Mismatch negativity generation in the human 5HT2A agonist and NMDA antagonist model of psychosis

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Abstract

RATIONALE: Many studies have reported deficits of mismatch negativity (MMN) in schizophrenic patients. Pharmacological challenges with hallucinogens in healthy humans are used as models for psychotic states. Previous studies reported a significant reduction of MMN after ketamine (N-methyl-D-aspartate acid [NMDA] antagonist model) but not after psilocybin (5HT2A agonist model). OBJECTIVES: The aim of the present study was to directly compare the two models of psychosis using an intraindividual crossover design. MATERIALS AND METHODS: Fifteen healthy subjects participated in a randomized, double-blind, crossover study with a low and a high dose of the 5HT2A agonist dimethyltryptamine (DMT) and the NMDA antagonist S-ketamine. During electroencephalographic recording, the subjects were performing the AX-version of a continuous performance test (AX-CPT). A source analysis of MMN was performed on the basis of a four-source model of MMN generation. RESULTS: Nine subjects completed both experimental days with the two doses of both drugs. Overall, we found blunted MMN and performance deficits in the AX-CPT after both drugs. However, the reduction in MMN activity was overall more pronounced after S-ketamine intake, and only S-ketamine had a significant impact on the frontal source of MMN. CONCLUSIONS: The NMDA antagonist model and the 5HT2A agonist model of psychosis display distinct neurocognitive profiles. These findings are in line with the view of the two classes of hallucinogens modeling different aspects of psychosis.
Mismatch negativity generation in the human 5HT\textsubscript{2A} agonist and NMDA antagonist model of psychosis

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Objectives The aim of the present study was to directly compare the two models of psychosis using an intra-individual crossover design.

Materials and methods Fifteen healthy subjects participated in a randomized, double-blind, crossover study with a low and a high dose of the 5HT\textsubscript{2A} agonist dimethyltryptamine (DMT) and the NMDA antagonist S-ketamine. During electroencephalographic recording, the subjects were performing the AX-version of a continuous performance test (AX-CPT). A source analysis of MMN was performed on the basis of a four-source model of MMN generation.

Results Nine subjects completed both experimental days with the two doses of both drugs. Overall, we found blunted MMN and performance deficits in the AX-CPT after both drugs. However, the reduction in MMN activity was overall more pronounced after S-ketamine intake, and only S-ketamine had a significant impact on the frontal source of MMN.

Conclusions The NMDA antagonist model and the 5HT\textsubscript{2A} agonist model of psychosis display distinct neurocognitive profiles. These findings are in line with the view of the two classes of hallucinogens modeling different aspects of psychosis.

Keywords Mismatch negativity · Model psychosis · Dimethyltryptamine · S-Ketamine

Introduction
Disturbances of both automatic and controlled mechanisms of information processing and attention are core symptoms of schizophrenia, and recordings of event-related potentials are commonly used to investigate them. Apart from the well-documented deficits of P300 (Pfefferbaum et al. 1989; Winterer et al. 2003), which reflect conscious attention to expected salient stimuli, several studies demonstrated impairments of the mismatch negativity (MMN), which is
a “preattentive” component of the auditory-evoked potentials (Umbricht and Krljes 2005).

MMN occurs after any discriminable deviation in an ongoing repetitive acoustic stimulation with identical tones. The repetitive standard stimuli are thought to generate a memory template, and any incoming stimulus is compared against it. If the incoming stimulation does not match the template, a MMN is generated (Näätänen 1995; Ritter et al. 1995). Since MMN occurs whether or not stimuli are being attended, it is supposed to reflect an automatic, i.e., preattentive process for detecting change (Picton et al. 2000). Hence, the MMN represents context-dependent information processing at the level of the auditory sensory cortex (Näätänen et al. 2001). The main generators of the MMN lie bitemporally within the primary and secondary auditory cortices (Alho et al. 1996; Tiitinen et al. 1993). However, frontal cortical areas seem to be also involved in the generation of MMN (Rinne et al. 2000; Waberski et al. 2001).

The findings of deficient MMN in schizophrenia support the hypothesis of impaired early information processing in this disorder (Umbricht and Krljes 2005). MMN deficits appear to be relatively specific for schizophrenia, since they were not observed in other mental illnesses such as major depression or bipolar disorder (Umbricht et al. 2003a; Catts 1995). Two recent studies failed to demonstrate abnormal MMN in first-episode patients; hence, it is possible that the MMN impairment develops in the ongoing course of the schizophrenia (Salisbury et al. 2002; Umbricht et al. 2006).

Dopaminergic, glutamatergic, and serotoninergic systems are all involved in the pathophysiology of schizophrenia but may modulate different symptom domains within this complex disorder. Acute dopamine receptor stimulation did not affect MMN in healthy subjects (Leung et al. 2007). In contrast, dysfunction in the N-methyl-D-aspartic acid (NMDA) receptor system is considered to play an important role in schizophrenia-related deficits in MMN (Light and Braff 2005a, b). Competitive and noncompetitive NMDA antagonists selectively block the generation of MMN in awake monkeys (Javitt et al. 1996). It is interesting to note that NMDA receptor antagonists such as phencyclidine and ketamine elicit psychosis-like symptoms in humans, and pharmacological challenges with ketamine are used as a model for psychosis in human experimental research. Ketamine in subanesthetic dosages decreased MMN without affecting other event-related potential (ERP) activity in healthy humans (Umbricht et al. 2000; Kreitschmann-Andermahr et al. 2001). However, a study that used an even lower ketamine dose, which elicited only very subtle psychological effects, reported no MMN deficit (Oranje et al. 2000).

The NMDA antagonist model is the most widely accepted model of psychosis, and it is thought to be an appropriate model for undifferentiated or disorganized psychoses with positive and negative symptoms. However, lysergic acid diethylamide (LSD) and LSD-type hallucinogens are also used to model psychoses in animal and human experimental research. LSD-type drugs are agonists at serotonin 5HT₂(A) receptors, and the 5HT₂(A) agonist model of psychosis is thought to resemble more the positive symptoms of schizophrenia (Abi-Saab et al. 1998; Gouzoulis-Mayfrank et al. 2005; Vollenweider et al. 1998). It is interesting to note that a previous study of MMN in the 5HT₂(A) agonist model of psychosis showed no significant effect of the serotonergic hallucinogen psilocybin on MMN (Umbricht et al. 2003a, b). However, acute tryptophan depletion, which reduces the brain synthesis of serotonin, did lead to increased MMN amplitude (Kähkönen et al. 2005).

The aim of the present study was to investigate the effects of the 5HT₂(A) agonist hallucinogen N,N-dimethyltryptamine (DMT) and the NMDA antagonist hallucinogen S-ketamine on the generation of MMN using two different dosages of each drug. Both drugs can be given intravenously and have similar pharmacokinetics with rapid onset at the beginning and rapid fading of action after the end of the infusion. Hence, it is possible to study the effects of the two drugs in a randomized, double-blind design. Based on the principles of model psychosis and the robust findings of diminished MMN in patients with schizophrenia, we expected a dosedependent decrease in MMN activity after both hallucinogens. Furthermore, this study aimed to analyze possible differences between the two hallucinogens in terms of the modulation of the frontal and temporal sources of MMN.

Material and methods
The present study was part of a more comprehensive investigation, which also assessed the psychological effects, spatial orienting of attention, and startle modification in healthy subjects after S-ketamine and DMT intake (for details, see Gouzoulis-Mayfrank et al. 2005, 2006; Heekeren et al. 2007). The study was carried out in accordance with the Declaration of Helsinki and was approved by the local ethics committee at the Medical Faculty of the University of Technology Aachen and the Federal Health Administration (Berlin). Written informed consent was obtained from all subjects after we described the experimental procedures in detail and explained that they might withdraw from the study at any time, if they wished so, without having to explain the reasons.

Subjects
Fifteen healthy volunteers (nine men, six women; mean age 38.0 years, range=28–53) with no current physical and no current or previous history of neurological or psychiatric...
disorder (axis I and II according to Diagnostic and Statistical Manual of Mental Disorders [DSM]-IV criteria) were included in the study. Subjects with a positive family history of severe psychiatric disorder in first-degree relatives, a personal history of current or previous drug abuse, or any regular medication were excluded. All subjects were screened with a medical history, a standardized psychiatric interview according to DSM-IV (Structured Clinical Interview for DSM) and a physical examination including a clinical test for normal hearing, electrocardiogram, and a routine laboratory testing. Twelve subjects completed the experimental day with both doses of DMT, and ten subjects completed the day with both doses of S-ketamine. Nine subjects completed both experiments with both doses of DMT and S-ketamine. Data are presented for these nine subjects (for details on subjects and reasons for dropouts, see Gouzoulis-Mayfrank et al. 2005).

Drugs

DMT fumarate was synthesized in the Pharmaceutical Institute, University of Tübingen (Germany), and prepared as solution for intravenous use by Wülfing Pharma (Gronau, Germany). Two different DMT dosages were used:

1. Low DMT: a bolus injection over 5 min with 0.15–0.2 mg/kg followed by a break of 1 min, followed by continuous infusion with 0.01125–0.015 mg/kg×min over 84 min
2. High DMT: bolus injection with 0.2–0.3 mg/kg and continuous infusion with 0.015–0.02 mg/kg×min

S-Ketamine (Ketanest® S, Parke-Davis, Karlsruhe, Germany) was administered in the following dosages:

1. Low S-ketamine: a bolus injection over 5 min with 0.1–0.15 mg/kg followed by a break of 1 min, followed by continuous infusion with 0.0066–0.01 mg/kg×min over 54 min, followed by continuous infusion at a rate of 75% of the previous dose over 30 min
2. High S-ketamine: bolus injection with 0.15–0.2 mg/kg, continuous infusion with 0.01–0.015 mg/kg×min over 54 min, followed by continuous infusion at a rate of 75% of the previous dose over 30 min

Due to interindividual differences in the strength of psychological effects to the same drug dose, we always started with a medium dose, which was on the maximum of the low and at the same time at the minimum of the high dose range. Depending on the intensity of effects during the first infusion period, we decided to go higher or lower for the second infusion period. This procedure leads to comparably strong psychological effects within each dose condition in spite of the interindividual differences in responsiveness to the drug. To avoid a cumulation of plasma levels and clinical effects, the S-ketamine infusion rate was reduced after 60 min. Due to the fast elimination time of DMT, a reduction in the DMT dosage over the 90-min administration period was not necessary. With these doses, the psychological effects of both drugs developed fully within about 15 min and were kept relatively constant over the following period of 75 min from the start to the end of the infusion (for details on the dosage regimes, see Gouzoulis-Mayfrank et al. 2005).

Study design

On a separate day prior to the first experiment, all participants underwent a baseline MMN recording without drug administration. Thereafter, each subject participated in one experiment with DMT and one experiment with S-ketamine 2 to 4 weeks apart in a double-blind, crossover design and in a pseudorandomized order. On each experimental day, the same substance (DMT or S-ketamine) was administered in a low and a high dosage with a 2-h break between.

The order of administration of the two dosages was single blind and was low-high on ten and high-low on 12 experiments. The drugs were administered by a physician, who had no other role in these experiments and did not communicate with the subjects and the other members of the research team. Both drugs were administered intravenously by an automatic infusion pump (Perfusor®, Braun, Melsungen, Germany). Blood pressure and heart rate were monitored automatically (Dinamap®, Critikon, Tampa, FL, USA) during the entire duration of the experiment. About 20 min after the onset of the infusion, the recording of the MMN started and lasted for about 30 min. After stopping the infusion, the psychological effects of the drugs completely vanished within 10 to 30 min.

EEG recording and AX-CPT

For the recording of the electroencephalogram (EEG), we used a 94-channel montage equally spaced around the reference electrode (Cz). Two additional channels were used to monitor vertical and horizontal electrooculogram (EOG). The individual position of each electrode was determined for each subject with a three-dimensional digitizer (ZEBRIS®, Isny, Germany). Electrode impedance was kept below 5 kΩ. The activity was recorded with an amplifier system (NeuroScan® Labs, El Paso, USA) and digitized continuously at a sampling rate of 1 kHz. Recording band pass was 0.3 to 250 Hz (6 dB). Three thousand auditory stimuli were presented binaurally with foam insert earphones at an intensity of 75 dB and with an interstimulus interval (ISI) of 500 ms. The acoustic stimuli consisted of 80% standard stimuli with a 50-ms duration at
1,000 Hz intermixed pseudorandomly with 10% pitch-deviant (50 ms at 1,200 Hz) and 10% duration-deviant (100 ms at 1,000 Hz) stimuli. During the recording of the EEG, subjects performed a visual AX-continuous performance task (AX-CPT), which distracted their attention from the acoustic stimuli. The AX-CPT requires the subjects to press a button, whenever the letter X follows the letter A. Whenever a letter different than A is presented prior to X ("BX") the subject has to inhibit the tendency to respond to it. It is interesting to note that schizophrenic patients commit more BX errors, suggesting a deficient use of contextual information in this task (Cohen et al. 1999; Javitt et al. 2000; Umbricht et al. 2003a, b). Therefore, the influence of the two drugs on the utilization of contextual information in this AX-CPT was also an object of our study.

The visual AX-CPT was programmed using the presentation software (Neurobehavioral Systems, Albany, USA) according to Umbricht et al. (2000): Single letters were presented for 250 ms visually on a computer screen, which was positioned in front of the subject. The instruction was to press a button whenever the letter A (correct cue) was followed by the letter X (correct target), "AX." The three other orders (correct cue–incorrect target "AY," incorrect cue–correct target "BX," and incorrect cue–incorrect target "BY") had to be ignored. Incorrect cues and targets consisted of all letters other than A or X. Fifty percent of the cue–target sequences were presented pseudorandomly intermixed with a short ISI of 0.8 s and the remaining 50% with a long ISI of 4 s. The time between stimulus pairs was constant at 0.8 s. The correct cue–target sequence (A–X) occurred with a probability of 70% and the three other orders with a probability of 10% each.

Data analysis

**MMN and N1**

Digital tags were logged to all auditory stimuli, and the continuous data were divided on the basis of these tags into 600-ms epochs (100 ms pre- and 500 ms poststimulus). Parallel to the EEG, we registered two EOG channels, one for vertical and one for horizontal eye movements. If there was an eye movement registered in either EOG channel, the contemporaneous EEG epoch was rejected. After correction for blinks, epochs with amplitudes exceeding ±80 µV were also rejected offline during the averaging procedure (BESA 2000 software, MEGIS, Munich, Germany). Grand averages were built separately for the standard and the two deviant stimuli. Data were digitally filtered using a 30-Hz low-pass and a 1-Hz high-pass (12 dB) filter. After averaging and artifact rejection, the MMN waveform was calculated separately for each subject and each condition (baseline, DMT moderate/high, S-ketamine moderate/high) by subtracting the standard waveform from the deviant (frequency-respective duration) waveform using the BESA software. In a first step, we assessed the peak MMN amplitude by using the MMN waveforms from the surface electrodes Fz, F3, and F4. The peak negativity within a latency window of 100–200 ms poststimulus for the frequency deviant and 150–250 ms for the duration deviant in the corresponding surface waveforms was defined as the MMN peak amplitude. The effects of the two drugs on the MMN peak amplitude were analyzed separately for the duration and the frequency deviants by means of a repeated-measures analysis of variance (ANOVA) using the position of the electrode as a within-subject factor. Initially, we performed analyses of variance for each of the two drugs with the factor condition (baseline, low dose, high dose). Then, to directly compare the two drugs with each other, we performed ANOVAs with the factors drug (DMT, S-ketamine) and dosage (low, high). Post-hoc least-square difference (LSD) tests were performed if indicated.

In a second step, individual electrode positions from all nine subjects were matched to a common head model to perform the source analysis of the MMN. A source analysis was performed individually for each subject, deviant stimulus, and drug condition with the BESA software on the basis of the four generators model of MMN as described by Waberski et al. (2001). Figure 1 displays the location of the four sources: S1 right superior temporal lobe, S2 left superior temporal lobe, S3 right inferior temporal lobe, and S4 anterior cingulate gyrus. The Talairach coordinates for the sources are presented in Table 1. The peak values of the MMN amplitude were determined at each source in a time window of 100–200 ms poststimulus for the frequency deviant and 150–250 ms for the duration deviant in the corresponding source waveforms.

In addition to the MMN, we assessed the N1 amplitude by using the waveforms generated by the standard stimulus at electrode Fz. The peak negativity within a latency window of 50 to 150 ms poststimulus was defined as the N1 amplitude. The N1 peak amplitudes were measured to ensure that MMN deficits under the drug conditions are not only caused by a general reduction in EEG activity.

We analyzed the effects of the two drugs on the MMN amplitude separately for the duration and the frequency deviants and for each source by means of ANOVAs. Initially, we performed ANOVAs for each of the two drugs with the factor condition (baseline, low dose, high dose). Then, we performed ANOVAs with the factors drug (DMT, S-ketamine) and dosage (low, high). Post-hoc LSD tests were performed if indicated. Similarly, the amplitude and latency of the N1 to the standard stimulus were analyzed by means of ANOVAs, first separately for each drug with the factor condition and then without the baseline data using the factors drug and dosage.
AX-continuous performance task

The dependent parameter missings (no response after “AX” combination) were also analyzed by means of ANOVAs, initially, separately for each drug with the factors condition (baseline, low dose, high dose) and ISI (0.8 s, 4 s.) and then with the factors drug (DMT, S-ketamine) and dosage (low, high). For the analysis of the false-alarm rates (response after “AY,” “BX,” or “BY” combination), we also performed two ANOVAs, separately for each drug, with the factors condition, ISI (0.8 or 4 s), and false-alarm type (“AY,” “BX,” or “BY”). Finally, we performed an ANOVA with the factors drug (DMT, S-ketamine), dosage (low, high), false-alarm type, and ISI.

All analyses were performed using the SPSS software (version 12.0). Statistical significance was set at $p<0.05$.

Results

Psychological effects

The global intensity of psychological effects was similar for DMT and S-ketamine and was dose dependent. With the low dosage, most subjects displayed some degree of positive formal thought disorder such as loosening of associations and heightened distractibility, and some subjects reported alterations of visual perception and visual hallucinations. With the high dosage, all subjects had significant psychotomimetic effects including perceptual distortions and hallucinations, transient paranoid ideation, alterations of mood and drive, prominent formal thought disorder, and attention deficits. Phenomena resembling positive symptoms of schizophrenia, particularly positive formal thought disorder and inappropriate affect, were stronger after DMT intake. Phenomena resembling negative symptoms of schizophrenia such as hypomimia and psychomotor poverty, attention deficits, body perception disturbances, and catatonia-like motor phenomena were stronger after S-ketamine intake. The global scores of the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) are presented in Fig. 2. Repeated-measures ANOVAs revealed significant main effects of drug and dose for the global SAPS ($F=20.76$, $p=0.002$ and $F=32.19$, $p<0.0001$) and the global SANS scores ($F=29.41$, and $F=26.32$, both $p<0.001$). For details on the psychopathological effects, see Gouzoulis-Mayfrank et al. (2005).

AX-CPT performance

The descriptive statistics for missings (AX errors) and false alarms (BX, AY, and BY error rates) are presented in Fig. 3. There was a significant main effect of condition on the missings rate for both DMT ($F[2, 7]=8.26$, $p=0.019$) and S-ketamine ($F[2, 7]=10.22$, $p=0.012$). The post-hoc LSD tests revealed a significantly lower missings rate in the baseline condition compared to low DMT ($p=0.009$), high DMT ($p=0.008$), low S-ketamine ($p=0.021$), and high S-ketamine ($p=0.002$). There was no significant main effect of the factor ISI on the missings rate. Remarkably, the descriptive data showed a tendency for the expected effect of ISI for ketamine but not for DMT. The ANOVA with the factors drug and dosage revealed no significant effect of any factor on the missings rate.

Regarding the false-alarm rates, there were significant main effects of the factors ISI and false-alarm type under both drugs and the interaction of the two factors was also significant (ISI: $F[1, 8]=13.24$, $p=0.008$ for DMT and $F[1$, $S1 49.2 5.3 −6.2$

| Source | x     | y     | z      |
|--------|-------|-------|--------|
| S1     | 49.2  | 5.3   | −6.2   |
| S2     | −42.4 | −18.0 | 8.3    |
| S3     | 48.1  | −67.9 | 1.1    |
| S4     | 2.2   | 38.1  | 8.3    |
$F[2, 7] = 12.56, p = 0.007$ for DMT and $F[2, 7] = 13.20, p = 0.006$ for S-ketamine; interaction: $F[2, 7] = 6.69, p = 0.030$ for DMT and $F[2, 7] = 5.72, p = 0.041$ for S-ketamine). The effect of condition was significant with S-ketamine ($F[2, 7] = 8.83, p = 0.016$) and approached significance with DMT ($F[2, 7] = 3.66, p = 0.091$). The second ANOVA computed without the baseline data revealed a significant effect of the factors ISI ($F[1, 8] = 13.19, p = 0.008$) and false-alarm type ($F[2, 7] = 10.62, p = 0.011$) and a trend for the factor drug ($F[1, 8] = 4.14, p = 0.081$). The simple interactions were not significant. However, two higher-level interactions with the factor drug passed the significance level (drug × alarm type × ISI: $F[2, 7] = 7.71, p = 0.022$; drug × dose × ISI: $F[1, 8] = 5.65, p = 0.049$). According to the post-hoc tests, there were significantly less “BY” compared to “BX” ($p = 0.003$) and “AY” ($p = 0.015$) errors. To explore the drug effect on the utilization of contextual information, we analyzed the “BX” error rates by means of a separate ANOVA with the factors drug, dosage, and ISI, and we found significant effects of the
Table 2 Peak amplitudes (μV) and latencies (ms) of N1

|                  | Baseline | Low DMT | High DMT | Low S-ketamine | High S-ketamine |
|------------------|----------|---------|----------|----------------|----------------|
| Amplitude (μV)   | −0.67    | −0.34   | −0.58    | −0.86          | −0.57          |
| Latency (ms)     | 119.44   | 112.44  | 109.33   | 119.78         | 111.67         |

factors drug \( (F[1, 8]=6.94, \ p=0.034) \) and ISI \( (F[1, 8]=12.74, \ p=0.009) \). Hence, the “BX” error rate was higher under the DMT conditions compared to S-ketamine.

N1 peak amplitude and latency

Mean peak amplitudes and latencies of N1 are displayed in Table 2. The separate ANOVAs for the two drugs with the factor condition (baseline, low dose, high dose) revealed a significantly diminished amplitude of N1 only after DMT intake compared to baseline \( (F=6.20, \ df=2.7, \ p=0.028) \). The post-hoc tests revealed a lower peak amplitude of the low DMT dose compared to baseline \( (p=0.008) \). The second ANOVA with the factors drug and dosage revealed a significant main effect of drug indicating a lower amplitude of N1 under the DMT condition compared to S-ketamine \( (F=5.62, \ df=1.8, \ p=0.045) \). There where no significant changes in N1 latencies between the different conditions in all performed ANOVAs.

MMN surface waveforms

The grand average MMN surface waveforms of the electrodes F3, Fz, and F4 are presented in Fig. 4. For the duration-deviant-induced MMN, we found a significant effect of the factor condition over all three waveforms only for S-ketamine \( (F[2, 7]=4.97, \ p=0.045) \) but not for DMT. For the frequency-deviant-induced MMN, the factor condition showed only a trend for S-ketamine \( (F[2, 7]=3.70, \ p=0.08) \). In the second ANOVA with the factors drug and dosage, there was a significant effect of the factor drug \( (F[1, 8]=9.01, \ p=0.017) \), indicating a lower MMN peak amplitude under the S-ketamine condition compared to DMT.

MMN source activity

The time course of duration-deviant-induced MMN activity at the four sources is presented in Fig. 5. In the separate ANOVAs for each drug, we found a significant main effect for S-ketamine at all four sources, S1 \( (F[2, 7]=6.31, \ p=0.027) \), S2 \( (F[2, 7]=9.48, \ p=0.01) \), S3 \( (F[2, 7]=6.46, \ p=0.026) \), and S4 \( (F[2, 7]=5.09, \ p=0.043) \), and for DMT only at S1 \( (F[2, 7]=5.04, \ p=0.044) \). These results indicate a diminished MMN activity in the drug conditions compared to baseline. The significant results of the post-hoc LSD tests are presented in Fig. 5. In the second ANOVA with the factors drug and dosage, we found only a significant effect of the factor drug at S4 \( (F[1, 8]=5.62, \ p=0.045) \) and a significant interaction of drug and dosage at S3 \( (F[1, 8]=11.81, \ p=0.009) \). These results indicate that only S-ketamine affects the frontal generator.

The frequency-deviant-induced MMN at the four sources is presented in Fig. 6. In the separate ANOVA for S-ketamine, we found a marginal effect of condition at S3 \( (F[2, 7]=4.17, \ p=0.064) \) and S4 \( (F[2, 7]=4.19, \ p=0.064) \). The separate ANOVA for DMT revealed a significant effect of condition at S1 \( (F[2, 7]=5.22, \ p=0.041) \) and S3 \( (F[2, 7]=4.86, \ p=0.048) \). The significant results of the post-hoc LSD tests are presented in Fig. 6. The second ANOVA with the factors drug and dosage revealed no significant effects.

Discussion

The present investigation studied the influence of the two hallucinogens N,N-DMT and S-ketamine on the generation of MMN and performance in an AX-CPT. Overall, the intensity of the hallucinogenic effects of both drugs was similar; however, phenomena that resemble positive symptoms of schizophrenia were more pronounced after DMT intake, and phenomena that resemble negative and catatonic symptoms of schizophrenia were clearly more pronounced after S-ketamine intake (Gouzoulis-Mayfrank et al. 2005). Taken together, these results are in line with the assumption that the two classes of drugs tend to model different aspects of psychoses. The NMDA antagonist state (S-ketamine) may be an appropriate model for psychoses with prominent negative and possibly also catatonic features, while the 5-HT\(_{2A}\) agonist state (DMT) may be a better model for psychoses with prominent positive symptoms (Abi-Saab et al. 1998; Gouzoulis-Mayfrank et al. 2005).

Inspection of the descriptive data suggests a decrease in the generation of MMN under both substances. However, this effect was more pronounced after S-ketamine. The analyses of the grand average data showed that the MMN to the duration deviant was significantly reduced by S-ketamine. Moreover, there was a trend reduction for the frequency-deviant-induced MMN. According to the source analyses, S-ketamine reduced the duration-deviant MMN
activity of the temporal (S1, S2, S3) and the frontal sources (S4). Regarding the frequency-deviant stimuli, the effect of S-ketamine was somewhat weaker: We found only a marginal MMN reduction at one temporal source (S3) and at the frontal source (S4). Nevertheless, the difference between frequency- and duration-deviant MMN did not reach statistical significance. The activity of the frontal source was only affected by S-ketamine and not by DMT.
S-Ketamine had no effect on the N1 amplitude; therefore, the reduction in MMN by S-ketamine was not caused by a general weakening of ERP activity.

Our findings regarding the NMDA antagonist S-ketamine are in line with the observation that MMN deficits in schizophrenia are more pronounced to duration deviants than to frequency-deviant stimuli (Michie et al. 2000). A recent study also found a reduction in MMN to duration but not to frequency deviants in patients with schizophrenia and a short length of illness (Todd et al. 2008). Remarkably, in the same study, patients with a longer length of illness showed a stronger reduction to frequency compared to duration deviants. The authors interpreted their findings as a result of a pronounced age-related decline in duration-deviant
MMN in the healthy control group (Todd et al. 2008). Baldeweg et al. (2002) found a pronounced reduction in MMN at frontocentral electrodes in patients with schizophrenia in the presence of normal activity at mastoid electrodes and concluded that the frontal generators of MMN may be preferentially affected in schizophrenia. However, our descriptive data suggest that S-ketamine affected the frontal and temporal sources of MMN generation. Since magnetoencephalography (MEG) predominantly detects the temporal sources of MMN generation (Rinne et al. 2000; Rosburg et al. 2004), the MEG findings of reduced MMN activity in schizophrenia (Kreitschmann-Andermahr et al. 1999; Pekkonen et al. 2002) also support the involvement of temporal sources in reduced MMN activity.

Fig. 6 Time course of MMN activity in nanoampere meters at the four sources for the frequency-deviant stimuli (baseline=solid line; low dosage=dotted line; high dosage=dashed line; means; p values from post-hoc tests; n=9)
in patients with schizophrenia. The detection of frontal sources only in EEG and not in MEG recordings is in line with the assumption that these sources are either predominately radial in orientation or located deeply in the brain (Rinne et al. 2000; Waberski et al. 2001). Nevertheless, even though several studies support a frontal lobe involvement in MMN generation (for a review, see Näätänen et al. 2007), we cannot exclude that the frontal source is simply an artifact due to the inverse problem of source analyses.

The lack of influence on peak amplitude and latency of N1 and the predominant reduction in MMN activity after duration deviants in the NMDA antagonist model of psychosis are in line with observations in schizophrenic patients. It is noteworthy that recent studies reported an association between MMN deficits and poor functioning in schizophrenia (Light and Braff 2005a, b). These reports are in line with the psychological findings in our study, which suggest that the NMDA antagonist state (S-ketamine) is an appropriate model for psychoses with prominent negative symptoms (Gouzoulis-Mayfrank et al. 2005). Furthermore, two studies that investigated first-episode patients failed to find alterations in MMN activity (Salisbury et al. 2002; Umbricht et al. 2006). These findings suggest that the MMN impairment may develop in the ongoing course of the schizophrenic disorder. Hence, in terms of our model, the S-ketamine state may resemble not only the negative syndrome but also the more advanced stages of schizophrenia.

Unlike S-ketamine, the 5HT2A agonist DMT reduced the N1 peak amplitude. This finding is in line with the increase of the N1 amplitude after treatment with 5HT2A antagonists (Juckel et al. 2003). On the basis of the grand average data, DMT had no significant effect on MMN activity. However, regarding the sources of MMN, DMT diminished the MMN activity to frequency-deviant stimuli at the two right hemispheric sources (S1 and S3). Noteworthy, Umbricht et al. (2003a, b) also found a significant reduction in the N1 amplitude and a stronger effect on MMN to frequency compared to duration deviants after administration of the 5HT2A agonist hallucinogen psilocybin. However, we cannot exclude that the changes in MMN activity under DMT are confounded by the significant reduction in the N1 amplitude.

Both drugs led to higher missing and error rates, particularly for “BX” errors, in the AX-CPT. Javitt et al. (2000) reported a similar AX-CPT response pattern in patients with schizophrenia (Javitt et al. 2000). This is in line with an impairment in the use of contextual information, as indicated by a selective deficit in the ability of schizophrenia patients to inhibit responses to targets following presentation of incorrect no-go cues (Cohen et al. 1999). Hence, in terms of the context-dependent visual information processing at an attention-dependent level, both models of psychosis seem to match previous findings with schizophrenic patients.

It must be acknowledged that our study has methodological limitations mainly due to the absence of a blinded placebo condition and the small sample sizes for completers, which limited the statistical power. These limitations and the rationale for our study design were discussed in detail in our previous publications (Gouzoulis-Mayfrank et al. 2005, 2006). Taken together, although methodological caveats have to be taken into account, the data from the present study suggest that the NMDA antagonist and the 5HT2A agonist models of psychosis share common features regarding both automatic and conscious attentional mechanisms. However, in terms of the automatic acoustic MMN generation, the NMDA antagonist model of psychosis appears to be more close to the findings in schizophrenia, whereas in terms of the visual context-dependent AX-CPT, both drugs lead to a performance deficit pattern, which comes close to previous findings in schizophrenic patients.

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