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Prepulse inhibition of the startle reflex and its attentional modulation in the human S-ketamine and N,N-dimethyltryptamine (DMT) models of psychosis

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Abstract

Patients with schizophrenia exhibit diminished prepulse inhibition (PPI) of the acoustic startle reflex and deficits in the attentional modulation of PPI. Pharmacological challenges with hallucinogens are used as models for psychosis in both humans and animals. Remarkably, in contrast to the findings in schizophrenic patients and in animal hallucinogen models of psychosis, previous studies with healthy volunteers demonstrated increased levels of PPI after administration of low to moderate doses of either the antiglutamatergic hallucinogen ketamine or the serotonergic hallucinogen psilocybin. The aim of the present study was to investigate the influence of moderate and high doses of the serotonergic hallucinogen N,N-dimethyltryptamine (DMT) and the *N*-methyl-D-aspartate antagonist S-ketamine on PPI and its attentional modulation in humans. Fifteen healthy volunteers were included in a double-blind cross-over study with two doses of DMT and S-ketamine. Effects on PPI and its attentional modulation were investigated. Nine subjects completed both experimental days with the two doses of both drugs. S-ketamine increased PPI in both dosages, whereas DMT had no significant effects on PPI. S-ketamine decreased and DMT tended to decrease startle magnitude. There were no significant effects of either drug on the attentional modulation of PPI. In human experimental hallucinogen psychoses, and even with high, clearly psychotogenic doses of DMT or S-ketamine, healthy subjects failed to exhibit the predicted attenuation of PPI. In contrast, PPI was augmented and the startle magnitude was decreased after S-ketamine. These data point to important differences between human hallucinogen models and both animal hallucinogen models of psychosis and naturally occurring schizophrenia.

Keywords

startle reaction, prepulse inhibition, attention, dimethyltryptamine, S-ketamine

Introduction

Prepulse inhibition (PPI) of the acoustic startle reflex is a well established model for sensorimotor gating (Braff and Geyer, 1990). Sensorimotor gating and also habituation are considered to serve as mechanisms that protect early stimulus processing and prevent the organism from experiencing sensory overload. Habituation refers to a decrease in startle response after repeated stimulation, whereas PPI refers to the reduction of the reflex amplitude by presentation of a weak prestimulus 30–500 ms prior to the startle-eliciting stimulus. Several studies indicate that PPI does not reflect a pure preattentive (automatic) mechanism but is also influenced by controlled attentional processes (Filion *et al.*, 1998).

Deficits in gating of cognitive and sensory information are clinically important features of schizophrenia spectrum disorders and PPI is considered a suitable measure of sensorimotor gating deficits in

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clinical populations. Although most studies found a diminished PPI in schizophrenic patients (Braff *et al.*, 1992, 2001b), some recent studies failed to verify this deficit (Ford *et al.*, 1999; Wynn *et al.*, 2004). Variations in the experimental parameters may contribute to these inconsistencies, e.g. the Wynn *et al.* (2004) study measured electromyographic activity (EMG) from the left eye and did not use any background noise and the Ford *et al.* (1999) study also used a relatively low background noise, whereas most studies that found PPI deficits in schizophrenic patients measured startle eye blink from the right eye and used a relatively strong background noise. Remarkably, one study reported normal PPI but impaired attentional modulation of PPI in a population of patients with schizophrenia (Dawson *et al.*, 1993).

Pharmacological challenges with hallucinogens are used as models for psychosis in animal and human experimental studies (Geyer, 1998; Geyer *et al.*, 2001; Gouzoulis-Mayfrank *et al.*, 1998b, 1999). In animals, both *N*-methyl-D-aspartate (NMDA) antagonists such as phencyclidine and ketamine (Swerdlow *et al.*, 1998; Mansbach and Geyer, 1989, 1991) and serotonin agonists such as lysergic acid diethylamide or 2,5-dimethoxy-4-iodoamphetamine (Geyer *et al.*, 2001) disrupt PPI. However, in human studies S-ketamine produced either an increase in PPI together with a decrease in startle magnitude (Duncan *et al.*, 2001; Abel *et al.*, 2003), or it had no significant effect on PPI (van Berckel *et al.*, 1998; Oranje *et al.*, 2002). Only Karper *et al.* (1995) reported a significant reduction in PPI with ketamine, using the simple arithmetic difference scores. However, as the reduction in PPI was no longer significant using percent scores, this effect was likely to be due to a decrease in startle amplitude.

Similarly, human studies with the serotonin receptor agonist psilocybin (Gouzoulis-Mayfrank *et al.*, 1998a) and the serotonin reuptake inhibitor 3,4-methylenedioxymethamphetamine (Vollenweider *et al.*, 1999) also reported an increase of PPI, in this case in the absence of any decrease in startle magnitudes. Furthermore, Riba *et al.* (2002) reported no distinct effects on PPI of Ayahuasca, a beverage containing the serotonergic hallucinogen N,N-dimethyltryptamine (DMT). Regarding these discrepancies between animal and human studies, one should consider that the hallucinogen doses used in animals have been higher compared to the human studies, and that the doses used in human studies have mostly induced a 'pre-psychotic' rather than a full-blown psychotic state (Gouzoulis-Mayfrank *et al.*, 1998a). Therefore, it is conceivable that enhanced sensorimotor gating in human hallucinogen studies might be the expression of a compensatory mechanism aiming to overcome the imminent flooding of the organism with sensory overload. Hence, we expected that PPI might be disrupted in human studies with higher, truly psychotogenic doses of hallucinogenic drugs.

The aim of the present study was to investigate whether high doses of hallucinogenic drugs (NMDA receptor antagonist S-ketamine and serotonin receptor agonist DMT) disrupt PPI and its attentional modulation in humans.

Material and methods

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 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 and a physical examination including a clinical test for normal hearing, electrocardiogram and a routine laboratory testing. All subjects were involved in work with psychiatric patients (physicians, psychologists and psychiatric nursing staff). They had a scientific or clinical interest in the study and did not receive any payment for their participation. 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 (Bundesinstitut für Arzneimittel und Medizinprodukte, Bundesopiumstelle, 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. Nine subjects completed both experimental days with the two doses of both drugs. The six dropouts (two men, four women) were due to unpleasant psychological effects (two subjects under S-ketamine, one subject under DMT), nausea (one subject under DMT), hypotonia (one subject under DMT), headache and mild orthostatic complaints (one subject on the day following an experiment with DMT).

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 or 0.2 mg/kg followed by a break of one minute, followed by continuous infusion with 0.01125 or 0.015 mg/kg*min over 84 min.
2 High DMT: bolus injection with 0.2 or 0.3 mg/kg and continuous infusion with 0.015 or 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 or 0.15 mg/kg followed by a break of 1 min, followed by continuous infusion with 0.0066 or 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 or 0.2 mg/kg, continuous infusion with 0.01 or 0.015 mg/kg*min over 54 min, followed by continuous infusion at a rate of 75% of the previous dose over 30 min.

The dosages for both drugs were determined in a previous open study with six subjects where we monitored psychopathology and plasma levels (unpublished data). The low dose range was determined so as

to evoke relative subtle psychopathological alterations, below the threshold of psychotic symptoms (a so called 'prepsychotic' state), and the high dose range so as to evoke more profound alterations including true psychotic symptoms such as hallucinations and transient delusional misinterpretations of the experimental situation. 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 individual 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 rate of DMT, a reduction of 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.

Study design

Participants had a baseline examination without drug administration. We decided to omit a placebo condition, because the effects of hallucinogens are so prominent that blinding is not really possible. Furthermore, the fact that we would have needed a third experimental day for the placebo condition would have been critical for the recruitment of volunteers for our study. Because of this, we decided that, on balance, it was reasonable and acceptable to omit the placebo condition.

After that, each subject participated in one experiment with DMT and one experiment with S-ketamine 2–4 weeks apart in a double-blind, cross-over design and pseudorandomized order. On each experimental day the same substance (DMT or S-ketamine) was administered in a low and a high dosage with a break of 2 h between. The order of administration of the two dosages was single-blind and was low-high on ten and high-low on twelve experiments.

Experiments were performed in a quiet laboratory room in the Department of Psychiatry at the University of Aachen. In the morning subjects had a light breakfast and during the break between the two dosages they received a small standardized meal. Both drugs were administered intravenously by an automatic infusion pump (Perfusor®, B. Braun, Melsungen, Germany). Blood pressure and heart rate were monitored automatically (Dinamap®, Critikon Tampa, FL, USA) during the whole experiment. Beside the modulation of the startle reflex we studied the psychological effects and the orienting of attention (Gouzoulis-Mayfrank *et al.*, 2005, 2006). The startle session was always performed in the last 25 min of each of the drug infusions. After stopping the drug infusion the psychological effects of the drugs completely vanished within 10–30 min. Details on the general experimental procedures and the psychological effects of the drugs are presented in Gouzoulis-Mayfrank *et al.*, 2005.

Startle measurement

For measurement of the acoustic startle, the EMG of the right orbicularis oculi muscle was recorded with a commercially available startle system (SR-Lab, San Diego Instruments, San Diego, CA, USA). The two miniature electrodes of the startle device were positioned below and lateral to the right eye and the ground electrode was placed behind the right ear over the mastoid. Acoustic startle stimuli were presented binaurally through headphones (TDH-39-P, Maico, Minneapolis, MN, USA).

All acoustic stimuli were bursts of broadband white noise with duration of 20 ms. Startle-eliciting stimuli were 115 dB bursts, the identical discrete prepulse and postpulse stimuli were 10 dB above the 70 dB white noise background. Starting with the onset of the startle stimulus, startle reaction was recorded in 250 1-ms epochs. The digitized electromyographic signal was bandpass filtered (100–1000 Hz) and analysed for startle responses. The criteria for reflex amplitude and latency as well as the software parameters were identical to previous reports (Braff *et al.*, 1992, 2001a; Heekeren *et al.*, 2004a, b). Trials were excluded when the peak amplitude occurred after 80 ms following the onset of the startle stimulus or when the baseline shifted more than 40 digital units (1 digital unit = 1.72 μV). If there was no detectable blink response, the amplitude was scored as zero and latency data were discarded.

The startle session consisted of 76 trials with six different trial types in three blocks: 1) pulse alone trials, 2) prepulse trials with an interval of 100 ms between onset of prepulse and onset of pulse (lead interval), 3) prepulse trials with a lead interval of 240 ms, 4) postpulse trials with a lead interval of 100 ms, 5) postpulse trials with a lead interval of 240 ms and 6) prepulse alone trials. The first and the last block consisted of only five pulse alone trials each which were presented in the relaxed condition. The 66 trials of the second block were 16 pulse alone trials, 16 prepulse trials for each lead interval, six prepulse-alone trials and six postpulse trials for each lead interval. One half of the trials were presented in the attended and the other half in the relaxed condition. The order of presentation of the trials was pseudo randomized. Before the baseline examination and again at the beginning of each experiment, subjects underwent a short training session in order to learn to discriminate 'simple' (pulse alone or prepulse alone) from 'composite' (prepulse + pulse or pulse + postpulse) stimuli. In the training session, the six different trial types were presented in a fixed order, which was known by the subjects. Each trial type was presented once. During the subsequent test session, subjects were seated comfortably in a bed with head and upper trunk supported. The instruction to attend to the pulse or to relax was presented visually trial-by-trial by means of two different slides on a computer screen in front of the subject. Subjects had to discriminate simple from composite stimuli only in the attended condition and they should respond to simple stimuli (pulse alone) by raising their hand. In the relax condition they should simply ignore all stimuli. Slides were initiated 4000 to 5000 ms before the onset of each trial (randomly) and remained on the screen until 200 ms after presentation of the startle stimulus. Intertrial intervals (range 4–17 s) were used randomly. Slides were presented by Presentation software (Neurobehavioral Systems, Albany, CA, USA)

which was triggered by the startle system (for details of this paradigm see Heekeren *et al.*, 2004b).

Data analysis

Only the pulse alone and the prepulse trials entered the statistical analyses. Postpulse and prepulse alone trials were included in the task only to ensure that subjects sustained their attention to the startle stimulus until its end and to confirm that the prepulse itself was too weak to induce a startle reaction. To make sure that in the attended condtition the subjets had directed their attention to the stimuli, trials with incorrect responses were excluded from further analyses. Task performance in the attention task was assessed as percent score of trials with correct discrimination of the stimulus ('simple' versus 'composite'). Thereafter, habituation and prepulse inhibition were calculated as percentage scores for each subject. Habituation was calculated using the formula: [(mean amplitude first block – mean amplitude last block)/mean amplitude first block], and PPI using the formula: 100 – [(mean amplitude prepulse second block/pulse-alone trial second block) × 100].

Differences in task performance between the five conditions (baseline, low DMT, high DMT, low S-ketamine, high S-ketamine) were analysed by repeated measures ANOVA.

To investigate drug effects on startle reactivity, the differences between baseline condition and each drug condition were analysed by paired *t*-tests using the mean amplitude of the first blocks from the nine subjects who completed both experimental days with both doses of both drugs. Startle amplitudes of the second block from these nine subjects were analyzed by means of an ANOVA with the factors drug condition (baseline, low DMT, high DMT, low S-ketamine, high S-ketamine), trial type (pulse alone, prepulse 100 ms lead interval, prepulse 240 ms lead interval) and attention (attend, relax).

For the analysis of PPI, data from sessions with a mean amplitude of less than 20 digital units in the first block (pulse alone trials) were discarded. Due to the suppressing effects of both drugs (particularly S-ketamine) on startle amplitude (see results), we were able to study PPI in eleven subjects at baseline, seven subjects after DMT and only five subjects after S-ketamine. Only four subjects displayed sufficiently high amplitudes in all five conditions. Therefore, we performed separate analyses of the effects of the two drugs on PPI. For the baseline condition, PPI was analysed by means of an ANOVA with the factors attention (attend, relax) and lead interval (100 ms, 240 ms) and differences between the single PPI scores (attend versus relaxed and 100 ms versus 240 ms lead interval) were analysed by subsequent *t*-tests.

Due to the small number of remaining subjects in the two substance groups after exclusion of data sets with low startle amplitude we used simple two-tailed *t*-tests (and in addition Wilcoxon matched-pairs tests) to investigate drug effects on PPI. First we focused on the passive part of the paradigm and compared the three conditions (baseline, low dose, high dose) separately for each lead interval and each substance. To analyse drug effects on attentional modulation of PPI difference scores (PPI attend–PPI relax) were calculated. The resulting difference scores were also analysed separately for each lead interval and substance.

Differences regarding the habituation were analysed in the nine subjects who completed both experimental days with DMT and S-ketamine by means of an ANOVA with the factor condition (baseline, low DMT, high DMT, low S-ketamine, high S-ketamine).

All analyses were performed using the SPSS software (version 11.0) Statistical significance was set at $p \leqslant 0.05$.

Results

From the 15 subjects who entered the study 12 subjects completed the experiment with both doses of DMT and 10 subjects completed the experiment with both doses of S-ketamine. So we had 13 subjects who completed at least one experimental day. From these thirteen subjects, two were nonresponders in the baseline condition; therefore, we were able to analyse the data of eleven subjects for the baseline condition. Nine of these eleven subjects completed both experimental days with the two doses of both drugs. Due to the suppressing effects of both drugs (particularly S-ketamine) on startle amplitude it was not possible to calculate PPI in all drug conditions. Therefore statistical analyses were performed with seven subjects in the DMT and only five subjects in the S-ketamine group. In all dropout cases undesirable effects were self-limited and required no additional medication. The interviews conducted 7 days and 10–12 months after the experiments revealed no aspects of psychopathology or substance abuse that might be related to participation in our study. Both drugs dose-dependently induced psychotic symptoms similar to schizophrenic manifestations. Phenomena resembling positive symptoms of schizophrenia, particularly positive formal thought disorder and inappropriate affect, were stronger after DMT. Phenomena resembling negative symptoms of schizophrenia and attentional deficits were stronger after S-ketamine. The high doses of both DMT and S-ketamine induced truly psychotic symptoms such as hallucinations and transient delusional misinterpretations of the experimental situation. Details on psychopathological effects, after-effects and plasma levels are presented in Gouzoulis-Mayfrank *et al.* (2005).

Task performance

Data are reported for the nine subjects who completed both experiments with both doses of DMT and S-ketamine. Subjects responded correctly in 94.6% of the trials at baseline, 90.7% at low DMT, 94.5% at high DMT, 91.3% at low S-ketamine and 89.3% at high S-ketamine. The ANOVA revealed no significant difference between the five conditions ($p = 0.174$). Only the data from correct trials entered further analyses.

Amplitude

The descriptive statistics for startle amplitudes of the first block of the nine subjects with available data for all five drug conditions are presented in Fig. 1. The mean amplitude of the first block was significantly lower in the high S-ketamine condition compared to the baseline condition ($t = 2.52$, df = 8, $p = 0.036$) and there were also trends for lower amplitudes in the low S-ketamine ($t = 2.20$, df = 8,

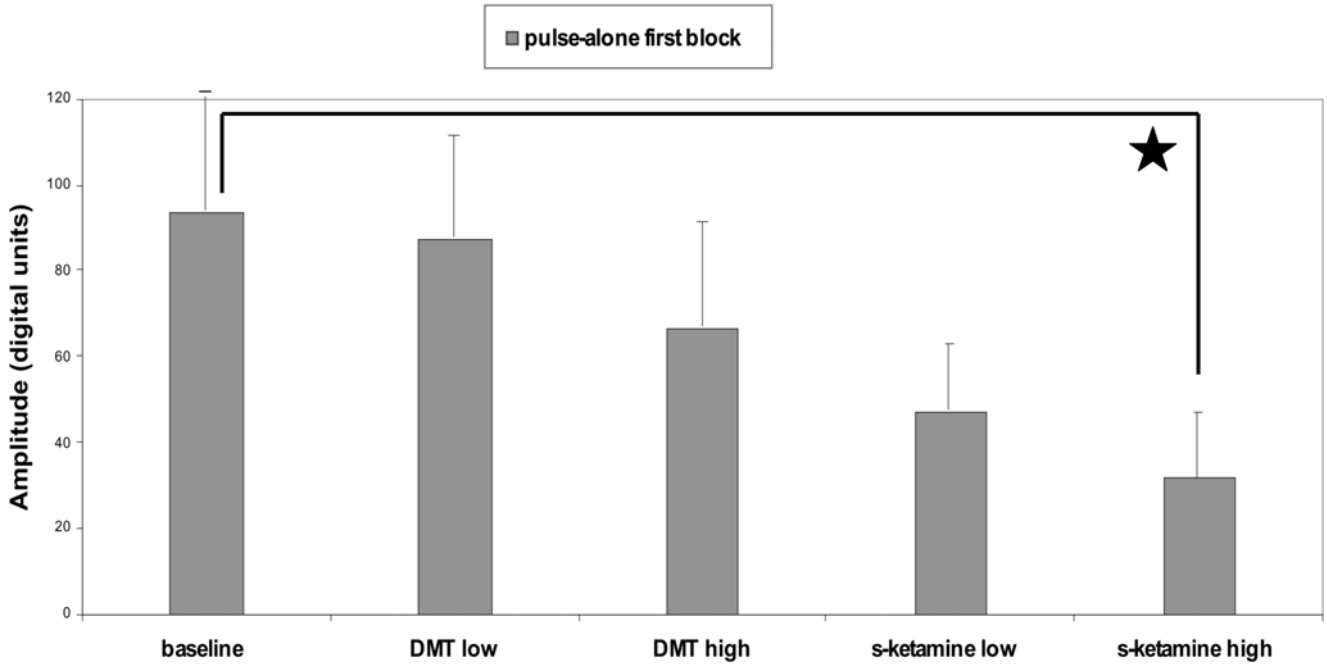

Figure 1 Startle reflex amplitude of the first block from subjects with available data for all five conditions (digital units, means ± standard errors of the mean, $n = 9$), $^*p \leq 0.05$, two-tailed *t*-test.
DMT = N,N-dimethyltryptamine.

$p = 0.059$) and the high DMT condition ($t = 1.87$, df = 8, $p = 0.098$). Because of the small sample we calculated additional Wilcoxon matched-pairs tests. With this nonparametric test, the mean amplitude of the first block was significantly smaller in both S-ketamine conditions (low dosage $p = 0.021$, high dosage $p = 0.008$).

The complete descriptive statistics for startle amplitudes of the second block are presented in Fig. 2. There was a significant main effect of trial type ($F = 6.42$, df = 2,7, $p = 0.026$) indicating that the pulse-alone trials had the highest and the prepulse with 100 ms lead interval had the lowest amplitudes. The main effect of drug condition approached but did not reach significance ($F = 4.65$, df = 4,5, $p = 0.061$). Attentional modulation had no significant effect on startle amplitude ($p = 0.171$).

PPI

Percent PPI scores in the baseline condition are presented in Fig. 3. There was a significant effect of the factor lead interval ($F = 19.05$, df = 1,10, $p < 0.001$), indicating a stronger PPI with the 100 ms than with the 240 ms lead interval. The factor attention just failed significance ($F = 4.69$, df = 1,10, $p = 0.056$) and there was a trend towards a lead interval x attention interaction ($F = 3.49$, df = 1,10, $p = 0.091$). Subsequent *t*-tests confirmed previous observations (Heekeren *et al*., 2004b) of a significant influence of attention only in prepulse trials with a 240 ms lead interval ($t = 2.28$, df = 10, $p = 0.046$) and a significant influence of lead interval only in the relaxed condition ($t = 4.89$, df = 10, $p < 0.001$).

The PPI scores for DMT and S-ketamine are presented in Figs. 4 and 5. After both S-ketamine doses PPI was marginally or significantly increased compared to baseline at the 100 ms ($t = -2.61$, df = 4, $p = 0.059$ and $t = -4.47$, df = 4, $p = 0.011$), but not at the 240 ms lead interval. Because the S-ketamine sample was very small we performed additional non-parametric analyses by means of Wilcoxon tests. In these analyses, PPI after S-ketamine was significantly higher than baseline for both doses at the 100 ms and for the high dose at the 240 ms lead interval (all $p < 0.05$). There was no significant difference in PPI between baseline and DMT (*t*- and Wilcoxon-tests).

In order to investigate the influence of the drugs on attentional modulation of PPI, difference scores (PPI attend–PPI relax) were calculated (data not shown). Although descriptive statistics suggest an impaired attentional modulation of PPI under both drugs and dosages (Fig. 2), this effect was not confirmed by statistical analyses using either parametric or nonparametric procedures.

Habituation

We found no significant effects of drug condition on habituation (data not shown).

Discussion

The present investigation studied the influence of DMT and S-ketamine on PPI and its attentional modulation in humans.

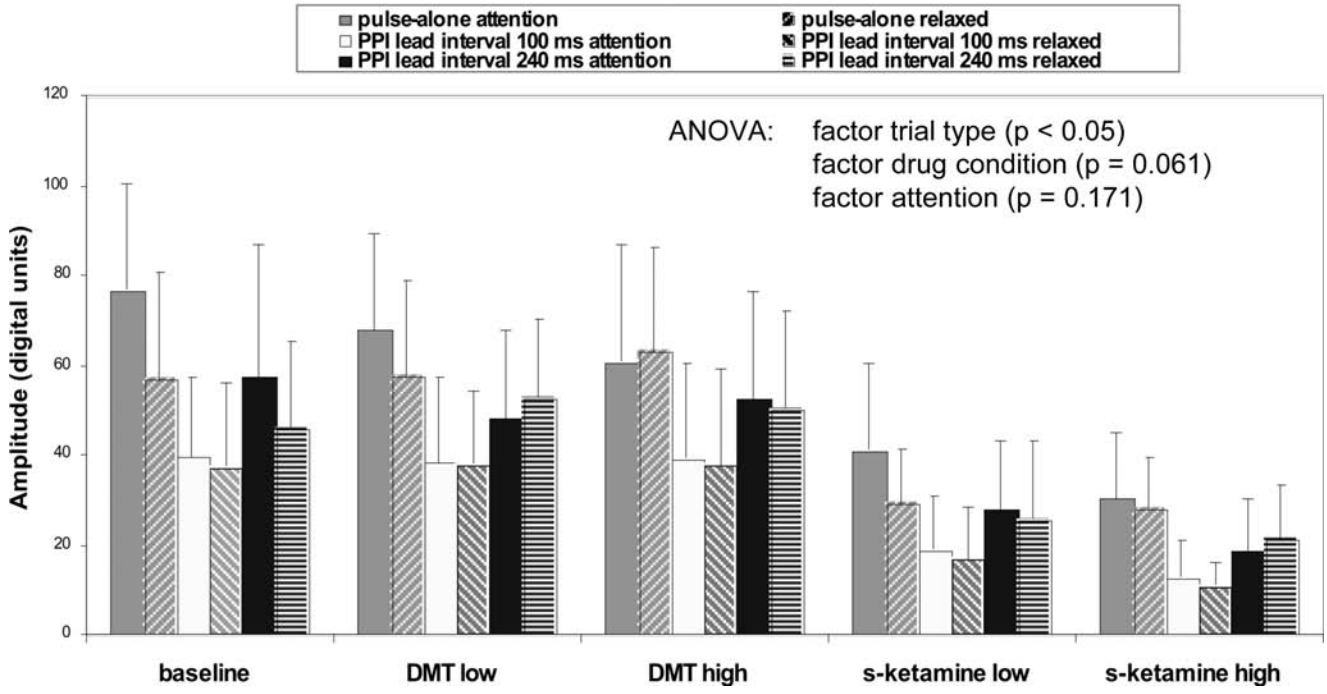

Figure 2 Amplitude of the startle eyeblink reflex of subjects who completed all five conditions (digital units, means ± standard errors of the mean, $n = 9$).
DMT = N,N-dimethyltryptamine; PPI = prepulse inhibition.

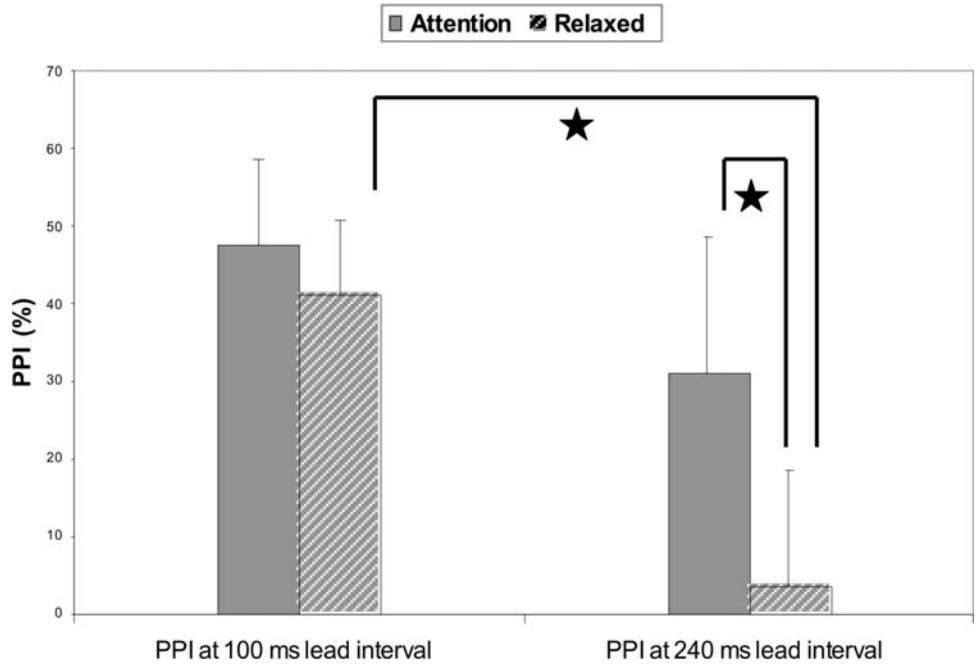

Figure 3 Prepulse inhibition (PPI) of the startle reflex in percent of all subjects at baseline (means ± standard errors of the mean, $n = 11$), $^*p \leq 0.05$, two-tailed *t*-test.

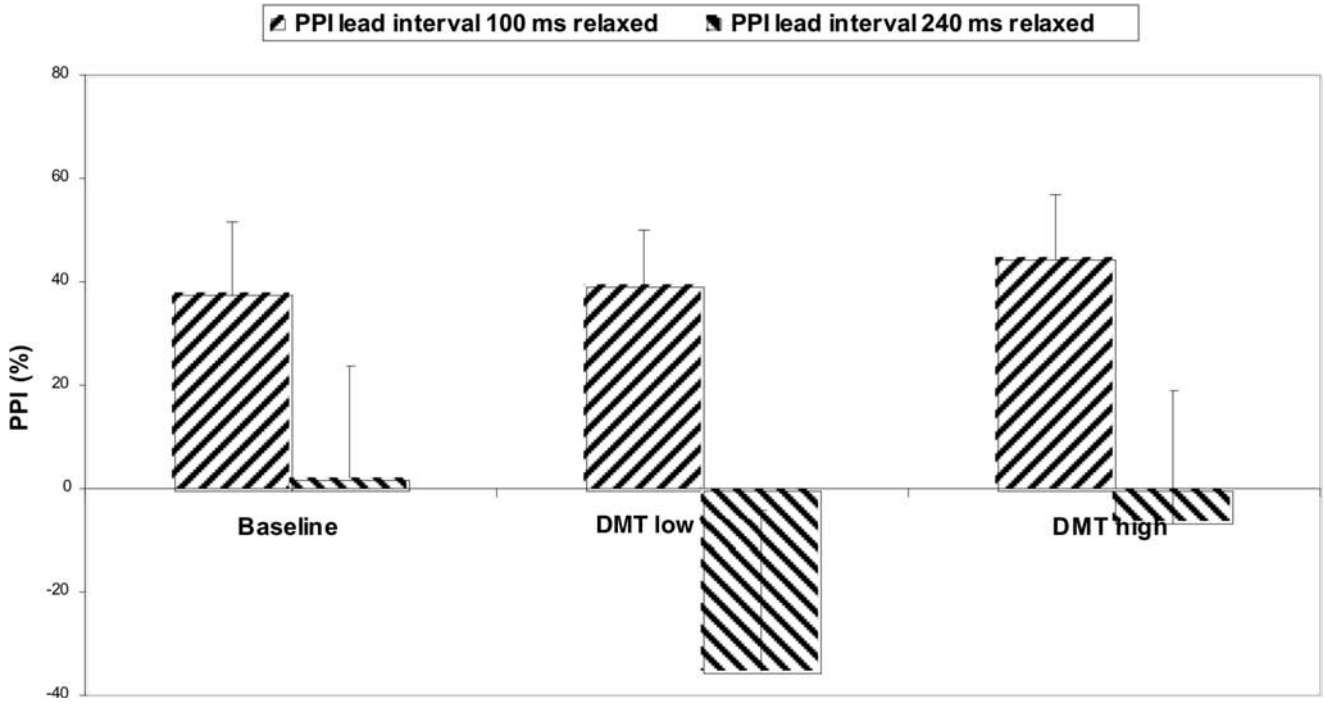

Figure 4 Baseline and N,N-dimethyltryptamine (DMT): prepulse inhibition (PPI) of the startle reflex in percent, only relaxed condition (means ± standard errors of the mean, $n = 7$).

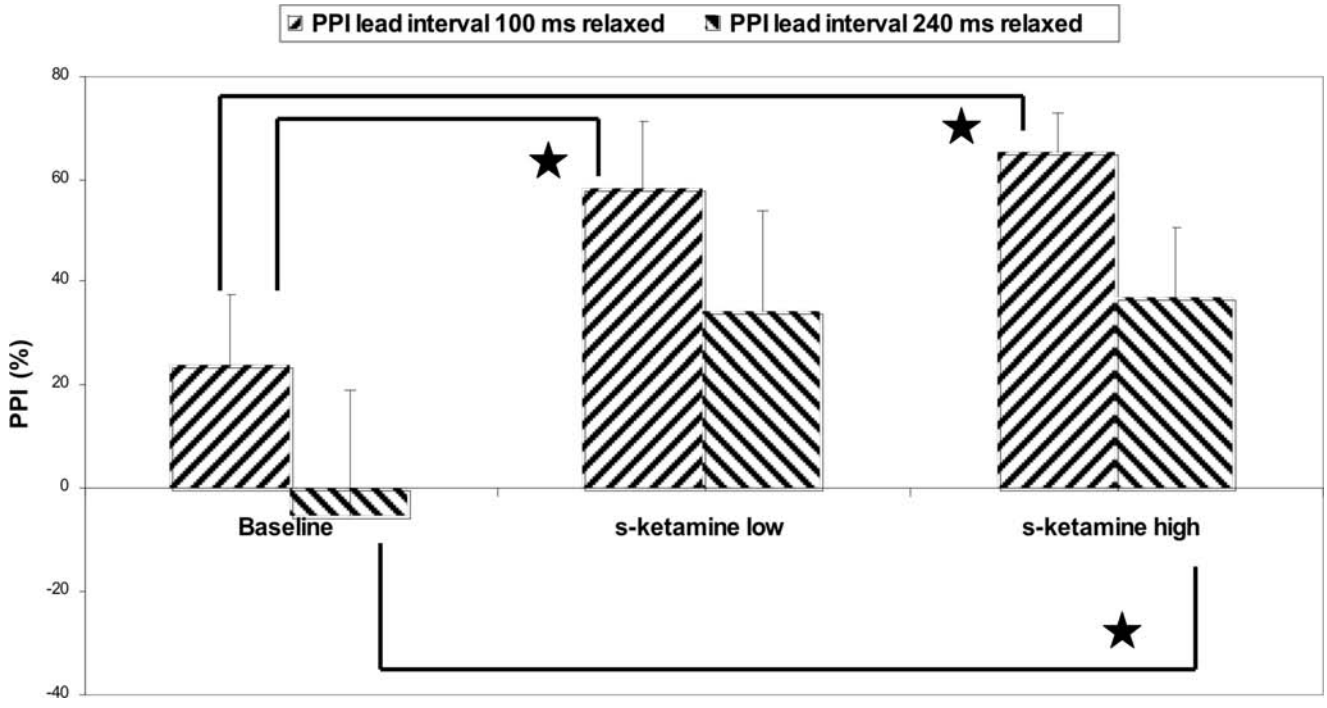

Figure 5 Baseline and S-ketamine: prepulse inhibition (PPI) of the startle reflex in percent, only relaxed condition (means ± standard errors of the mean, $n = 5$), $^*p \leq 0.05$ Wilcoxon matched pair test.

Contrary to findings with schizophrenia patients and animal studies of hallucinogens (Braff *et al*., 2001b; Geyer, 1998; Geyer *et al*., 2001), previous investigations with healthy volunteers reported increases of PPI after low to moderate doses of both the antiglutamatergic hallucinogen S-ketamine and the serotonergic hallucinogen psilocybin (Gouzoulis-Mayfrank *et al*., 1998a; Duncan *et al*., 2001; Abel *et al*., 2003). We speculated that this effect might be related to the relatively low doses given in human studies resulting in a 'pre-psychotic' rather than a full-blown psychotic state (Gouzoulis-Mayfrank *et al*., 1998a). Based on this hypothesis, we expected to find an increase of PPI after moderate, but a decrease of PPI after high, truly psychotogenic doses of both substances. In addition, we expected to find a dose-dependent impairment of the attentional modulation of PPI. This second hypothesis was based on data demonstrating disturbed attentional modulation of the PPI in schizophrenia patients even in the presence of normal PPI in a passive paradigm (Dawson *et al*., 1993).

At baseline, we found stronger PPI with the 100 ms lead interval and stronger attentional modulation of PPI with the 240 ms lead interval. These findings corroborate our previous report from a larger sample (Heekeren *et al*., 2004b). Both drugs elicited schizophrenia-like psychopathology, although full-blown psychotic symptoms such as hallucinations and paranoid ideation occurred only after the high doses of either DMT or S-ketamine (Gouzoulis-Mayfrank *et al*., 2005). After S-ketamine, startle reactivity was diminished, which is consistent with previous findings (Abel *et al*., 2003, Karper *et al*., 1995). To our surprise, however, DMT had no detectable effect on PPI and S-ketamine increased PPI after both doses. Clearly, these results are not in line with our hypothesis, that a possible compensatory mechanism during prepsychotic states after low hallucinogen doses should break down after high doses that produce truly psychotic symptoms and result in deficits of sensorimotor gating (Gouzoulis-Mayfrank *et al*., 1998a).

One alternative explanation for our unexpected observation of an apparent increase in PPI after the high dose of S-ketamine is that the assessment of PPI is confounded by the marked decrease in startle magnitudes produced by this drug in our study and in previous studies showing increases in PPI after ketamine (Abel *et al*., 2003). In both mice and rats, ketamine can reduce PPI without having any effect on startle magnitudes (Brody *et al*., 2003; Mansbach and Geyer, 1991). As discussed elsewhere (Swerdlow *et al*., 2000), it is difficult to be certain that a dramatic change in startle such as produced by ketamine in humans has not contributed to an apparent change in PPI despite the use of percentage scores. Indeed, in the case of high dose DMT, the robust psychotomimetic effects of the drug did not lead to significant changes in either percent PPI or startle magnitudes. Thus, PPI was only increased by a drug treatment when startle was decreased simultaneously. Another alternative explanation of our findings with S-ketamine derives from the demonstration by Moghaddam *et al*. (1997) that low doses of ketamine cause an increase of glutamatergic outflow from prefrontal cortex in rats. Abel *et al*. (2003) referred to this study and argued that if low dose NMDA antagonists (e.g. S-ketamine) act paradoxically as glutamate releasers, then this effect might result in an enhancement of sensorimotor gating. However, we found enhancement of sensorimotor gating after both a moderate and a high, psychotogenic dose of S-ketamine.

Nevertheless, we should acknowledge that our study has methodological limitations mainly due to the very small remaining sample sizes resulting after exclusion of nonresponders and drop outs. Also the order of the drug and gender distribution was not balanced in the remaining sample. Because of the small sample size we did not adjust for the alpha level in our analyses. Due to the firm restrictions in our permissions to conduct this study with a scheduled drug (DMT) we were not able to increase the sample in order to replace the drop outs. Therefore, these findings should be regarded as preliminary.

In summary, our data do not support the hypothesis of sensorimotor gating deficits in human experimental psychoses with hallucinogens and they are not in line with experimental studies in animals. Similarly, we found no clear deficits in the attentional modulation of PPI after either hallucinogen. Finally, neither drug influenced habituation of the startle reflex. This finding is in accordance with the findings from other studies with S-ketamine (Abel *et al*., 2003) and Ayahuasca, a beverage containing DMT (Riba *et al*., 2002).

In conclusion, even after high doses of the serotonergic hallucinogen DMT or the antiglutamatergic hallucinogen S-ketamine, both of which elicited clear psychosis-like psychopathological alterations, healthy subjects did not show any attenuation of PPI. Rather, PPI was augmented and startle was decreased after S-ketamine, in contrast to the decreases in PPI produced by ketamine in animals. In our view there is no indication that the conflicting PPI findings between naturally occurring and experimental psychoses are related to any limitations of the startle PPI paradigm. Rather, because PPI is reduced in patients with schizophrenia, these data point to important differences between human hallucinogen models and both animal hallucinogen models of psychosis and schizophrenia.

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