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Effects of the Hallucinogen Psilocybin on Covert Orienting of Visual Attention in Humans

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Key Words

Psilocybin · Experimental psychosis · Ecstasy · MDE · d-Methamphetamine · Covert orienting of attention · Disengagement of attention · Inhibition of return

Abstract

Hallucinogenic drug-induced states are considered as models for acute schizophrenic disorders (experimental psychoses). In a double-blind study with healthy volunteers we investigated the influence of the serotonergic hallucinogen psilocybin, the ecstasy-like drug 3,4-methylenedioxyethylamphetamine (MDE), the stimulant d-methamphetamine and placebo on covert orienting of spatial attention (n = 8 in each group). Reaction times were prolonged after ingestion of psilocybin > MDE, but not after d-methamphetamine. In addition, subjects on psilocybin exhibited particularly slow reaction times in invalid trials at short cue target intervals and failure of response inhibition in valid trials at long cue target intervals for right visual field targets. Despite some methodological limitations, these results are in line with both bilateral impairment of disengagement of attention and a lateralized impairment of inhibition of return (IOR) in productive psychotic states. Additional investigations with larger samples, different hallucinogenic substances (serotonergic agonists vs. NMDA antagonists) and different dose regimens are needed in order to further explore the suggested relationship between visuospatial attentional dysfunction and acute psychotic conditions.

Introduction

Hallucinogenic drug-induced states are considered as experimental models for schizophrenic and schizophrenia spectrum psychoses. In recent years animal models of schizophrenia employing hallucinogens have become a crucial instrument in developing new antipsychotic drugs [1]. Furthermore, human experimental psychoses with hallucinogens are currently used as research tools for explorations into the neurobiological mechanisms of acute psychotic states with prominent positive symptoms [2–4]. In this respect, it is noteworthy that hallucinogens from different pharmacological classes such as 5-HT_{2A} receptor agonists (mescaline, psilocybin) and NMDA antagonists (ketamine) seem to exert similar effects on cere-

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bral activity: in recent PET- and SPECT-studies all three drugs were found to induce a hyperfrontal pattern of regional cerebral blood flow or metabolism in humans [5–9]. These results contradict the frequent finding of hypofrontality in chronic or remitted schizophrenics, but they are in line with some few studies with acute schizophrenic patients [10–12]. Hence, these parallels corroborate the view that hallucinogenic drug states and acute schizophrenic psychoses may share similar neurobiological mechanisms.

Generalized cognitive and particularly attentional deficits are common symptoms in schizophrenia and they are mostly thought to represent trait markers of the disorder [13]. However, there is some indication that reaction time disadvantages for targets in the right visual field particularly when covert attention was first summoned to the contralateral direction might represent a state or intermediate marker of acute psychosis [14–16]. However, findings have not always been consistent [14, 17–20]. The biological heterogeneity of schizophrenia, aspects of the age of onset and long term course of the disorder, as well as different medications may account for a large bulk of these contradictory results [21, 15, 16].

Similar to the global attentional deficits in schizophrenia, early human experimental studies with hallucinogens provided evidence in favor of an overall impaired performance under these drugs with slowing down of reaction times [22]. Due to the legal status of hallucinogens only few controlled data from recent, modern studies on their acute cognitive effects on humans are available [5, 23, 24]. In particular, there are no recent human studies on the effects of hallucinogens on attentional performance.

In the present double-blind placebo-controlled study we investigated the effects of the serotonergic hallucinogen psilocybin on spatial orienting of visual attention in healthy humans. This study was part of a more comprehensive investigation on the effects of psilocybin on several measures which are relevant for psychotic behavior. Because of the complex behavioral effects of hallucinogens we included two more psychoactive control substances in the study design: the ecstasy-like drug 3,4-methylenedioxyethamphetamine (MDE) and the stimulant d-methamphetamine. The results on the psychopathological, neurometabolic, electrophysiological and neuroendocrine effects of the drugs were already published elsewhere [9, 25–27]. In summary, only psilocybin was found to induce a psychosis-like state which was characterised by high frontal and low thalamic metabolic activity and by an increased prepulse inhibition of the startle reflex. In the part of the study that we are reporting on here, we examined both the overall speed of reaction on simple visual stimuli and the effects of spatial cues on target detection by means of a covert orienting of attention task [28]. Based on the literature on hallucinogens and schizophrenia, we expected that the serotonergic hallucinogen psilocybin should prolong reaction times and interact with the orienting effect of peripheral cues. Furtheron, based on the results of previous studies with stimulants, we expected that the indirect dopamine agonist d-methamphetamine might have a facilitating effect on psychomotor speed, but no influence on the orienting effect of peripheral cues [29, 30–32]. Finally, ecstasy and ecstasy-like drugs are mixed indirect serotonin and dopamine agonists and they were shown to display both stimulant-like and hallucinogen-like clinical effects in humans [33, 34]. Hence, we had no specific hypothesis on the effects of MDE on performance in this attentional task.

Materials and Methods

The details of the general experimental procedures and some results on measures other than attention were already published elsewhere [9, 25–27]. 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 RWTH and the Federal Health Administration (Bundesinstitut für Arzneimittel und Medizinprodukte, Bundesopiumstelle Berlin). Written informed consent was obtained from all subjects.

Subjects

Thirty-two healthy volunteers (male/female: 21/11; mean age: 34 years, range: 27–47; 25 physicians, 7 psychologists) with no current or previous history of significant physical or psychiatric disorder, no family history of severe psychiatric disorder in first degree relatives, and no regular medication were included. Volunteers had a scientific or clinical interest in the study and received no payment for their participation. Before entering the study, subjects were screened by means of a medical history, clinical examination, electrocardiogram, routine laboratory testing, as well as a standardized psychiatric interview according to DSM-III-R (SCID) supplemented by a clinical interview. No subject met DSM-III-R criteria for alcohol or substance abuse at present or in the past. Current abstinence was not verified by toxicology screens. Each subject had been without any medication and had not been subject to excessive caffeine intake and stressful life events during the last 4 weeks prior to the study.

Substances

All drugs were obtained from the Pharmaceutical Institute of the University of Tuebingen. They were prepared as capsules of identical appearance and were administered orally with some water in typical recreational, but not very high doses, in order for the subjects to be able to perform the experimental tasks. The doses were: psilocybin: 0.2 mg/kg, but not more than 15 mg total dose (n = 8); MDE: 2 mg/kg, but not more than 140 mg total dose (n = 8) ; d-methamphetamine: 0.2 mg/kg, but not more than 17.5 mg total dose (n = 4). In an interim

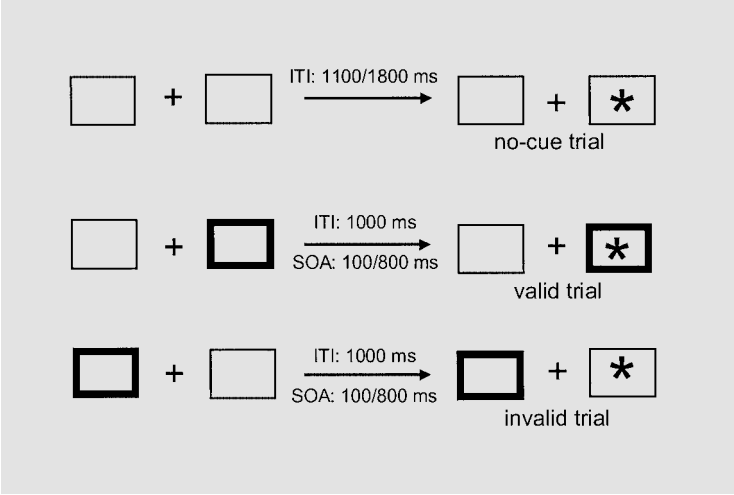

Fig. 1. Schematic presentation of the covert orienting of attention task (COVAT). Abbreviation: ITI: intertrial interval in ms, SOA: stimulus onset asynchrony in ms (time from the onset of the cue to the onset of the target).

evaluation this initial d-methamphetamine dose was shown to induce only slight clinical effects. The d-methamphetamine dose was therefore increased to 0.4 mg/kg, but not more than 35 mg total dose. However, clinical effects did not intensify substantially with the higher dose. Therefore, data of the two d-methamphetamine groups were pooled together for statistical analysis (n = 8).

Experimental Procedures

The design of the study was double-blind. Following the randomization plan subjects were allocated to one of four drug groups (psilocybin, MDE, d-methamphetamine, placebo, n = 8 each) according to the sequence of their entering the study. Subjects were accompanied by one experienced psychiatrist and were monitored for psychological effects, cardiovascular parameters and body temperature throughout the experiment (for details of the general experimental procedures see [9, 26]). They remained in the Psychiatric Department for at least two hours after resolution of the psychological effects (6–8 h after drug ingestion).

The covert orienting of attention task (COVAT) was administered one hour prior to ingestion of the drug (pre-drug session), and again starting 75–95 min after drug ingestion, while psychological drug effects were prominent (on-drug session). In the cases where no apparent psychological changes occurred, the on-drug session began 90 min after ingestion of the drug. A schematic presentation of the task is given in figure 1. Task stimuli were presented on an Apple Macintosh Quadra 840AV Microcomputer. Data presentation and collection was controlled by the program MacLab [35]. During performance of the task subjects were seated in front of the computer monitor and were instructed to maintain fixation on a centrally presented cross. The task was to respond as rapidly as possible to the target by pressing a single key with the index finger of the dominant hand. The target was a star, which appeared on each trial within one of the two peripheral square boxes at about 5° right or left from the central fixation cross, and remained present until the subject responded. In both sessions (pre-drug and on-drug) subjects performed two blocks of 120 trials each. In each block 20% of the trials were uncued. In these no-cue trials the target occurred in the center of one of the two boxes with equal probability following intervals of 1100 or 1800 ms after the previous key press (intertrial interval: ITI). In the remaining cued trials one of the two boxes was brightened with equal probability (peripheral cue), and the target followed either 100 ms or 800 ms after cue onset with equal probability (stimulus onset asynchrony: SOA). In these cued trials the cue appeared always following an ITI of 1000 ms. In the valid trials (75% of the cued trials), the target appeared in the middle of the brightened square. In the remaining invalid trials (25% of the cued trials), the target appeared opposite to the former cue location.

Data Analysis

Trials with reaction times (RTs) less than 100 ms or exceeding 2000 ms were excluded, because they were considered either anticipatory or most likely to be due to brief periods of general inattention to the task. Median RT values of the remaining trials were calculated for every subject and type of trial. Validity effects were calculated by subtracting the median RT of the valid from the median RT of the invalid trials for every subject and type of trial ($\Delta RT_{invalid} - RT_{valid}$). RTs were analyzed by means of a repeated measures ANOVA with the between subject factor substance group (MDE, psilocybin, d-methamphetamine, placebo) and the within subject factors cue (no-cue, valid, invalid), stimulus onset asynchrony (SOA) and visual field (VF). In order to further explore the orienting effect of peripheral cues we ran additional analyses of the validity effects by means of a repeated measures ANOVA with the between subject factor substance group and the within-subject factors SOA and VF. Post-hoc analyses were performed according to Scheffé's α-error correction (Scheffé test). p-values < 0.05 were considered significant. All statistical procedures were performed using SAS version 6.12.

Results

The mean reaction times (RT) of all drug groups in each condition are presented in figure 2. In general, only very few trials were excluded from analyses (pre-drug sessions: <0.2% of the trials; on-drug sessions: placebo: 0.05% due to anticipatory responses; d-methamphet-

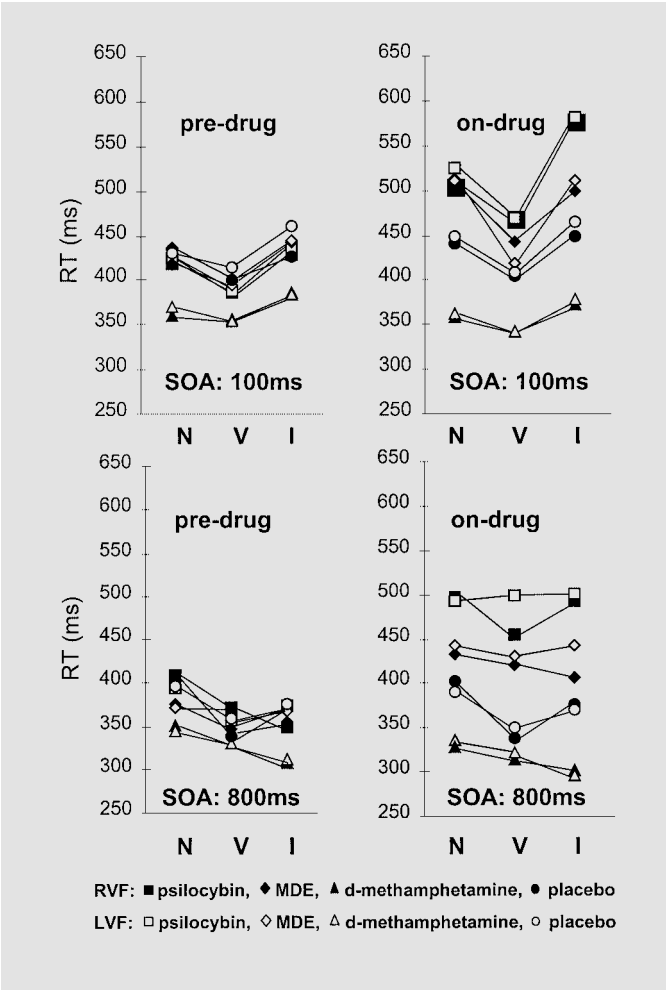

Fig. 2. Mean reaction times (RT) in ms in the covert orienting of attention task before and after intake of psilocybin, MDE, d-methamphetamine and placebo (n = 8 in each group). Abbreviations: N = no-cue, V = valid cue, I = invalid cue, RVF = target in the right visual field, LVF = target in the left visual field, SOA = stimulus onset asynchrony.

amine: 0.20% due to anticipatory responses; MDE: 0.20% due to RT >2000 ms; psilocybin: 0.93% due to RT > 2000 ms, and 0.31% due to anticipatory responses). Mean values and standard deviations of the validity effects (Δ Median-$RT_{invalid}$ – Median-RT_{valid} in ms) are presented in figure 3.

The repeated measures analysis of variance of the RTs revealed significant main effects of group ($F = 12.83$, $p = 0.0001$), cue ($F = 33.77$, $p = 0.0001$), SOA ($F = 159.13$, $p = 0.0001$) and time (pre-drug/on-drug: $F = 30.47$, $p = 0.0001$). The main effect of visual field approached statistical significance ($F = 3.18$, $p = 0.085$). There were significant interactions cue × SOA ($F = 28.15$, $p = 0.0001$), cue × SOA × VF ($F = 3.99$, $p = 0.024$) and cue × SOA × group ($F = 2.54$, $p = 0.03$). In addition, there were significant interactions time × group ($F = 13.72$, $p = 0.0001$), time × cue ($F = 4.60$, $p = 0.014$) and time × cue × group ($F = 3.41$, $p = 0.006$). All other interactions failed to reach statistical significance. Post hoc analyses of the RT data of the pre-drug session revealed that the d-methamphetamine group had shorter RTs than the placebo group (signifi-

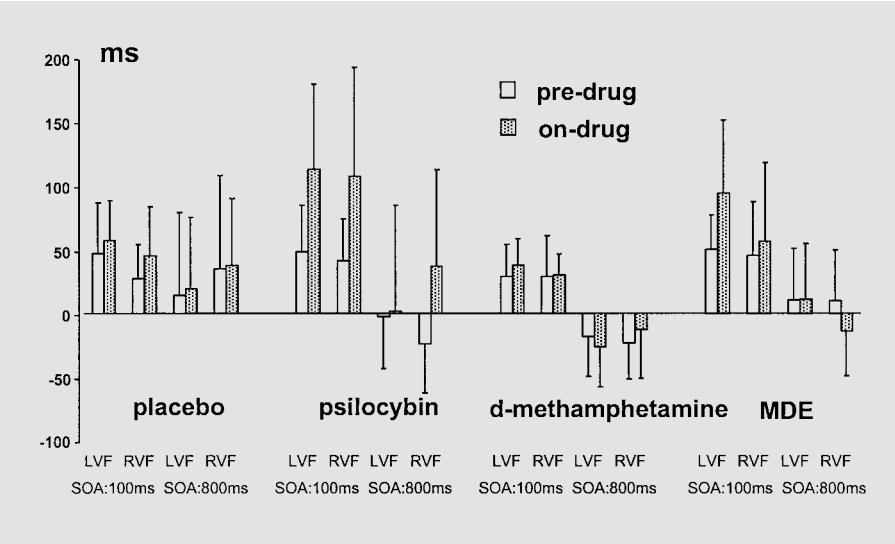

Fig. 3. Mean values and standard deviations of the validity effects in the covert orienting of attention task (Δ Median-$RT_{invalid}$ – Median-RT_{valid} in ms, n = 8 in each group). Abbreviations: RVF = target in the right visual field, LVF = target in the left visual field, SOA = stimulus onset asynchrony.

cant for SOA: 100 ms, left VF, invalid and valid trials). Post hoc analyses of the RT data of the on-drug session revealed that the psilocybin group had significantly longer RTs than the placebo group in most types of trials (SOA: 100 ms, right VF, invalid and valid; SOA: 100 ms, left VF, invalid; SOA: 800 ms, right VF, invalid and valid; SOA: 800 ms, left VF, no-cue, invalid and valid). In addition, the psilocybin group had significantly longer RTs than the MDE group in one type of trial (SOA: 800 ms, right VF, invalid), and significantly longer RTs than the d-methamphetamine group in all types of trials. The MDE group had significantly longer RTs than the d-methamphetamine group in all types of trials and significantly longer RTs than the placebo group in one type of trials (SOA: 800 ms, right VF, valid). Finally, the d-methamphetamine group had significantly shorter RTs than the placebo group in two types of trials (SOA: 100 ms, left VF, valid and invalid). In summary, the descriptive statistics and post hoc results suggest that both psilocybin and MDE slowed down reaction times, although the effect of MDE was less pronounced.

The repeated measures analysis of variance of the validity effects ($RT_{invalid} - RT_{valid}$) revealed significant main effects of group ($F = 3.22$, $p = 0.037$), SOA ($F = 51.48$, $p = 0.0001$) and time (pre-drug/on-drug: $F = 12.05$, $p = 0.0017$), but no effect of visual field ($F = 0.31$, $p = 0.58$). There was a significant time × group interaction ($F = 4.63$, $p = 0.009$). The interactions SOA × VF ($F = 2.93$, $p = 0.09$), SOA × group ($F = 2.91$, $p = 0.052$), time × SOA ($F = 3.07$, $p = 0.09$) and time × SOA × VF ($F = 3.13$, $p = 0.088$) approached significance. All other interactions were insignificant. Post hoc tests failed to distinguish validity effects between the four groups.

Discussion

The effects of typical recreational doses of the serotonergic hallucinogen psilocybin, the ecstasy-like drug MDE and the stimulant d-methamphetamine on visual attention were investigated in a double-blind human experimental study using a covert orienting of attention task (COVAT) with predictive peripheral cues [28]. The mean reaction times in the pre-drug session reflect the usual advantage of valid over neutral and the disadvantage of invalid over valid trials at short cue target intervals, as well as the response facilitation with longer intertrial and cue target intervals both in valid and invalid trials. The commonly observed response inhibition in valid over invalid trials at the long cue target interval (inhibition of return = IOR) [28, 36] was observed in some, but not all subjects. IOR is thought to be an automatic mechanism preventing attention from returning to a previously inspected unimportant location and therefore protecting the organism from overload with irrelevant information. The lack of consistent demonstration of IOR in our study may have been due to the predictive nature of the peripheral cues in our version of the COVAT (75% valid vs. 25% invalid cues), which probably acted against the IOR. This interpretation is in line with data from several other studies which used similar tasks with predictive peripheral cues and also failed to demonstrate the IOR effect [37, 15, 16, 18, 20].

Psilocybin and MDE both caused overall slowing of reaction times, although psychomotor retardation was less pronounced after MDE. In contrast, the stimulant d-methamphetamine did not affect reaction times substantially, although there was a slight tendency for the psychomotor speed to be enhanced after d-methamphetamine. Behavioral activation under stimulants with increased alertness and psychomotor facilitation and impaired performance under hallucinogens with slowing down of reaction times are well recognized phenomena [29, 22]. Our MDE data suggest that attentional performance and response readiness may be also impaired under the influence of ecstasy. Hence, they contradict previous studies demonstrating no effects of ecstasy on elementary cognitive operations [38–41].

Beside the overall psychomotor retardation after psilocybin and MDE, analyses of variance suggest that the four drugs interacted differently with the orienting effect of peripheral cues (significant interactions: RTs: time × cue × group; validity effects: time × group). Although the subsequent post-hoc tests of the validity effects failed to clearly confirm differential effects of the four drugs on orienting of attention, the ANOVA and descriptive statistics suggest that subjects on psilocybin exhibited particularly slow reaction times in invalidly cued trials at the short cue target interval. This result probably indicates difficulty in disengaging attention from previously attended locations and reorienting it to targets in the contralateral visual field. Moreover, after psilocybin a positive validity effect ($RT_{invalid} > RT_{valid}$) persisted at the long cue target interval for right visual field targets, whereas prior to the ingestion of the drug the same subjects had exhibited response inhibition (IOR: $RT_{invalid} < RT_{valid}$) in the same trial condition (fig. 2, 3). In contrast, neither MDE nor d-methamphetamine interacted with the orienting effect of cues. Although inspection of the mean RT data suggests a slight increase of the costs of invalid cueing for

left visual field targets after MDE, this effect was much less pronounced compared to psilocybin.

Increased costs of invalid cueing for right visual field targets in schizophrenic patients was reported by several authors and was interpreted as an expression of a left hemispheric dysfunction in attentional networks [15, 37, 42]. However, others did not confirm this finding of a lateralized impairment in disengagement of spatial attention [14, 17–20]. Carter et al. [43] reported slower reaction times for the detection of right vs. left visual field targets irrespective of the cue condition and Maruff et al. [44] reported increased costs of invalid cueing irrespective of the visual field. Some studies suggest that a lateralized deficit in visuospatial attention for right visual field targets especially following contralateral cues (increased costs of invalid cueing) may be present during acute stages of the disorder and in drug-free patients, but not during remission or after neuroleptic medication [15–17]. Other studies focused on IOR impairments at longer cue target intervals and reported associations between IOR deficits and other neuropsychological abnormalities such as high distractability and impairments of sensorimotor gating [12, 45, 46]. However, one recent study failed to demonstrate blunted IOR in schizophrenic patients [47]. In conclusion, the literature on covert orienting of visual attention in schizophrenia is inconsistent. The conflicting results may be due to variations across the employed tasks as well as differences in the type and stage of the schizophrenic disorder and medications across the different studies. The present study of a hallucinogen model of acute psychosis supports both bilateral impairment of disengagement of attention and a lateralized impairment of IOR for right visual field targets in productive psychotic states. These features may well be accompanied by deficient filter mechanisms of information processing, high distractability and behavioral disorganization, which are typical cognitive symptoms of acute unmedicated schizophrenic disorders.

Needless to say, our investigation has significant methodological limitations: first, drugs were given only in single medium doses, which were meant to induce significant, but not maximal psychological effects. Therefore, we cannot rule out the possibility, that different cognitive effects might be elicited by other doses. Second, the drug groups were of small sample size. This made it difficult to obtain statistically significant group differences and perform meaningful correlation analyses of the attentional with the psychological and other neurobiological effects of the drugs. And, finally, our d-methamphetamine subjects happened to have faster baseline reaction times than the remaining subjects and they happened to be relatively insensitive to the psychological and physiological effects of the drug, although their drug plasma levels were substantial [26]. These limitations are related to the apparent difficulties in planning and performing human studies with restricted drugs, which do not permit for multiple dose designs and pre-testing procedures. Thus, our study should be viewed as a pilot investigation and our results as preliminary. Further investigations with larger samples, different hallucinogenic substances (serotonergic agonists vs. NMDA antagonists) and different dose regimens are needed in order to elucidate the effects of hallucinogenic drugs on measures of attentional functions. In addition, longitudinal studies with schizophrenic patients in different stages of the disorder would be highly desirable. Together, these studies should shed more light on the suggested relationship between visuospatial attentional dysfunction and psychotic symptoms, irrespective of their endogenous or pharmacological origin.

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