Mismatch Negativity Predicts Psychotic Experiences Induced by NMDA Receptor Antagonist in Healthy Volunteers

Daniel Umbricht, Rene Koller, Franz X. Vollenweider, and Liselotte Schmid

Background: *Previous studies indicate that mismatch negativity (MMN)—a preattentive auditory event-related potential (ERP)–depends on NMDA receptor (NMDAR) functioning. To explore if the strength of MMN generation reflects the functional condition of the NMDAR system in healthy volunteers, we analyzed correlations between MMN recorded before drug administration and subsequent responses to the NMDAR antagonist ketamine or the 5-HT2a agonist psilocybin.*

Methods: *In two separate studies, MMN was recorded to both frequency and duration deviants prior to administration of ketamine or psilocybin. Behavioral and subjective effects of ketamine and psilocybin were assessed with the Brief Psychiatric Rating Scale and the OAV Scale—a rating scale developed to measure altered states of consciousness. Correlations between ERP amplitudes (MMN, N1, and P2) and drug-induced effects were calculated in each study group and compared between them.*

Results: *Smaller MMN to both pitch and duration deviants was significantly correlated to stronger effects during ketamine, but not psilocybin administration. No significant correlations were observed for N1 and P2.*

Conclusions: *Smaller MMN indicates a NMDAR system that is more vulnerable to disruption by the NMDAR antagonist ketamine. MMN generation appears to index the functional state of NMDAR-mediated neurotransmission even in subjects who do not demonstrate any psychopathology.* Biol Psychiatry 2002;51:400–406 © *2002 Society of Biological Psychiatry*

Key Words: NMDA receptor, 5-HT2A receptor, mismatch negativity, psychosis, ketamine, psilocybin

Introduction

Mismatch negativity (MMN) is an auditory event-related potential (ERP) indexing preattentive detection of stimulus deviance (Näätänen 1995). It is automatically generated with a latency of 100 to 200 ms after the presentation of a stimulus that deviates in one of its physical dimensions (pitch, intensity, duration, location) from preceding frequently repeated standard stimuli (Näätänen 1995; Novak et al 1990; Ritter et al 1995). Mismatch negativity is thus the manifestation of a preattentive process that compares the deviant stimulus to the sensory memory trace of the standard stimulus (Näätänen 1990; Novak et al 1990; Ritter et al 1995).

Mismatch negativity-like activities can also be recorded in animals and thus are amenable to investigations of its underlying neurobiological substrate (Csépe et al 1987; Javitt et al 1994; Javitt et al 1996). Studies in monkeys and cats show that MMN specifically involves activation of the supragranular layer of the primary and secondary auditory cortices (Karmos et al 1998; Javitt et al 1994; Javitt et al 1996). It has been hypothesized that this activation involves excitation of pyramidal neurons as a net result of two processes: 1) reduction of tonic inhibition (disinhibition) due to stimulation by the standard tone, and 2) excitation of NMDA receptor (NMDAR) in response to the deviant stimulus (Schroeder et al 1997; Karmos et al personal communication; Javitt et al 1996). NMDAR functions are uniquely sensitive to membrane potential (Cotman et al 1995); thus, the magnitude of stimulation-induced current flow through NMDAR depends upon the degree of neuronal disinhibition. This property makes the NMDAR uniquely suited for mediating conditional responses such as MMN. Studies in monkeys have indeed demonstrated that intracortical and systemic application of NMDAR antagonists selectively abolishes MMN-like activities without affecting such sensory ERPs as N1 (Javitt et al 1996; Javitt et al 1994). In addition, we recently demonstrated that ketamine, a noncompetitive NMDAR antagonist, selectively impairs MMN generation in humans without reducing sensory ERPs (Umbricht et al

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2000). Furthermore, ketamine significantly reduced the magnetic counterpart of MMN, MMNm, in healthy volunteers (Sauer et al 2000). The NMDAR antagonist nitrous oxide (N2O) (Jevtovic-Todorovic et al 1998) has also been reported to induce a significant reduction of MMN (Pang et al 1999). In contrast, the psychotomimetic psilocybin does not significantly affect MMN in healthy volunteers, although it reduces N1 (Umbricht et al 2001).

Psilocybin (O-phosphoryl-4-hydroxy-N,N-dimethyltryptamine)—a naturally occurring indoleamine hallucinogen—is readily metabolized to psilocin after ingestion (Hasler et al 1997). In rats, psilocin binds with high affinity to the 5-HT2A (Ki = 6.0 nM) and with moderate affinity to the 5-HT1A receptor (Ki = 190 nM) (McKenna et al 1990). Although indoleamine hallucinogens bind to various subtypes of serotonin receptors, the hallucinogenic and cognitive effects are primarily believed to be mediated through agonist action at the 5-HT2A receptor (Aghajanian et al 1999a, Vollenweider et al 1998). Moreover, the affinity of indoleamine hallucinogens at the 5-HT2A receptor is highly correlated with their hallucinogenic potency in humans (Aghajanian et al 1999a).

In summary, the available evidence strongly indicates a central role of the NMDAR in MMN generation. Thus, deficits in MMN generation as observed in such neuropsychiatric disorders as schizophrenia (Catts et al 1995; Javitt et al 1995; Umbricht et al 1998) may be a manifestation of deficient NMDAR-dependent neurotransmission (Olney et al 1995; Javitt et al 1991).

Furthermore, these data suggest that even in non-patient subjects the strength of MMN generation may reflect the functional condition of NMDAR systems. To explore this hypothesis, we examined the correlations between MMN recorded prior to drug administration and psychosis-like experiences and behavioral effects induced by the subsequent administration of ketamine or the psychotomimetic psilocybin. Ketamine, and to a lesser extent psilocybin, can induce signs and symptoms in healthy volunteers that mimic some psychotic symptoms of schizophrenia (Krystal et al 1994; Vollenweider et al 1998). Thus, we hypothesized that if the strength of MMN indeed reflects the functional condition of the NMDAR system (i.e., its efficiency or redundancy), then the effects of ketamine should be more disruptive. (i.e., stronger in a subject with a smaller MMN at baseline). In other words, an inverse correlation between baseline MMN and ketamine-induced psychosis-like experiences should exist. On the other hand, such a correlation should not be observed between MMN and the effects of psilocybin.

To test this hypothesis, data from two separate studies on the effects of ketamine and psilocybin in healthy volunteers were analyzed. The main goal of both studies was to assess the effects of ketamine or psilocybin, respectively, on MMN generation. The results of these studies have been (Umbricht et al 2000) or will be reported elsewhere (Umbricht unpublished). Here, we only report on the session with active drug administration (ketamine infusion or psilocybin administration, respectively).

Methods and Materials

Data from two separate studies of effects of ketamine and psilocybin in healthy volunteers (ketamine study: N = 20, M/F = 14/6, mean age = 24.6 ± 2.9 y; psilocybin study: N = 18, M/F = 10/8, mean age = 25.1 ± 4.3 y) were analyzed. The details of the methodology—identical in many aspects for both studies—have been published previously (Umbricht et al 2000). Both studies had been approved by the ethics committee of the Psychiatric University Hospital Zurich. Briefly, prior to study entry, all subjects underwent a detailed screening to ensure the absence of any personal or family psychiatric history and signed informed consent after having been informed in detail about the study and the expected drug effects. Subjects underwent two sessions (placebo/active drug) in counterbalanced and randomized order in both studies. Ketamine was administered intravenously (a bolus dose of 0.24 mg/kg was given over 5 min, then a maintenance ketamine infusion at 0.9 mg/kg/hour was started after a pause of 5 min). Psilocybin was given po at a dose of 0.28 mg/kg. Here, were only report on aspects of the active drug session.

In each session, EEG recordings were acquired with a Neuroscan Scan system (Neuroscan Labs; Sterling Virginia) and obtained from 28 scalp locations, consisting of standard 10/20 placements plus right and left mastoid placements, along with right vertical and horizontal EOG electrodes. An electrode placed on the nose served as reference. Electrode impedance was kept below 5 kΩ. The sampling rate was 500 Hz.

Auditory stimuli consisted of 100 ms, 1000 Hz standard intermixed with 100 ms, 1500 Hz pitch deviants and 250 ms, 1000 Hz duration deviants. Stimuli were presented in a fixed order (nine standards, one pitch deviant, nine standards, one duration deviant) with stimulus onset asynchrony of 300 ms presented through foam insert earphones at a nominal intensity of 75 dB SPL. Rise/fall time was 5 ms for all stimuli. Stimuli were presented in four blocks with a total of 1517 stimuli. During presentation of the auditory test paradigm, subjects performed a visual AX-Continuous Performance Task.

For the analyses of the auditory ERPs, epochs with a 100-ms prestimulus baseline and a 500-ms poststimulus interval were constructed. After correction of horizontal eye movements and blinks, epochs with amplitudes that exceeded ± 75 μV at any electrode except the vertical eye leads were excluded from further averaging. Following artifact rejection, epochs were averaged offline for each subject and stimulus type and were digitally filtered with a low-pass filter of 15 Hz (24 dB down). Analyses focused on N1 and P2 to the standard stimuli and MMN generation to pitch and duration deviant stimuli as measured at electrode Fz. The N1 amplitude was measured as peak negativity within the 50 to 150 ms latency; P2 amplitude as peak positivity within the 150 to 250 ms latency. Mismatch

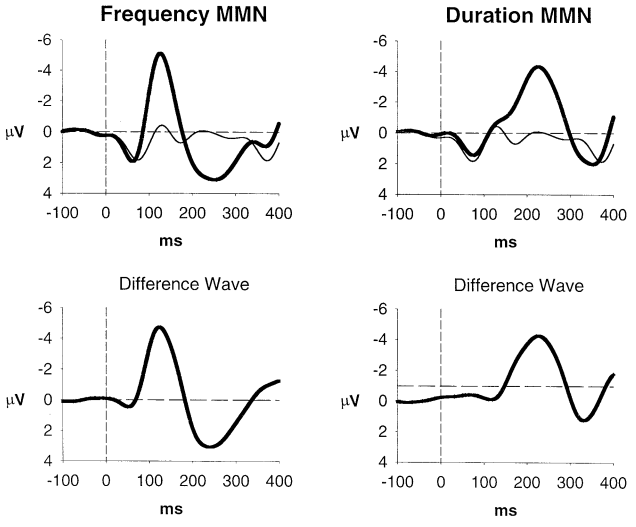

Figure 1. ERPs to standard stimuli (thin line, both panels upper row) and frequency deviants (thick line, left panel, upper row) and duration deviants (thick line, right panel, upper row). Difference waves (ERP to deviant stimuli minus ERP to standard stimuli) are presented in the lower row (left panel: frequency deviant condition; right panel: duration deviant condition). MMN amplitudes were measured in these differences waves.

negativity to pitch deviants was measured as peak negativity within the 100 to 225 ms latency window and MMN to duration deviants within the 200 to 300 ms range in the difference waveforms (deviant minus standard waveforms; see Figure 1). Waveforms were mathematically referenced to an average-mastoid reference prior to peak detection.

Drug-induced signs and symptoms were assessed both with an observer administered rating scale, the Brief Psychiatric Rating Scale (BPRS) (Overall et al 1962), and with a self-rating scale (the OAV questionnaire [Dittrich 1998]). An anchored version of the BPRS with scale points of 1 to 7 was used (Woerner et al 1988). For this analysis, the BPRS total score and the BPRS psychosis factor score (sum of the items "conceptual disorganization", "suspiciousness," "hallucinatory behavior," "unusual thought content") were used. Although the BPRS has been used previously (Krystal et al 1994; Anand et al 2000) to assess drug-induced psychotic symptoms in healthy volunteers, it was not developed and validated for that purpose and thus may not capture some of the more subtle effects induced by psychotomimetics. For this reason, we chose to use the OAV questionnaire as an additional assessment. The OAV questionnaire is a visual analog scale version of the APZ questionnaire that has been well validated as a tool to measure altered states of consciousness (Dittrich 1998; Bodmer et al 1994). It contains three factor-analytically derived subscales: "Oceanic Boundlessness (OSE)" "Dread of Ego Dissolution (AIA)" and "Visionary Restructuralization (VUS)." "Oceanic Boundlessness" describes a positive state similar to mystic experiences. "Dread of Ego Dissolution" reflects an unpleasant state characterized by anxiety, feelings of being disconnected from the surroundings, and not in control of one's own thoughts. "Visionary Restructuralization" refers to illusionary experiences, ideas of reference, and changes in the meaning of things. Subjects were asked to fill out this questionnaire on the evening after each study session. All subjects in the ketamine study and 16 subjects in the psilocybin study returned completely filled out questionnaires after the active drug session. Statistical analyses were thus performed with the data from these subjects.

Pearson product correlations were calculated between ERP measures (amplitudes of N1, P2, mean MMN, and MMN to frequency and duration deviants individually) and the behavioral measures (BPRS total score, BPRS psychosis factor score, OAV total score and its three factors) separately for the ketamine and the psilocybin study. Correlations were compared between groups using ANOVAs with the behavioral measures as dependent variable, group membership (drug) coded as dummy variable, and the ERP measure as covariate. Alpha levels of .05 were considered significant.

Results

Both ketamine and psilocybin administration induced robust behavioral effects as evidenced in significant increases of the BPRS total and the BPRS psychosis factor scores and strong subjective effects as rated on the OAV questionnaire (see Table 1). The increase of the BPRS total and psychosis factor score was greater during ketamine than psilocybin administration. The difference of the BPRS psychosis factor score was significant ($t = 3.15$,

Table 1. OAV and BPRS Scores during Ketamine and Psilocybin Administration

	Ketamine		Psilocybin		
	Mean ± SD	Range	Mean ± SD	Range	Significance
TOTAL OAV SCORE	2257 ± 947	1006 to 4282	2126 ± 1141	60 to 3836	$t = .38$, $df = 34$, $p = .7$
OSE SCORE	938 ± 511	94 to 2125	880 ± 583	0 to 1812	$t = .32$, $df = 34$, $p = .8$
AIA SCORE	645 ± 408	71 to 1502	543 ± 523	1 to 1475	$t = .66$, $df = 84$, $p = .5$
VUS SCORE	673 ± 292	182 to 1177	703 ± 361	58 to 1201	$t = .27$, $df = 34$, $p = .8$
BPRS TOTAL SCORE	31.5 ± 7.9[a]	20 to 52	27.5 ± 9.0[a]	18 to 53	$t = 1.80$, $df = 85$, $p = .08$
BPRS PSYCHOSIS FACTOR SCORE	9.2 ± 2.8[b]	4 to 13	6.5 ± 2.5[b]	4 to 15	$t = 3.15$, $df = 35$, $p < .05$

BPRS, Brief Psychiatric Rating Scale; OSE, Oceanic Boundlessness; AIA, Dread of Ego Dissolution; VUS, Visionary Restructuralization.
[a]Minimum = 18.
[b]Minimum = 4.

Table 2. Mean Peak Amplitudes and Latencies of MMN, N1, and P2 at Electrode Fz

		Ketamine Study		Psilocybin Study		Significance	
		Peak Amplitude	Peak Latency	Peak Amplitude	Peak Latency	Amplitude[a]	Latency[a]
MMN	Pitch Deviant	−5.4 ± 2.02	126 ± 15	−5.1 ± 3.3	129 ± 16	$t = -.46$, $p = .6$	$t = .52$, $p = .6$
	Duration Deviant	−4.3 ± 1.9	228 ± 20	−4.6 ± 2.4	227 ± 20	$t = .49$, $p = .6$	$t = .11$, $p = .9$
N1		−.6 ± .9	129 ± 20	−.6 ± .8	133 ± 9	$t = .14$, $p = .9$	$t = .73$, $p = .5$
P2		.8 ± .5	177 ± 21	.9 ± .9	181 ± 21	$t = .51$, $p = .6$	$t = .64$, $p = .5$

Amplitudes ± SD in μV; latencies ± SD in ms.
MMN, mismatch negativity.
[a] $df = 36$.

$df = 35$, $p < .05$). However, the subjectively rated effects of ketamine and psilocybin as assessed by the OAV scale and its three factors were not significantly different (see Table 1).

The peak amplitudes and latencies of N1, P2, and MMN to pitch and duration deviants prior to drug administration did not differ between subjects in the ketamine study and those in the psilocybin study (see Table 2). In the ketamine study, the mean MMN amplitude prior to drug administration correlated significantly with the BPRS total score, the OAV total score, and its three factor scores (see Table 3). Subjects with smaller amplitudes experienced stronger effects during ketamine administration. Examining MMN to frequency and duration deviants separately, we observed significant correlations between MMN to duration deviants and OAV total score and its three factors (see Table 3 and Figure 2). The correlation with the BPRS total score did not reach significance. Similarly, the correlations between MMN to frequency deviants and OAV total scores and the OSE and VUS factors were significant, while the correlation with the BPRS total score dropped below significance level. In contrast, in the psilocybin study, no significant correlations between mean MMN or separate MMNs and any of the behavioral measures were observed; however, only the correlation between mean MMN and total OAV score was significantly greater in the ketamine than the psilocybin group (see Table 3).

Peak amplitudes of neither N1 or P2 were significantly correlated with any behavioral measure both in the ketamine and the psilocybin studies.

Table 3. Correlations of MMN Amplitudes Recorded Prior to Drug Administration and Drug-Induced Effects

	Mean MMN			Pitch MMN			Duration MMN		
	r	F^a	Sig	*r*	F^a	Sig	*r*	F^a	Sig
TOTAL OAV SCORE		4.06	.05		2.51	.12		1.26	.27
Ketamine Infusion	.74[b]			.63[c]			.64[c]		
Psilocybin Administration	.37			.33			.38		
AIA SCORE		.77	.39		.10	.76		.77	.39
Ketamine Infusion	.45[d]			.27			.52[d]		
Psilocybin Administration	.24			.22			.24		
OSE SCORE		3.84	.06		4.12	.05		.75	.39
Ketamine Infusion	.65[c]			.65[c]			.45[e]		
Psilocybin Administration	.27			.26			.39		
VUS SCORE		2.09	.16		1.39	.25		.38	.54
Ketamine Infusion	.63[c]			.53[d]			.58[c]		
Psilocybin Administration	.38			.30			.44		
BPRS TOTAL SCORE		.68	.42		.26	.62		.15	.69
Ketamine Infusion	.48[d]			.41[e]			.39[e]		
Psilocybin Administration	.38			.38			.33		
BPRS PSYCHOSIS FACTOR		.37	.55		.18	.68		.05	.83
Ketamine Infusion	.35			.34			.26		
Psilocybin Administration	.38			.42[e]			.29		

The F values and significance levels are given for the interaction of drug × ERP measure in an univariate ANOVA with the behavioral measure as dependent variable, group membership (drug) as the independent factor and the ERP measure as covariate. A significant value for the interaction indicates that the correlations are significantly different in the two groups.
MMN, mismatch negativity; AIA, Dread of Ego Dissolution; OSE, Oceanic Boundlessness; VUS, Visionary Restructuralization; BPRS, Brief Psychiatric Rating Scale.
[a] $df = 1,30$.
[b] $p < .001$ (2-tailed).
[c] $p < .005$ (2-tailed).
[d] $p < .05$ (2-tailed).
[e] $p < .1$ (2-tailed).

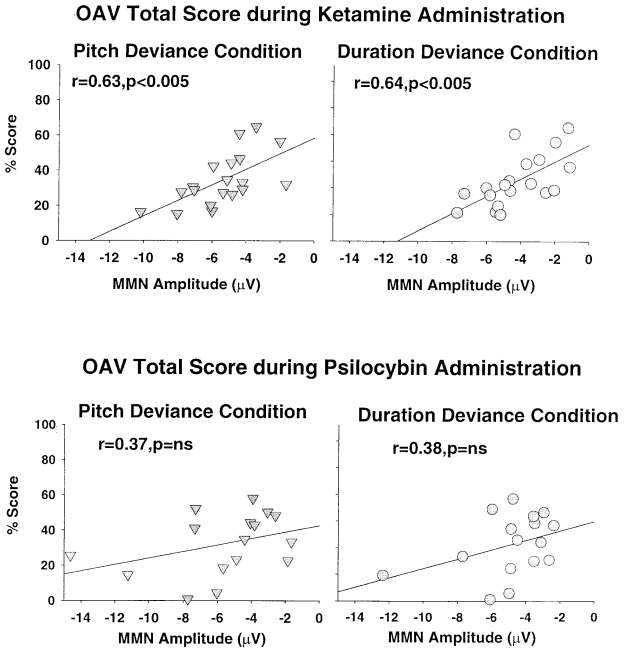

Figure 2. Scatterplot of MMN to pitch or duration deviants prior to drug administration and subjective experiences during ketamine (upper panel) or psilocybin administration (lower panel) as assessed by the OAV self-questionnaire. The OAV rating is expressed as percentage of the maximum points possible.

Discussion

Previous studies have demonstrated that the auditory event-related potential MMN is significantly reduced or abolished by NMDAR antagonists in humans and nonhuman primates, indicating a role of the NMDAR in its generation (Umbricht et al 2000; Javitt et al 1996; Sauer et al 2000; Pang et al 1999). We recently reported that ketamine significantly reduced MMN in healthy volunteers (Umbricht et al 2000). In this additional study, we explored the hypothesis that MMN in these healthy volunteers—recorded prior to drug administration—should therefore correlate with psychosis-like behavioral effects and experiences induced by subsequent administration of the NMDAR antagonist ketamine. Indeed, we found strong correlations between the magnitude of MMN in a baseline condition and subjectively rated ketamine-induced effects, whereas the clinician-rated effects showed weaker correlations albeit in the right direction. In contrast, in the psilocybin study, none of the corresponding correlations reached significance. Furthermore, significant correlations were only observed with MMN amplitudes, but not between the effects of ketamine and the amplitudes of the sensory ERPs N1 and P2 (i.e., with those ERPs that are thought to depend less on NMDAR functioning, and indeed are not diminished by NMDAR blockade in humans) (Umbricht et al 2000). Thus, our findings lend some support to our hypothesis that the strength of MMN generation as expressed in its amplitude reflects the resilience of the NMDA system to perturbation by an acute administration of NMDAR antagonists. It has been previously demonstrated that the relative affinity of (S)- and (R)-ketamine enantiomeres at the NMDAR complex correlates with the degree of psychosis-like experiences (Oye et al 1992; Vollenweider et al 1997). The magnitude of pharmacologically induced deficits in NMDAR-dependent functions is therefore reflected in the magnitude of psychosis-like symptoms. Conversely, stronger psychosis-like effects at the same dose of NMDAR antagonist are likely reflecting a greater disruption in NMDAR-dependent neurotransmission. Given the correlation of MMN with the psychosis-like effects of ketamine, MMN—recorded in a normal state of consciousness—can thus be regarded as an in vivo indicator for the vulnerability to disruption of NMDAR-dependent systems. Thus, MMN provides some information about the functional "condition" of NMDAR-mediated neurotransmission: a smaller MMN indicates a less resilient or less redundant NMDAR system; such a system is also more perturbed by NMDAR antagonist given at comparable doses. The fact, however, that similar, albeit weaker, correlations were observed in the psilocybin study that—with the exception of the correlation between mean MMN and total OAV—were not significantly different from the corresponding correlations in the ketamine study indicates that a smaller MMN may also manifest a general vulnerability to the effects of psychotomimetics. Interestingly, both NMDAR antagonists and 5-HT2A receptor agonists induce excessive glutamate release, thus sharing a final common pathway that has been suggested to account for their overlapping cognitive and psychotomimetic effects (Aghajanian et al 2000; Aghajanian et al 1999b; Moghaddam et al 1997; Moghaddam et al 1998). In addition, both NMDAR antagonists and 5-HT2A agonists lead to excessive dopamine release in humans (Kegeles et al 2000; Breier et al 1998; Vollenweider et al 2000; Vollenweider et al 1999). In other words, both compounds appear to induce abnormalities in the dynamics of these neurotransmitter systems. It is conceivable, but speculative, that the functional state of the NMDARs may modulate the effects of 5-HT2A agonists on glutamate and dopamine release. In such a scenario, the magnitude of MMN as an indirect expression of NMDAR functioning would be expected to show some correlation with 5-HT2A agonist-induced effects. The results of our study are consistent with such a view.

We used the analog scale version of the APZ questionnaire (Dittrich 1998; Bodmer et al 1994) to assess the drug-induced subjective effects. While less known than the BPRS, this scale was specifically developed and validated to measure

drug-induced states of altered consciousness in healthy subjects; however, in a recent study, schizophrenic patients rated the OAV questionnaire as a moderate to very good instrument for the assessment of their psychotic experiences (Gouzoulis-Mayfrank et al 1998). Furthermore, a principal component analysis revealed a similar three-factor structure in schizophrenic patients as in altered states of consciousness in healthy volunteers, supporting the observation that symptoms induced by psychotomimetics in healthy subjects resemble psychotic symptoms of schizophrenia. In addition, the total OAV score was found to correlate significantly with the score on the BPRS thought disorder factor. Thus, these findings strongly suggest that subjectively rated drug-induced effects in healthy volunteers are similar to genuine psychotic experience. The use of this self-rating scale permits to capture drug effect in a detailed way that does not always seem possible with the BPRS that focuses on some key psychotic symptoms, but may fail to assess more subtle effects, particularly in subjects who become completely withdrawn and mute. This may explain why the correlations of MMN and BPRS scores were weaker in our study.

This study has several limitations. We did not obtain blood levels of ketamine and psilocin, the main active metabolite of psilocybin. Even though we used the same dose per kilogram body weight for each person, it is conceivable that the actual concentration of ketamine and psilocybin and their psychoactive metabolites at the receptor differed between subjects, thus accounting for the differently strong subjective effects. Yet, since MMN was recorded prior to drug administration, such a possibility can hardly explain our findings unless one postulates rather implausible correlations between strength of MMN generation and factors influencing the metabolism of ketamine and psilocin or their transfer through the blood brain barrier. Secondly, the number of subjects available for analysis of the subjectively rated effects was lower in the psilocybin study, thus reducing the power to find significant correlations in this group. Thirdly, we performed multiple correlational analyses, thus inflating the probability of type-I errors; however, the overall pattern of significant correlations (only between MMN and behavioral effects and only in the ketamine study) would argue against our results being a chance finding.

In conclusion, the results of our study suggest that MMN in a normal state of consciousness is an indicator for the vulnerability to disruption of NMDAR-dependent systems in healthy volunteers. Smaller MMN manifested a state that was more vulnerable to disruption and, thus, functionally closer to a deficient NMDAR system. MMN generation appears to index the functional state of NMDAR-mediated neurotransmission, even in subjects who do not demonstrate any psychopathology. MMN may thus become a useful tool in studies on NMDAR functioning in humans.

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