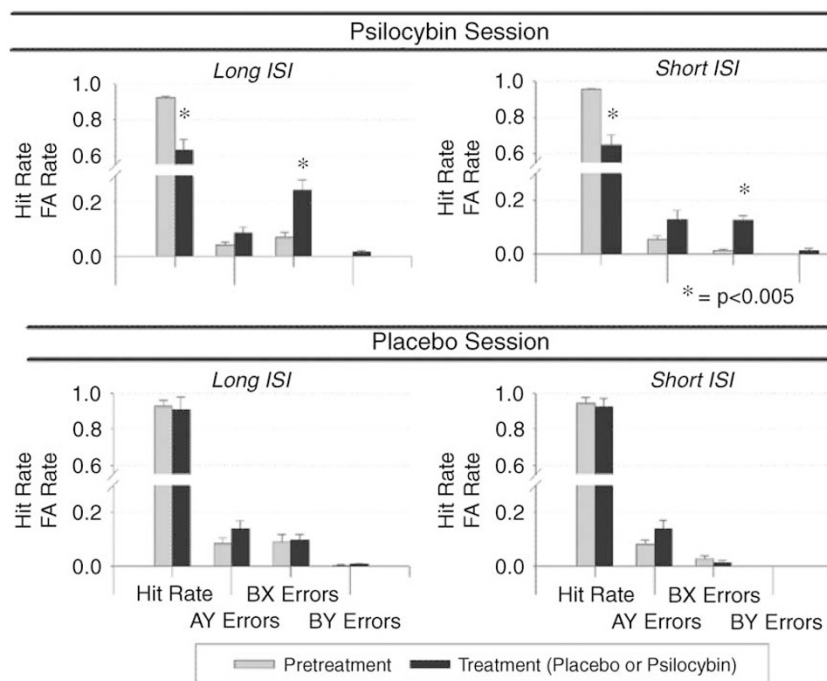
Effects of Psilocybin on AX-CPT Performance

Subjects performed the AX-CPT during the collection of ERP data. Psilocybin administration was associated with a significant decline of the hit rate at both ISIs (infusion × time interaction: $F_{1,15} = 23.92$, $p < 0.001$) (Figure 3) The infusion × time × ISI interaction was not significant, indicating no differential impairment of performance at the two ISIs ($F_{1,15} = 0.72$, $p = 0.4$). *Post hoc* paired *t*-tests confirmed significantly lower hit rates during psilocybin administration than during the baseline of the psilocybin infusion (short ISI: $t = -5.03$, df $= 15$, $p < 0.001$; long ISI: $t = -4.96$, df $= 15$, $p < 0.001$).

Psilocybin administration was associated with an increase of false alarms, which was most pronounced for false alarms to BX sequences at both short and long ISIs. A repeated-measures ANOVA demonstrated a significant three-way interaction of infusion × time × false alarm type ($F_{2,14} = 13.51$, $p = 0.001$). The infusion type × ISI × time × false alarm type effect was not significant, indicating a similar increase of false alarms across both delays ($F_{2,16} = 0.63$, $p = 0.5$). When we contrasted BX error rates with rates of AY and BY errors, a significantly greater increase of BX errors than both AY and BY errors was observed during psilocybin administration as compared with baseline and placebo administration (contrasts—psilocybin *vs* placebo session, baseline *vs* infusion phase, BX *vs* AY error rates: $F_{1,15} = 16.03$, $p = 0.001$; contrasts—psilocybin *vs* placebo session, baseline *vs* infusion phase, BX *vs* AY error rates: $F_{1,15} = 28.30$, $p < 0.001$). Paired *t*-tests confirmed significantly higher BX error rates during psilocybin administration than during baseline of the psilocybin session for both ISIs (short ISI: $t = 5.95$, df $= 15$, $p < 0.001$; long ISI: $t = 5.23$, df $= 15$, $p < 0.001$).
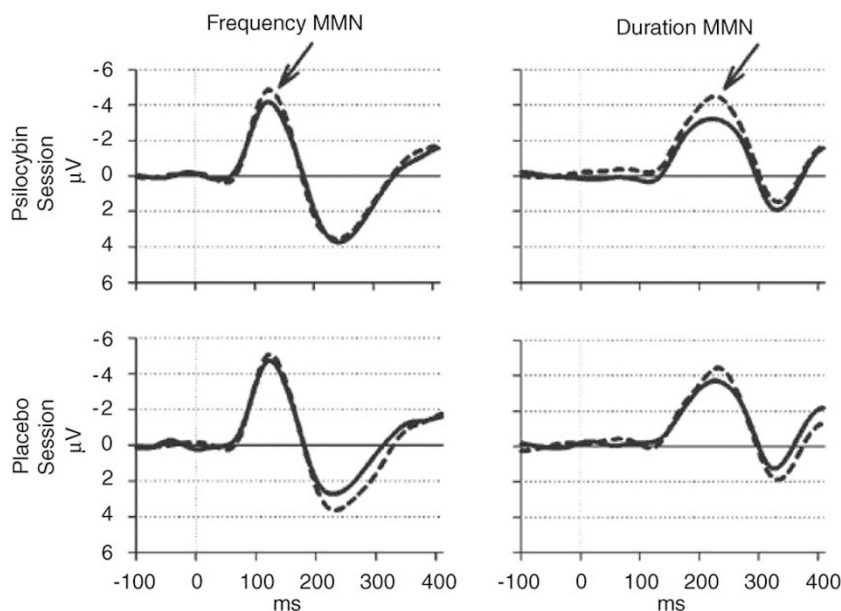
Figure 2 Grand average difference waves (MMN). Baseline recording (dashed line); administration of psilocybin or placebo (solid line).

Figure 3 Effects of psilocybin (upper panel) and placebo (lower panel) administration on AX-CPT performance ($n = 16$). Bars indicate mean $\pm$ SEM.

Table 2 Discrimination Index d' ($\pm$ SD) During Performance of the AX-CPT

	Baseline	Psilocybin/placebo administration
Psilocybin session		
Short ISI	3.70 $\pm$ 0.42	1.71 $\pm$ 0.96*
Long ISI	3.17 $\pm$ 0.57	1.55 $\pm$ 0.79*
Placebo session		
Short ISI	3.56 $\pm$ 0.57	3.31 $\pm$ 0.67
Long ISI	3.10 $\pm$ 0.54	2.91 $\pm$ 0.73

*Post hoc $p < 0.001$ compared with session baseline.

Similarly, when we used d' as the dependent measure, a repeated-measures ANOVA demonstrated a significant decrease of d' during psilocybin administration that was independent of ISI (interaction of session $\times$ phase: $F_{1,16} = 52.49$, $p < 0.001$; interaction of session $\times$ phase $\times$ ISI: $F_{1,16} = 1.43$, $p = 0.2$) (Table 2). This decrease was not because of a more liberal response bias induced by psilocybin, as mean B_r decreased in both ISI conditions during psilocybin administration (data not shown; repeated-measures ANOVA session $\times$ phase interaction: $F_{1,16} = 2.34$, $p = 0.13$).

DISCUSSION

In a previous study, we have shown that the NMDAR antagonist ketamine reduced MMN generation and AX-CPT performance in a fashion similar to the deficits observed in schizophrenic patients, thus providing supporting evidence

for the NMDA/glutamate hypothesis of schizophrenia (Umbricht *et al*, 2000). The present study investigated the effects of the 5-HT$_{2A}$ agonist psilocybin on these measures, to explore the potential role of 5-HT$_{2A}$ receptor dysfunction in such deficits and to address the question of whether abnormalities in 5-HT$_{2A}$ receptor-dependent neurotransmission might also contribute to similar deficits in schizophrenia. Administration of the 5-HT$_{2A}$ agonist psilocybin induced a significant reduction of the sensory ERP N1, but was not associated with significant decreases of MMN to frequency and duration deviants. In contrast, psilocybin administration was associated with deficits in AX-CPT performance that were particularly characterized by a failure to use contextual information (BX errors), whereas the rates of other possible errors where contextual information is not important were not significantly altered. Furthermore, the absence of a delay effect indicates that psilocybin did not adversely affect the maintenance of contextual information.

The significant reduction of N1, but not of MMN, during administration of psilocybin differs from the pattern of effects (significant reductions of MMN, but not of N1) during ketamine administration (Umbricht *et al*, 2000). In contrast, the profile of psilocybin-induced deficits in AX-CPT performance is remarkably similar to the deficits observed in healthy volunteers during ketamine administration and in schizophrenic patients (Cohen *et al*, 1999; Javitt *et al*, 2000; Servan-Schreiber *et al*, 1996; Umbricht *et al*, 2000). To the extent that these differences and similarities reflect the underlying mechanisms, our results indicate that the pharmacological properties unique to ketamine and psilocybin (ie the NMDAR antagonist and 5-HT$_{2A}$ receptor agonist action, respectively) are the important factor determining their

effects on MMN and N1 generation. Thus, together with the findings of our previous study, the results of this investigation support the conclusion that the generation of MMN indeed depends strongly on NMDAR functioning, whereas the 5-HT_{2A} receptor plays a lesser role. Conversely, deficits in AX-CPT performance induced by both ketamine and psilocybin may result not only from their direct antagonist and agonist actions at their respective receptor sites, but also from secondary pharmacological effects that appear to be similar in nature for both drugs and take place downstream to these receptor sites in dopamine and glutamate systems.

Both NMDA and 5-HT_{2A} receptors exert strong modulatory effects on dopaminergic and glutamatergic systems in rodents and humans. The blockade or activation, respectively, of these receptors leads to changes that seem to affect the dynamic properties of these neurotransmitter systems. In animals, the administration of NMDAR antagonists leads to target-specific disruption of the normal functioning of ascending dopaminergic pathways (Takahata and Moghaddam, 1998). Both activation and blockade of 5-HT_{2A} receptors have been demonstrated to exert strong modulatory effects on dopaminergic neurotransmission (Lucas *et al*, 2000; Yan, 2000). In humans, ketamine administration increases spontaneous and amphetamine-induced dopamine release (Breier *et al*, 1998; Kegeles *et al*, 2000; Vollenweider *et al*, 2000). Similarly, administration of psilocybin in healthy volunteers is associated with increased dopamine release (Vollenweider *et al*, 1999). In addition, both NMDAR antagonists and 5-HT_{2A} agonists induce excessive release of glutamate in rodents, an effect that can be blocked in both cases by group II metabotropic receptor agonists (Adams and Moghaddam, 1998; Aghajanian and Marek, 1999b; Moghaddam *et al*, 1997; Moghaddam and Adams, 1998). Consistently, in human volunteers lamotrigine, a drug that inhibits glutamate release, attenuates the cognitive effects of ketamine (Anand *et al*, 2000). Thus, NMDAR antagonists and 5-HT_{2A} agonists share some secondary pharmacological effects. Besides these similar effects, 5-HT_{2A} receptors have been shown to modulate NMDAR-dependent effects (Arvanov *et al*, 1999), and even antagonize effects of NMDAR antagonists (Farber *et al*, 1998).

In healthy volunteers, ketamine-induced cognitive deficits are ameliorated by haloperidol (a dopamine D_2 receptor blocker) and lamotrigine (Anand *et al*, 2000; Krystal *et al*, 1999). In contrast, psilocybin-induced cognitive deficits are only ameliorated by 5-HT_{2A} antagonists, but not by dopamine D_2 antagonists (Vollenweider *et al*, 1998). Hence, increased glutamatergic tone (ie, abnormal dynamics of this system) may be the common denominator underlying overlapping aspects of the cognitive effects of dissociative NMDAR antagonists and hallucinogenic 5-HT_{2A} agonists in humans (Aghajanian and Marek, 2000).

To the extent that deficits induced by acute drug challenges in healthy volunteers inform us about pathophysiological mechanisms underlying comparable deficits in schizophrenia, the findings of this and our previous study (Umbricht *et al*, 2000) have several implications for the investigation, pathophysiology, and treatment of cognitive deficits in schizophrenia. First of all, they suggest

that deficits of long-latency ERPs such as N1 and MMN may provide potentially useful markers of specific receptor-related abnormalities, whereas abnormal performance in tasks such as the AX-CPT may be similar in patients whose primary abnormality lies within quite different receptor systems (such as independent abnormalities in both NMDA receptor and 5-HT_{2A} receptor-dependent neurotransmission). Thus, profiling patients with regard to their performance on neuropsychological tests may not permit specifying etiologically heterogeneous subgroups. Conversely, using markers of early information processing such as ERPs may provide indices that are closer to suspected abnormalities in NMDAR and 5-HT_{2A} receptor-dependent neurotransmission.

Second, neurocognitive deficits have become a major treatment focus in recent years, with the growing realization that they constitute an important limiting factor for rehabilitation and outcome (Bilder, 1997; Bilder *et al*, 2000; Green, 1996). If indeed excessive glutamate release (ie abnormal dynamics of the glutamate system, whether as a result of NMDA receptor hypofunction or excessive signaling through the 5-HT_{2A} receptor) plays a role in these deficits, then 5-HT_{2A} receptor antagonists, but not dopamine D_2 receptor antagonists, would be expected to exert beneficial effects: In the scenario of a primary deficit in NMDAR-dependent neurotransmission, 5-HT_{2A} antagonists may counteract its secondary effects on the glutamate system, whereas in the case of 5-HT_{2A} receptor-related dysfunction their effect may be direct. Both scenarios would predict that atypical but not typical antipsychotic drugs improve cognitive deficits that result from secondary disturbances due to NMDAR hypofunction, such as deficits in AX-CPT and possibly other cognitive tasks that tax attention and working memory. In contrast, neither atypical nor typical antipsychotics would be expected to affect those deficits hypothesized to be a direct manifestation of NMDAR hypofunction such as deficient MMN generation. Indeed, there is accumulating evidence that atypical antipsychotics, in contrast to typical compounds, improve deficits in tasks assessing verbal memory, immediate recall, and attention (Green *et al*, 1997; Meltzer and McGurk, 1999; Purdon *et al*, 2000; Stip and Lussier, 1996). In addition, we and others have previously reported exactly such effects of clozapine and, to a lesser extent, risperidone in studies evaluating their effects on MMN and the attention-dependent ERP P3 (Schall *et al*, 1998; Umbricht *et al*, 1998, 1999). Clozapine and risperidone, but not typical antipsychotics, significantly improved the deficient generation of P3 (an attention-dependent ERP) in schizophrenia; like typical antipsychotics, however, clozapine and risperidone failed to affect MMN deficits (Ford *et al*, 1994; Schall *et al*, 1998; Umbricht *et al*, 1998, 1999). Consistent with these observations, we have found that both ketamine and psilocybin significantly reduce auditory P3 generation (Umbricht *et al*, 2001).

The finding of a significant decrease of N1 amplitude during psilocybin administration is consistent with studies demonstrating a tight modulation of the so-called N1 intensity dependence by the serotonergic system (Hegerl and Juckel, 1993, 1994a). N1 intensity dependence refers to the increase of N1 amplitude with increasing stimulus intensity (Hegerl and Juckel, 1994b). There is considerable

evidence that a low serotonergic tone is associated with an increased N1 intensity dependence (Gottfries *et al*, 1976; Hegerl *et al*, 1995; Juckel *et al*, 1999; Perris *et al*, 1979; Tuchtenhagen *et al*, 2000; von Knorring and Perris, 1981; Wang *et al*, 1996), an effect mediated in particular through the 5-HT$_{1A}$ and 5-HT$_{2A}$ receptor (Juckel *et al*, 1997). One would therefore expect a 5-HT$_{2A}$ agonist to reduce N1 intensity dependence or, with intensity kept constant, to reduce N1 amplitude. The latter is exactly the observation in this study. We note that early ERP studies reported a reduced N1 intensity dependence in schizophrenic patients (Buchsbaum, 1977; Landau *et al*, 1976; Roth *et al*, 1991; Schooler *et al*, 1976). This abnormality, if confirmed in studies using modern ERP methodology, might thus relate to dysfunction in 5-HT$_{2A}$ receptor-dependent neurotransmission.

Psilocybin administration was associated with a small but nonsignificant decrease of MMN. It is conceivable that psilocybin reduces MMN, but that our study lacked the power to detect significant changes. In our study on the effects of ketamine, however, a similar number of subjects (20) was investigated and significant effects were observed. Furthermore, a significant effect on N1 was observed in this study. Thus, any reducing effect of 5-HT$_{2A}$ agonism on MMN generation would be much smaller than the effect of NMDA blockade on MMN or the effect of psilocybin on N1 generation. Furthermore, psilocybin had a more pronounced effect on MMN to frequency deviants. This may actually reflect its reducing effect on N1, given that MMN elicited with the particular paradigm used in this study is confounded with an N1 to the deviant stimulus. Such a confound is not present in the MMN to duration deviants, where the effect of psilocybin was not even close to significance.

It is possible that the dose of psilocybin was not comparable to the ketamine dose used in our previous study; however, the cognitive and behavioral effects were of similar magnitude as observed in our previous ketamine study. Thus, at a dose that induced significant deficits in higher cognitive function, psilocybin had no effect on MMN. This could mean that the 5-HT$_{2A}$ receptor indeed plays no role in MMN generation or, alternatively, that the processes underlying MMN generation may be more impervious to abnormal 5-HT$_{2A}$ signaling, requiring a much higher dose for their disruption.

In conclusion, in healthy volunteers the 5-HT$_{2A}$ agonist psilocybin was associated with significant deficits in the AX-CPT performance similar to those previously observed during ketamine administration and in schizophrenia, but failed to reduce MMN generation. These findings suggest that deficits in higher cognitive functions in schizophrenia may result from independent abnormalities in both NMDA and 5-HT$_{2A}$ receptor systems. The disruption of normal glutamatergic signaling may be a candidate mechanism mediating these shared effects. In addition, the results of this study provide further, albeit circumstantial, support for the hypothesis that deficits in MMN generation in schizophrenia may be a relatively direct manifestation of deficient NMDAR functioning. Atypical antipsychotic drugs may affect NMDAR and 5-HT$_{2A}$ receptor-related dysfunctions similarly through their 5-HT$_{2A}$ antagonism.

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