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ORIGINAL INVESTIGATION

Psilocybin disrupts sensory and higher order cognitive processing but not pre-attentive cognitive processing—study on P300 and mismatch negativity in healthy volunteers

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Abstract

Rationale Disruption of auditory event-related evoked potentials (ERPs) P300 and mismatch negativity (MMN), electrophysiological markers of attentive and pre-attentive cognitive processing, is repeatedly described in psychosis and schizophrenia. Similar findings were observed in a glutamatergic model of psychosis, but the role of serotonergic 5-HT_{2A} receptors in information processing is less clear.

Objectives We studied ERPs in a serotonergic model of psychosis, induced by psilocybin, a psychedelic with 5-$HT_{2A/C}$ agonistic properties, in healthy volunteers.

Methods Twenty subjects (10M/10F) were given 0.26 mg/kg of psilocybin orally in a placebo-controlled, double-blind, cross-over design. ERPs (P300, MMN) were registered during the peak of intoxication. Correlations between measured electrophysiological variables and psilocin serum levels and neuropsychological effects were also analyzed.

Results Psilocybin induced robust psychedelic effects and psychotic-like symptoms, decreased P300 amplitude ($p = 0.009$) but did not affect the MMN. Psilocybin's disruptive effect on P300 correlated with the intensity of the psychedelic state, which was dependent on the psilocin serum levels. We also observed a decrease in N100 amplitude ($p = 0.039$) in the P300 paradigm and a negative correlation between P300 and MMN amplitude ($p = 0.014$).

Conclusions Even though pre-attentive cognition (MMN) was not affected, processing at the early perceptual level (N100) and in higher-order cognition (P300) was significantly disrupted by psilocybin. Our results have implications for the role of 5-HT_{2A} receptors in altered information processing in psychosis and schizophrenia.

Keywords Psilocybin · Model of psychosis · Human · ERP · MMN · P300

Introduction

One of the characteristic features in schizophrenia is the impairment of sensory and informational processing, which is believed to contribute to disturbed cognitive functioning in this disorder (Javitt and Sweet 2015). Event-related potentials (ERPs) represent electrophysiological tools for studying these deficits. Early components of ERPs such as P50 and N100 reflect sensory-related processing, whereas later components like mismatch negativity (MMN) and P300 reflect pre-attentive and attentive informational and cognitive processing (Donchin and Coles 1988; Rosburg et al. 2008; Sur and Sinha 2009). Deficits in both early as well as late ERPs are frequently reported as being a trait marker of schizophrenia,

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with MMN and P300 consistently referred as an endophenotype (del Re et al. 2015; Earls et al. 2016; Polich 2007).

Auditory MMN is a negative component of ERPs generated with a latency of 100–200 ms after the presentation of a stimulus that deviates in one of its physical dimensions (pitch, intensity, duration, and location) from the preceding frequently repeated standard stimuli (Näätänen and Alho 1995; Näätänen et al. 2014). It is considered to be an index of automatic context-dependent information processing and auditory sensory memory (Umbricht and Krljes 2005). A decrease in MMN amplitude is one of the most robust electrophysiological features in chronic schizophrenia with an overall large (> 0.95) effect size (Erickson et al. 2016; Haigh et al. 2017; Umbricht and Krljes 2005). MMN deficits have also been found to be linked with poor global functioning in schizophrenia (Light and Braff 2005).

P300 is typically elicited in oddball paradigms, where subjects attend and actively discriminate between stimuli that differ from each other in certain dimensions. Such discrimination produces a large-positive waveform with a modal latency of approximately 300 ms (Polich and Kok 1995; Sutton et al. 1965). Hence, it is suggested that P300 reflects cortical postsynaptic neuro-electric activity related to cognitive processes such as attention allocation, stimulus evaluation, and categorization with activation of immediate and working memory (Polich and Kok 1995). While the P3a component is thought to represent a mechanism involved in the rapid orienting of attention to events that are unexpected and contextually deviant, the P3b component probably reflects a mechanism involved in the updating of contextual representations in working memory (del Re et al. 2015). The reduced amplitude of P300 response also represents very robust electrophysiological abnormalities associated with psychosis and schizophrenia, being replicated across a number of studies with a large (> 0.8) effect size (Bramon et al. 2004; Jeon and Polich 2003).

Despite the fact that schizophrenia is believed to be a neurodevelopmental disorder, the most phenomenologically relevant animal and human models are induced by acute administration of three classes of psychotomimetic drugs: dopaminergic stimulants (e.g. amphetamines and cocaine), glutamate N-methyl-D-Aspartate (NMDA) receptor antagonists (e.g. ketamine, phencyclidine (PCP) and dizocilpine (MK-801)), and serotonergic 5-$HT_{2A/C}$ agonists (e.g. psilocybin, N,N-diethyllysergamide (LSD) and N,N-dimethyltryptamine (DMT)) (Frohlich and Van Horn 2014; Horacek et al. 2006; Nichols 2016). A growing body of evidence describes the effects of these pharmacological models on ERPs. Specifically, P300 disruption was shown to be induced by amphetamines (Albrecht et al. 2011; Silber et al. 2012) as well as by ketamine in humans (Gunduz-Bruce et al. 2012; Musso et al. 2011; Oranje et al. 2000). Robust evidence also exists for MMN attenuation in this model, e.g., (Gunduz-Bruce et al. 2012; Oranje et al. 2000; Schmidt et al. 2012; Umbricht et al. 2000) with a recently published effect size of $d = 0.49$ reported in a meta-analysis (Rosburg and Kreitschmann-Andermahr 2016). Furthermore, ketamine and MK-801 also disrupted MMN-like responses in rodents (Ehrlichman et al. 2008; Tikhonravov et al. 2008).

Compared to the previous models, the effects of serotonergic psychedelics on both ERPs are less clear. At the time of planning our experiments, only one study employed an auditory MMN paradigm during psilocybin intoxication (Umbricht et al. 2003) and another one during DMT intravenous infusion (Heekeren et al. 2008). In both cases, psychedelics failed to affect MMN; however, a disruptive effect on MMN during the later stages of LSD intoxication (after the peak had worn off) has recently been reported (Timmermann et al. 2017). Furthermore, until now there have been no human or animal studies with these serotonergic models exploring the effects on auditory P300 and P3-like potential. The only report of attenuated P300 by psilocybin was described by Kometer et al. (2012) in a visual task.

On the other hand, serotonergic psychedelics have been shown to alter several parameters in the cognitive domain and sensorimotor processing in healthy individuals in a manner that is characteristic for psychosis, e.g., alterations of temporal processing (Nichols 2016; Uyeno 1968; Wittmann 2015), disruption of prepulse inhibition (PPI) (Quednow et al. 2012), or emotional processing (Kraehenmann et al. 2015). Cognitive functions and sensorimotor processing are also affected in animal models with serotonergic psychedelics (Geyer 2015; Palenicek et al. 2008; Palenicek et al. 2010; Rambousek et al. 2014; Tyls et al. 2016).

Therefore, in order to elucidate whether the disruption of pre-attentive and/or attentive processing is present in a serotonergic psilocybin model of psychosis and to see possible relations between them, we evaluated both MMN and P300 in the same volunteers within the same session. This was possible due to psilocybin's intermediate duration of effects, which varies between 3 and 6 h (Hasler et al. 2004), producing a sufficient time window for measuring both ERPs in one subject. We hypothesized that psilocybin (1) will decrease P300 amplitude, (2) will reduce MMN when tested at later stages of intoxication, and (3) that these effects will be dependent on the plasma levels of psilocin as well as the magnitude of its effects measured by psychometric scales.

Experimental procedures

Participants and recruitment

All of the participants were recruited via a peer-to-peer method and initially pre-screened during a telephone interview or

via email to exclude those who did not meet the major inclusion criteria (healthy man or woman, 28–65 years old). Those who were pre-selected were invited for an introductory meeting, where the study design was presented and a structured psychiatric interview and psychological and basic physical examinations, including a urine drug test, were provided. The Minnesota Multiphasic Personality Inventory (MMPI-2) (Butcher et al. 1991) and the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al. 1998) were applied as the psychiatric/psychological tools to screen for any clinically significant psychopathology. Participants who screened positive for any psychiatric disorder (F10-F99 according to ICD-10) except tobacco harmful use/dependence as well as a positive family history of psychotic disorder (up to second degree relatives) were excluded from the study. Other exclusion criteria were major physical disorders (intracranial hypertension, arterial or pulmonary hypertension, a cerebral stroke in the past, cardiac insufficiency, coeliac disease, and liver dysfunction), regular use of medication (except contraceptives), pregnancy, presence of ferromagnetic materials and cardio-stimulator, and left-handedness (evaluated using the Edinburgh Handedness Inventory).

Finally, 20 healthy volunteers (10 males, 10 females—mean age of 36.81, age range of 28–48) were chosen. Subjects with a previous history of psychedelic use ($n = 14$) as well as drug naive ($n = 6$) were included. Fourteen of 19 subjects had previous experience with psilocybin (not fulfilling the ICD 10 criteria for harmful use or dependence) and one subject did not fill in the form of previous experiences. The lifetime frequency of use was as follows: four subjects 1–4×, four subjects 4–10×, three subjects 11–20×, one subject 21–50×, and one subject 51–100×. All of the subjects had a university degree with the mean time spent in education of 19.4 years.

During an approximately 2h-long interview, subjects were informed in detail of the nature of the study, the drug effects and safety. They were free to ask any questions related to the experiments or psilocybin. Blood samples were taken to determine the activity of liver enzymes (ALT, AST, and GMP/GGT) and bilirubin in order to exclude subjects with unexpected liver dysfunctions. Finally, study participants were instructed: (1) to remain drug free between the interview and the day of experiment, (2) to abstain from alcohol for at least 1 week prior to the session, (3) to come with an empty stomach and to not to drink a morning coffee on the day of the experiment, and (5) to not smoke at least 2 h prior to taking the study medication. The subjects were examined by the same research team that leaded them through all of the subsequent measurements and the whole duration of the study. The research team consisted of at least of one psychiatrist (MD) accompanied by a second researcher (psychologist or psychiatrist) and a laboratory EEG technician/nurse. Both of the researchers were always of the opposed sex to balance the team. The study design was elaborated to correspond to the Guidelines for Safety in Human Hallucinogen Research (Johnson et al. 2008).

Study approval

The study was approved by the local ethical committee of Prague Psychiatric Centre/National Institute of Mental Health and by the Czech legal authority "State institute for drug control." It was approved as a clinical trial registered under the EudraCT No. 2012-004579-37. All volunteers signed an informed consent prior to entering the study.

Drug and dosage

Psilocybin was manufactured according to good manufacturing practice (GMP) standards from THC-Pharm GmbH, Frankfurt, Germany. Gelatine capsules containing 1 and 5 mg of psilocybin homogenized with *Trittici amylum* were prepared in the hospital pharmacy of the Institute for Clinical and Experimental Medicine in Prague, Czech Republic. The dosage regime was set according to the volunteers' weight to be approximately 0.26 mg/kg (higher intermediate dose known to induce psychotic-like symptoms (Geyer and Vollenweider 2008; Griffiths et al. 2011; Kometer et al. 2013; Nichols 2016; Tyls et al. 2014)). The dose was increased by 1 mg per each 5 kg of body weight. The drug was administered orally in an adjusted number of capsules containing either 5 or 1 mg and swallowed after drinking 200 ml of water on an empty stomach.

Experimental design

Each subject underwent two sessions (placebo/active drug) in a counterbalanced and randomized order, in a double-blind experimental model. The time window between each of the measurements was set to a minimum of 28 days. In the case of women volunteers, testing was managed so as to not overlap with menses.

On the day of testing, subjects were carefully somatically examined by the MD of the experimenter's team; blood pressure and heart rate were gathered, and they were re-tested by a short interview to exclude new contraindications for enrolment. The participants were subsequently injected with an intravenous cannula for blood sampling, and an EEG cap was positioned on his/her head. After that, he/she entered the sound-attenuated and electrically insulated experimental room (Faraday's cage) where they remained throughout the test day with all of the members of the research team. The room was decorated to have a comfortable living room-like appearance. The whole test period after drug administration lasted approximately 6.5 h.

ERPs were registered at 100 min (P300) and 125 min (MMN) after ingestion of the drug, when the most intensive psychotic-like symptoms were expected. In between the ERP measurement, a blood sample was collected and blood pressure and pulse were registered.

The Brief Psychiatric Rating Scale (BPRS) (Overall et al. 1967), an instrument for evaluating psychopathology in patients with schizophrenia, was gathered several times during the measurement. The Hallucinogen Rating Scale (HRS) (Strassman et al. 1994) and the Standardized Psychometric Assessment of Altered States of Consciousness in Humans (APZ) (Dittrich 1998) were evaluated by the participants once at the end of the session (for timeline see Fig. 1). Two, 4, and 28 days after each session, the participants were screened to check his/her general psychological state and to exclude any psychotic symptoms using the Psychosis Screening Questionnaire (PSQ) (Bebbington and Nayani 1995) and MINI.

Serum levels of psilocin

Blood samples were centrifuged at room temperature for 10 min at 4000 rpm. The separated sera were then stored at − 20 °C until analyzed. Psilocin in sera was analyzed by gas chromatography/mass spectrometry (GC-MS). The methods previously published for psilocin analysis in serum or urine had to be partly modified and optimized due to the ascertained instability of psilocin in alkaline media (Sticht and Kaferstein 2000) and partly modified due to the adaptation to our available analytical technology (Kamata et al. 2005). In brief, our procedure consisted of the solid-phase isolation of psilocin from the serum with the addition of a deuterated internal standard psilocin-D4 at pH 6 using Bond Elut Certify LRC columns (10 ml/130 mg), evaporation of eluates until dry and sialylation with MSTFA. The analysis itself was performed on a GC HP model 6890 A with 5973 MSD and capillary HP5-MS, helium carrier gas with constant flow, injection in a splitless mode, temperature programmed in the range of 85–285 °C, standard electron impact ionization (70 eV), and selective ion monitoring mode. The calibration was based on a spiked blank serum and was linear in the range of 0–200 ng/ml with a quantification limit of 10 ng/ml and detection limit of 5 ng/ml.

Subjective and behavioral drug effect

Subjective acute drug effect was self-evaluated by two scales: the HRS (Strassman et al. 1994) and a revised version of the APZ (Dittrich 1998). The HRS includes 71 items distributed in six scales: somaesthesia, affect, volition, cognition, perception, and intensity. All of the items are rated 0–4 (from "not at all" to "extremely"). The APZ contains 72 dichotomous items covering a broad range of phenomena that are potentially present during altered states of consciousness. The subjects responded to each question by placing a mark on a horizontal visual analogue scale (VAS) 100 mm long. Three categories derived from the items are the following: oceanic boundlessness (OSE), dread of ego dissolution (AIA), and visionary restructuralization (VUS). The overall magnitude of the effect is defined as a "secondary scale" (VWB or G-ASC; comprising all of the items of the questionnaire).

The researchers further assessed the BPRS (Overall et al. 1967) several times over the session (before drug/placebo intake, 60, 180, and 360 min after). The BPRS contains 18 psychiatric symptoms (each rated 0–6 from not present to severe/very strong), which are clustered into five subscales (see Fig. 9 in online supplemental material).

EEG and ERP (event-related potentials) acquisition

The subjects were lying down on a bed with their eyes closed in a comfortable setting. The EEG signal was registered from 21 Ag/AgCl scalp electrodes fixed on a cap, in positions following the International 10/20 system (Electro-Cap International, Inc., ECI). Four electrooculogram (EOG) electrodes were added to monitor eye movement. Electrode impedances were kept below 5 kΩ. Data were acquired with a BioSDA09 standard 32-channel digital EEG amplifier (M&I Ltd., Prague, Czech Republic), with a band pass of 0.1–200 Hz and were digitalized continuously at a sampling

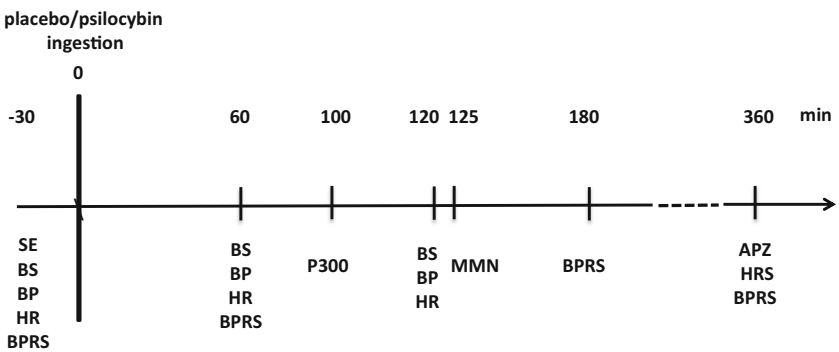


Fig. 1 Timeline of activities during the drug session before and after ingestion. Somatic examination (SE), taking blood samples (BS), checking blood pressure (BP) and heart rate values (HR), BPRS (before and at 60, 180, and 360 min after administration), and self-evaluating scales (APZ and HRS)

rate of 1000 Hz. The stimuli for ERP generation were presented by the software Presentation® (Neurobehavioral Systems, Inc., Albany, USA) through Sennheiser HAD 280 headphones.

Stimulation and data analysis

P300—An oddball paradigm with 120 standard (200 Hz, 40 ms, 75 dB SPL) and 30 target (500 Hz, 40 ms, 75 dB SPL) tones was presented binaurally in a pseudo-random order (inter-stimulus interval, ISI = 1200 ms). The subjects were instructed to keep their eyes closed and to count in their mind infrequent higher-pitched target tones in a background of standard stimuli.

MMN—A single deviant auditory paradigm was used, with 1350 standard tones (1000 Hz, 100 ms, 5 ms rise and fall, 75 dB SPL) and 75 frequency deviant tones (1200 Hz, 100 ms, 5 ms rise and fall, 75 dB SPL). Stimuli were presented binaurally in regular order, when every 20th was the deviant tone with a fixed ISI of 500 ms. The subjects had their eyes closed during the recording.

ERP analyses were performed in BrainVision Analyzer® (version 2.1, Brain Products GmbH, Munich, Germany)

P300—Data were filtered with a 0.1–20 Hz band-pass filter and re-referenced to linked mastoids. Artifacts were detected by visual inspection and rejected by means of semi-automatic artifact rejection (maximum gradient 50 μV, max-min 100 μV, minimum permitted amp − 100 μV, maximum permitted amp 100 μV, lowest permitted activity 0.05 μV). For eye-blinks detection and rejection, ocular ICA correction was used, while maximum two components were eliminated. EEG was segmented into 1000 ms epochs, baseline corrected (200 ms pre-stimulus) and averaged. Data with less than 15 valid trials were excluded. Amplitudes and latencies of N100 after the standard stimuli were evaluated in Fz, Cz, and Pz as the highest negative peak in the time window (70–120 ms). Amplitudes and latencies of N100, P200, N200, and P300 components after the target stimuli were evaluated in Fz, Cz, and Pz electrodes as the highest peak in their corresponding polarity and time windows (N100—70–120 ms, P200, N200—180–250 ms, P300—280–360 ms).

MMN—Data were filtered with a 1–30 Hz band-pass filter, and artifacts were rejected by a semi-automatic method of rejection (maximum gradient 50 μV, max-min 100 μV, minimum permitted amp − 100 μV, maximum permitted amp 100 μV, and lowest allowed activity 0.05 μV). For eye-blink detection and rejection, ocular ICA correction was used, while maximum two components were eliminated. The signal was re-referenced to linked mastoids and segmented into 450 ms epochs, with a 50-ms pre-stimulus interval, where baseline correction was applied. Epochs after the standard and deviant tones were averaged separately. N100 components were detected as the peak negativity 70–130 ms after the standard stimulus. The MMN was calculated by subtracting the average of the standard tones from the average of the deviants. The peak MMN was detected by semi-automatic method in the time window of 150–250 ms in the resulting difference wave. Amplitudes and latencies of N100 and MMN were evaluated from the Fz and Cz electrodes. For each subject, the area of MMN was calculated for the Fz and Cz electrode for an interval around the individual MMN peak (− 25 ms to + 25 ms). Data with less than 60 valid deviant trials were rejected.

Statistical analysis

The least-square (LS) mean, LS mean difference of the treatment groups, and 95% confidence interval (CI) for the difference between the two treatment groups were reported for all of the variables. A mixed model repeated measure analysis of variance (ANOVA) for a 2-sequence (psilocybin or placebo first), 2-period (timing of test administration), and 2-treatment crossover design, with fixed effects for treatment, time (both as within-subject factors), sequence (as a between-subject factor), treatment-sequence interaction, and random effects for subject nested within sequence, was applied to determine the difference between the psilocybin and the placebo in the rating scales (HRS, APZ, and BPRS) and safety parameters (blood pressure and heart rate). The same analysis with an additional effect of the electrodes (within-subject factor) was used to test differences in event-related potentials (MMN and P300 paradigms). In the case of non-significant interaction, both for the sequence (carry-over) and sequence-treatment interaction (period) along with significant treatment, treatment-time (BPRS) or treatment-electrode (N100, MMN, P300), a consequent Bonferroni's post hoc test was performed to assess the difference between the treatments. Associations between drug effects (placebo-psilocin difference) measured by psychometric scales, psilocin blood levels, evoked potentials as well as associations between P300 and MMN amplitudes were calculated as correlation coefficients. All of the analyses were performed using Statistica version 9.1 (StatSoft, Inc. 2010).

Results

Of the 20 volunteers, 19 underwent both of the sessions (placebo and psilocybin in a counterbalanced order). The average dose used was 17.67 mg (16–24 mg), and maximum psilocin serum levels were achieved 60 min after ingestion (mean 32.8; 95%CI 25.1–40.4 ng/ml), remained high for another 60 min (28.2; 95%CI 24.8–32.3 ng/ml) and then dropped to less than 10 ng/ml 360 min after ingestion (for Fig. 6, see online supplemental material). Psilocybin also led to a mild significant increase in systolic and diastolic blood pressure of about 10–20 mmHg and heart rate of about 10 beats per minute during peak intoxication (for details see online supplemental material including Fig. 7). Two out of the 20 subjects were initially excluded from further analyses; one subject

did not come to the placebo session, and the second was a non-responder to the psychological effects of the psilocybin, i.e., she did not experience any psychotomimetic effect according to the psychometric scales and had very low psilocin serum levels (max 10 ng/l). Psychological drug effects, as well as correlation with psilocin serum levels are therefore based on the data from the 18 volunteers (10 males (M) and 8 females (F)). After elimination of noisy data (a consequence of movement artifacts during the peak of intoxication), 13 subjects (7M, 6F) were included in the MMN analyses and 10 subjects (8M, 2F) were included in the P300 analyses.

Effects of psilocybin on subjective experience and psychopathology

According to the subjective scales APZ and HRS, subjects experienced intense psychedelic effects (scaled in the higher intermediate range) during psilocybin intoxication. The effects were significant in all subscales; in the APZ, the most pronounced effects were on visionary reconstruction (VUS) and oceanic boundlessness (OSE); on the HRS, increases in all subscales were of a similar intermediate magnitude.

The psychopathology measured by BPRS peaked at 60 min after ingestion and remained high at 180 min after ingestion. The effects were most pronounced on BPRS factor II (withdrawal and retardation) and factor III (though disturbance and hallucinations); however, some increases were also present for other factors mainly during the BPRS 60 min.

Several positive correlations between the psilocin serum levels and the magnitude of effects were found on the subjective as well as objective scales.

For details on subjective experience and psychopathology, see the online supplemental material including Fig. 8, Fig. 9 and Fig. 10.

Effects of psilocybin on auditory ERPs

P300 paradigm

N100 of standard stimuli Analyses of amplitudes of N100 reveal a significant effect of treatment ($F(1,8) = 6.1$, $p = 0.039$) and treatment x electrodes interaction ($F(2,16) = 11.32$, $p < 0.001$) with a non-significant sequence and treatment-sequence factors. The subsequent post hoc test revealed a significantly lower amplitude during psilocybin intoxication on the Fz and Cz electrodes: Fz—placebo-psilocin LS mean difference: 2.28; 95%CI 1.35–3.21; $p < 0.001$, Cz—LS mean diff 2.08; 95%CI 1.15–3.01; $p < 0.001$. Analyses of N100 amplitude in Pz and N100 latencies did not show any significant results.

Components after target stimuli Analyses of latencies and amplitudes of N100, P200, N200, and P300 (using treatment and electrodes as within factors) revealed a significant effect of psilocybin only on P300 amplitude (treatment—$F(1,8) = 11.77$, $p = 0.009$; treatment x electrode—$F(2,16) = 0.04$, $p = 0.97$; sequence—$F(1,8) = 0.04$, $p = 0.85$; treatment-sequence—$F(1,8) = 0.33$, $p = 0.58$). The subsequent post hoc test revealed a significantly lower amplitude during psilocybin intoxication on all electrodes: Fz—placebo-psilocin LS mean difference 5.17, 95%CI 2.26–8.08; $p < 0.001$, Cz—LS mean diff 4.88, 95%CI 1.97–7.79; $p < 0.001$, and Pz—LS mean diff 5.14, 95%CI 2.22–8.05, $p < 0.001$. Otherwise psilocybin did not have any effect on P300 latency or N200 and P200 parameters. The results are shown in Fig. 2. The mean values of P300 latencies and amplitudes in the placebo and psilocybin condition calculated for ten of the subjects are given in Table 1. It should be noted that of the ten subjects included in the analysis, four of them did not fulfill the instruction to calculate the target stimuli; they reported an inability to focus their attention due to being overwhelmed by the effects of the drug. In line with this, a further tentative comparison showed the association of lower P300 amplitudes with higher psilocin serum levels; however, due to the low number of subjects in these subgroups, it was not possible to perform the corresponding statistical analysis. When intra-individual data were explored, we can conclude that all subjects that were able to fulfill the task also decreased P300 amplitude.

Correlation analyses of P300 amplitude and BPRS, HRS, and APZ found a negative correlation between P300 amplitude at the Cz electrode and affect subscale of the HRS ($r = -0.63$, $p = 0.05$), P300 amplitude at the Pz electrode and cognition of the HRS ($r = -0.70$, $p = 0.02$), AIA ($r = -0.69$, $p = 0.03$) and VUS ($r = -0.70$, $p = 0.03$) of the APZ, BPRS 60 min factor IV ($r = -0.69$, $p = 0.03$) and total ($r = -0.66$, $p = 0.04$). The strongest correlations are shown in Fig. 3.

MMN paradigm

N100 of standard stimuli Analyses of latencies and amplitudes of N100 did not reveal significant treatment nor treatment-electrodes interactions for N100 latency (treatment—$F(1,11) = 2.96$, $p = 0.11$; treatment x electrode—$F(1,11) = 0.54$, $p = 0.48$) and for N100 amplitude (treatment—$F(1,11) = 1.99$, $p = 0.17$; treatment x electrode—$F(1,11) = 1.47$, $p = 0.25$).

MMN—Mismatch negativity to frequency deviants was obtained with maxima on the fronto-central area for both conditions (placebo and psilocybin). Analyses of latencies, amplitudes, and area under the curve of MMN did not reveal either significant treatment or treatment-electrode interactions: MMN latency (treatment—$F(1,11) = 1.92$, $p = 0.19$; treatment x electrode—$F(1,11) = 0.15$, $p = 0.70$) and MMN amplitude (treatment—$F(1,11) = 0.33$, $p = 0.59$; treatment x electrode—$F(1,11) = 0.01$, $p = 0.94$; MMN Fz AUC: treatment—

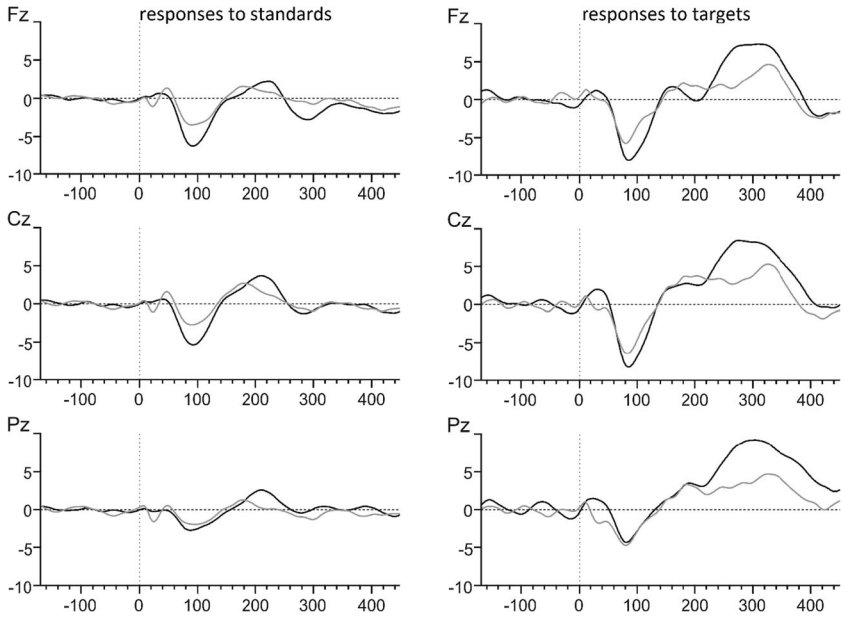


Fig. 2 Left: overlay of grand averages of auditory-evoked potentials after standard stimuli in ten subjects. Psilocybin (grey line) induced a significant reduction of N100 compared to the placebo (black line) on Fz and Cz, $p < 0.001$. Right: overlay of grand averages of P300 after psilocybin (grey line) and the placebo (black line) in ten subjects showing a significant reduction of P300 amplitude after psilocybin on Fz, Cz, and Pz electrodes, $p < 0.001$

$F(1,11) = 0.09$, $p = 0.77$) and MMN Cz AUC: treatment—$F(1,11) = 0.3$, $p = 0.59$). The results are shown in Fig. 4.

P300 and MMN correlation

Correlation analysis of the P300 and MMN in those subjects whose data had sufficient quality for both paradigms ($n = 8$) revealed a strong negative correlation between the P300 amplitude and the absolute MMN amplitude at the Cz electrode during psilocybin intoxication ($r = -0.813$, $p = 0.014$) as shown in Fig. 5. No correlation was found for the same parameters during the placebo session ($r = -0.303$, $p = 0.466$).

Long-term neuropsychiatric effects

According to PSQ and MINI examination on the 4th and 28th day, no psychotic symptoms and no other psychopathology were observed in any of the volunteers (data not shown).

Table 1 Mean values and P300 latencies and amplitudes at Fz, Cz, and Pz in the placebo and psilocybin condition calculated for ten subjects. Latency (ms) and amplitude (μV)

	Latency (+/−SD)		Amplitude (+/−SD)	
	Placebo	Psilocybin	Placebo	Psilocybin
Fz	307.1 (35.3)	313.9 (28.61)	11.22 (3.66)	6.05 (2.85)
Cz	294.9 (36.19)	316 (28.46)	11.51 (4.75)	6.63 (2.31)
Pz	308.4 (35.44)	308.6 (47.43)	11.4 (3.77)	6.26 (2.72)

Discussion

This is the first study that describes the effects of psilocybin on auditory P300 and its relation to the intensity of overall psychedelic effects. The main finding of our study was that psilocybin disrupted higher-order cognitive processing (significantly reduced auditory P300) accompanied by attenuation of early perceptual processing (decreased N100) but had no effect on auditory pre-attentive processing (MMN) in the same subjects within the same session. Furthermore, a negative correlation between P300 and MMN magnitudes was observed.

Psilocybin in our setting induced an intermediate to high intensity of psychological effects as described by Griffiths et al. (2011), with psychotic-like symptoms being presented 60–180 min after ingestion and the effect completely wearing off 360 min after administration. Regarding the safety profile, psilocybin possessed only mild sympathomimetic activation and did not cause any serious adverse events in our sample group.

Even though our P300 paradigm was not designed to detect the P3a and P3b subcomponents of P300, we observed the largest differences between the grand average waves (for psilocybin and placebo) in the anterior part of the wave (see in Fig. 2) referring most likely to P3a, which is strongly associated with attention (Polich 2007). Accordingly, attention and cognitive disruption during psilocybin intoxication has been described by others (Carter et al. 2005; Hasler et al. 2004). This also corresponds to our observation that the four volunteers who were not able to count the target tones had lower P300 amplitudes and higher psilocin serum levels compared to those who were able to perform the task. From a

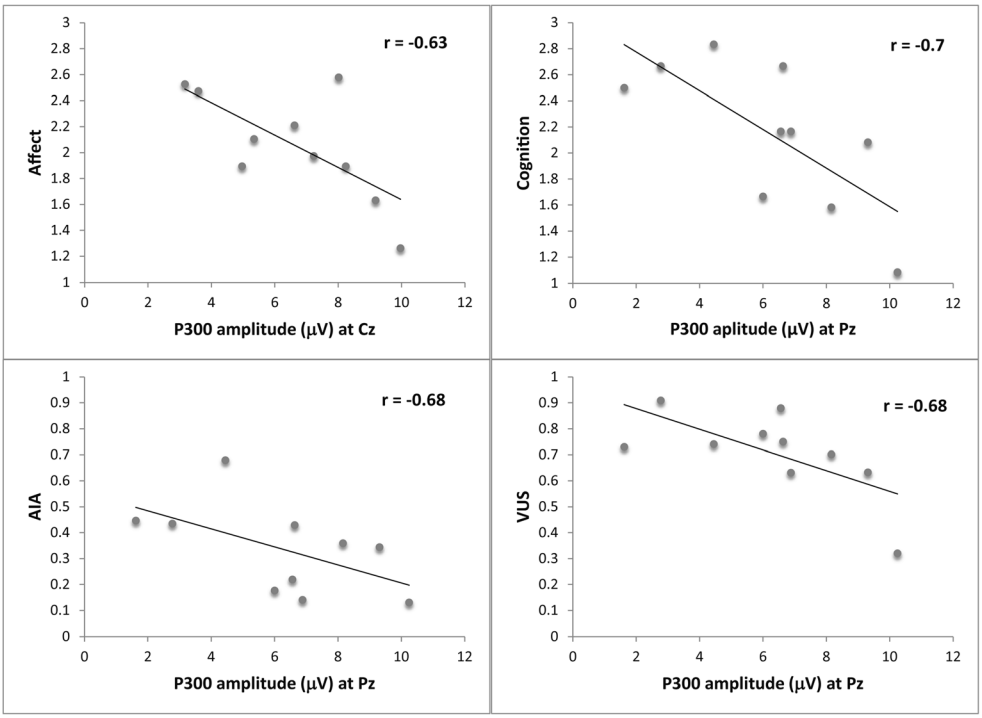


Fig. 3 Negative correlations between P300 amplitude and magnitude of effects in APZ and HRS in ten subjects. Self-experienced enhancement in Affect during psilocybin intoxication negatively correlated with P300 amplitude at the Cz electrode, $p = 0.05$. Subjective change in Cognition, AIA and VUS caused by psilocybin negatively correlated with P300 amplitude at the Pz electrode, $p < 0.05$

neurobiological perspective, since psilocybin was associated with a diminished P300 amplitude but no effect on P300 latency was observed, this may reflect that the amount of synchronized neuronal sources engaged in the given task is decreased, while the processing speed remains intact. This theory also fits with the "entropic brain hypothesis" and other studies on brain connectivity, according to which the activity in high-level brain networks becomes relatively disorganized under psilocybin and other serotonergic psychedelics (Carhart-Harris et al. 2013; Carhart-Harris et al. 2014; Carhart-Harris et al. 2016; Muthukumaraswamy et al. 2013).

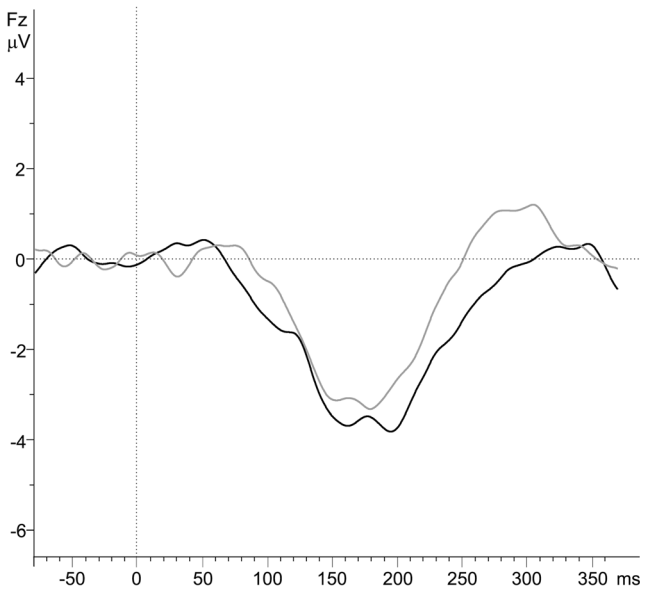


Fig. 4 Grand average of MMN (difference waves) on the Fz electrode in 13 subjects after placebo (black line) and psilocybin (grey line) administration

The fact that the early evoked auditory component N100 was also reduced in the P300 paradigm after standard stimuli indicates that information processing at the sensory cortical level is also attenuated. N100 amplitude reduction is typically found in schizophrenia (Brockhaus-Dumke et al. 2008; Rosburg et al. 2008) where it is reliably found in experiments with long ISIs (> 1 s) and extremely short ISIs (< 0.3 s) and less consistently in paradigms with ISI lying within this time window (Rosburg et al. 2008). This may explain why we only observed a decrease in amplitude in our P300 paradigm (ISI 1.2 s) but not in MMN (ISI 0.5 s), while Umbricht et al. (2003) observed N100 reduction during their auditory MMN paradigm with ISI 0.3 s.

Since psilocybin induces most of its behavioral and neuropsychological effects as well as the visual P300 deficit via 5-HT_{2A} receptors (Kometer et al. 2012), it is also likely that the same mechanism is implicated in our case. In line with this hypothesis, atypical antipsychotics with 5-HT_{2A} antagonistic properties have been shown to improve P300 deficits in schizophrenic patients (Park et al. 2010; Sumiyoshi et al. 2013; Zhang et al. 2009). However, the role of other serotonin receptors (especially 5-HT_{2C} and 5-HT_{1A}) in P300 generation still remains elusive. Polich and Criado (2006) offer evidence

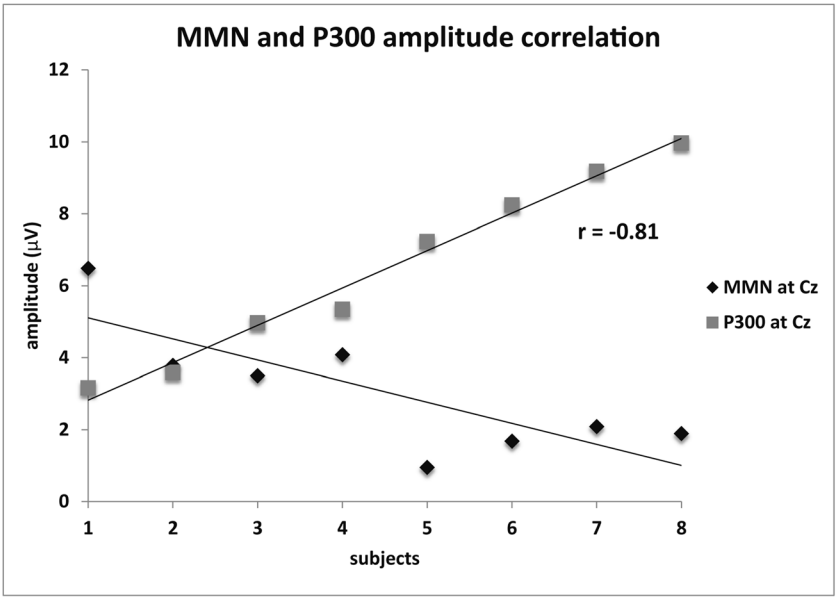


Fig. 5 Negative correlation between MMN amplitude (absolute values) and P300 amplitude in eight subjects during psilocybin intoxication, $p = 0.014$. The smaller MMN amplitude is at the Cz electrode; the higher P300 is at the Cz electrode during psilocybin intoxication

supporting the dual-transmitter P300 hypothesis: dopaminergic/frontal processes for P3a and locus-coeruleus—norepinephrine/parietal activity for P300. Nevertheless, psilocybin has also been shown to increase dopamine release in ventral striatum and frontal hypermetabolism, which depicts other possible mechanisms contributing to the observed deficits (Gouzoulis-Mayfrank et al. 1999). It stands to reason that experiencing strong or unstable emotions and thought flow may also result in attenuation of cognitive abilities (Mueller 2011). Since we found a negative correlation between P300 amplitude with the affect state and cognition on the HRS, we may assume that our results are in line with this statement. Similarly, the negative correlation of the AIA and VUS with P300 is indicative of the assumptions that subjects who are overwhelmed by vivid imaginary and experience of ego dissolution have affected cognitive processing. Other studies with psychedelics, including psilocybin and LSD, repeatedly showed that ego dissolution is linked to an increase in between network connectivity and a decrease in within network integrity (Carhart-Harris et al. 2013; Carhart-Harris et al. 2016; Muthukumaraswamy et al. 2013). We may speculate about the origin of these changes; theoretically, it can be related to a situation where introspective (as a function of the activated default mode network (DMN)) and exteroceptive (as a function of the central executive network (CEN)) processes are not anti-correlated but are running at the same time, similarly to what happens in psychosis (Nekovarova et al. 2014). In such a case, this overwhelming mental activity that is typically induced by psychedelics could in turn lead to attention disruption.

In contrast to psilocybin's effect on P300 and N100, it did not attenuate MMN even though we ran the paradigm during the later stages of intoxication and not during the ascending/peaking phase as did Umbricht et al. (2003). Whereas our statistical analyses provided no significant results, a closer look at the data revealed that psiocybin led to either a decrease (6/13) or increase (7/13) in MMN amplitude. Therefore, it is possible that a larger sample size would reveal two subgroups of people with an opposite influence of psilocybin on MMN. In line with our negative results, DMT also failed to induce the attenuation of MMN (Heekeren et al. 2008). However, as already mentioned, Timmerman et al. (2017) demonstrated significant reduction of MMN in the right hemisphere under the later phase of LSD intoxication, when the intensity of effects was already decreasing in magnitude. It has been described that the peak of the LSD effect is related to the stimulation of serotonergic 5-HT_{2A} receptors and is followed by the stimulation of dopaminergic D_2 receptors at later stages (Marona-Lewicka et al. 2005). Therefore, it is possible that the disruption of MMN after LSD is related to the stimulation of D_2 receptors, which in turn may explain the discrepancy between LSD as a mixed 5-HT/DA agonist and psilocybin and DMT as pure 5-HT agonists. Further support for the dopaminergic mechanisms may come from a study involving haloperidol in healthy volunteers, where haloperidol actually increased the MMN (Kahkonen et al. 2001).

As stated above, contrary to serotonergic psychedelics, NMDA antagonists typically disrupt both ERPs; therefore, there is a clear dissociation between the two models. Since P300 processing is disturbed in both models (Oranje et al. 2000), it can be mechanistically related to their propsychotic properties and independent of specific receptor mechanisms of action. On the contrary, dysfunctional NMDA receptors have been postulated to be a crucial mechanism for MMN (Lee et al. 2017).

An interesting finding was the negative correlation between the P300 and MMN amplitude during psilocybin

intoxication. Interpretation is difficult since very few studies examine the direct interrelationship between sensory and higher-order ERPs. Gjini et al. (2010) reported a positive correlation between MMN amplitude and P3b in healthy volunteers, indicating that these two components may be a part of one system that tends to work or fail together. In contrast, schizophrenia patients showed a negative correlation between P3b and MMN (Gjini et al. 2010) similarly to the findings of our study. In other words, this may indicate that the higher the sensitivity of brain structures involved in the pre-attentive detection of the deviant stimuli (bigger MMN amplitude), the lower the capacity for attentive and cognitive processing (smaller P300 amplitude). This would fit into a hypothesis that likewise in schizophrenia psychedelics induce a decrease in the signal to noise ratio (Rolls et al. 2008; Winterer and Weinberger 2004) most likely via 5-HT_{2A}-mediated attenuation of thalamic functions as a sensory filter for relevant information on the one hand with increased cortical excitability on the other hand, e.g. (Nichols 2016). This would make the whole system more sensitive to irrelevant/unimportant stimuli while not allowing for more complex performance such as attention and cognition reflected by the deficit in P300.

Finally, our study confirmed that psilocybin affects P300 in a similar way as seen in chronic and first-episode of schizophrenia (Bramon et al. 2004; Jeon and Polich 2003; Qiu et al. 2014). However, psilocybin did not attenuate MMN, which is in line with the recent review by Salisbury et al. (2017) stating that neither the frequency nor duration MMNs are reduced in the early stages of schizophrenia. This fits with the concept that psilocybin mainly resembles early stages of schizophrenia (Vollenweider et al. 1998).

One of the limitations of our study is the relatively low-total number of subjects included in the final analyses due to a considerable amount of motor artifacts in the EEG signal during intoxication. On the other hand, we recorded ERPs during the most intense parts of intoxication (100 and 125 min) where it was extremely difficult for subjects to remain relaxed. Also, the condition with the eyes closed at ERPs is not as common as the eyes open; however, it was much more comfortable for subjects, especially for those who were experiencing strong visual effects. Furthermore, a recent review and meta-analysis of P300 did not find any significant difference between the eyes open and eyes closed (van Dinteren et al. 2014). In line with this, according to the very early studies of Polich (1987), who compared different task-dependent conditions and within-subjects conditions, the highest amplitude of P300 was observed in the condition with counting stimuli in mind with eyes closed. Another limitation of the study was the instruction to count target tones in mind during the P300 paradigm, as it does not allow to precisely control the subject's cooperation even though we recorded the number of targets at the end of the task. Perhaps a button press in futures studies would have be a suitable way of ensuring that every single target was correctly detected. Finally, some subjects experienced visual synesthesia during MMN, seeing the sounds, indicative of the fact that contrary to the standard conditions they focused their attention on the stimuli. We also do not know whether psilocybin can disrupt processing of other deviants, e.g., duration or omission of MMN or more complex paradigms, but these issues shall be a matter of future studies with psilocybin and other psychedelics.

Conclusions

Psilocybin at its psychedelic dose-disrupted sensory (N100) and higher-order cognitive processing (P300) in healthy volunteers, while pre-attentive cognitive processing (MMN) was not affected. This pattern is in line with the findings observed in early-stage schizophrenia patients, meaning that psilocybin mainly resembles first episodes of the disease. Our results also implicate the role of the 5-HT_{2A} agonism in the disruption of information processing in psychosis and schizophrenia.

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