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Psilocybin-Induced Deficits in Automatic and Controlled Inhibition are Attenuated by Ketanserin in Healthy Human Volunteers

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The serotonin-2A receptor (5-HT_{2A}R) has been implicated in the pathogenesis of schizophrenia and related inhibitory gating and behavioral inhibition deficits of schizophrenia patients. The hallucinogen psilocybin disrupts automatic forms of sensorimotor gating and response inhibition in humans, but it is unclear so far whether the 5-HT_{2A}R or 5-HT_{1A}R agonist properties of its bioactive metabolite psilocin account for these effects. Thus, we investigated whether psilocybin-induced deficits in automatic and controlled inhibition in healthy humans could be attenuated by the 5-$HT_{2A/2C}$R antagonist ketanserin. A total of 16 healthy participants received placebo, ketanserin (40 mg p.o.), psilocybin (260 μg/kg p.o.), or psilocybin plus ketanserin in a double-blind, randomized, and counterbalanced order. Sensorimotor gating was measured by prepulse inhibition (PPI) of the acoustic startle response. The effects on psychopathological core dimensions and behavioral inhibition were assessed by the altered states of consciousness questionnaire (5D-ASC), and the Color-Word Stroop Test. Psilocybin decreased PPI at short lead intervals (30 ms), increased all 5D-ASC scores, and selectively increased errors in the interference condition of the Stroop Test. Stroop interference and Stroop effect of the response latencies were increased under psilocybin as well. Psilocybin-induced alterations were attenuated by ketanserin pretreatment, whereas ketanserin alone had no significant effects. These findings suggest that the disrupting effects of psilocybin on automatic and controlled inhibition processes are attributable to 5-HT_{2A}R stimulation. Sensorimotor gating and attentional control deficits of schizophrenia patients might be due to changes within the 5-HT_{2A}R system.
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INTRODUCTION

Automatic and controlled information-processing deficits, such as impairments in early and late inhibitory gating processes, are considered to constitute core symptoms of schizophrenia and appear to have a crucial role in the pathophysiology of schizophrenia (Braff *et al*, 2001; Geyer and Braff, 1987; McGhie and Chapman, 1961; Nuechterlein and Dawson, 1984; Nuechterlein *et al*, 1994; Venables, 1960). Although attentional and behavioral control processes have been linked to the serotonin system in general (Cools *et al*, 2008; Soubrié, 1986), early automatic inhibition of sensory stimuli (also called *sensorimotor gating*; Sipes and Geyer, 1997; Vollenweider *et al*, 2007) as well as controlled behavioral inhibition have been linked recently to the function of serotonin-2A receptors (5-HT_{2A}Rs) in particular (Robinson *et al*, 2008; Winstanley *et al*, 2004). Given the long-standing hypothesis that 5-HT_{2A}Rs are implicated in the pathogenesis of schizophrenia (Dean, 2003; Geyer and Vollenweider, 2008; Meltzer, 1999; Meltzer *et al*, 2003; Quednow *et al*, 2010), 5-HT_{2A}R changes might also contribute to disturbed inhibitory processes seen in schizophrenia patients. Therefore, we investigated the role of 5-HT_{2A}Rs in automatic and controlled inhibition processes in a model psychosis approach using the serotonergic hallucinogen psilocybin in healthy humans either pretreated with the 5-$HT_{2A/2C}$R antagonist ketanserin or placebo. Psilocybin (4-phosphoryloxy-*N*,*N*-dimethyltryptamine) is a prodrug that is rapidly metabolized into the bioactive main metabolite psilocin (4-hydroxy-*N*,*N*-dimethyltryptamine; Hasler *et al*, 1997, 2002) that acts as an agonist at 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, and 5-HT_7R (Blair *et al*, 2000; Sard *et al*, 2005; Psychoactive Drug Screening Program (PDSP): http://pdsp.med.unc.edu). Ketanserin has about a 50-fold greater antagonistic potency at 5-HT_{2A}R than 5-HT_{2C}R and also some weak affinity at 5-HT_{2B} and 5-HT_7R. Moreover, it is also strongly active at

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adrenergic α1 and histamine H1 receptors, and weakly active at some dopamine receptors (PDSP: http://pdsp.med.unc.edu). Given these activity profiles, it is conceivable that ketanserin blocks the activity of psilocin primarily at 5-$HT_{2A/2C}$Rs.

Prepulse inhibition (PPI)—which has been established as an operational measure of sensorimotor gating—is defined as a reduction of the startle reflex because of a weak sensory prestimulation (Braff *et al*, 1992; Graham, 1975). As patients with schizophrenia display impaired PPI (Braff *et al*, 1978, 1992; Kumari *et al*, 2000; Ludewig *et al*, 2003; Parwani *et al*, 2000; Quednow *et al*, 2006, 2008a; Swerdlow *et al*, 2006) drug-induced PPI deficits has become an important translational model of the gating impairment in schizophrenia.

Hallucinogenic 5-HT_{2A}R agonists such as LSD, 5-MeO-DMT, DOB, and DOI decrease PPI in rats (Johansson *et al*, 1995; Krebs-Thomson *et al*, 2006; Ouagazzal *et al*, 2001; Padich *et al*, 1996; Sipes and Geyer, 1995b, 1997). The PPI-disrupting effects of DOI and LSD are blocked by the selective 5-HT_{2A}R antagonist MDL100, 907, which supports the hypothesis that the PPI-disrupting effects of these hallucinogens are mediated by 5-HT_{2A}Rs (Halberstadt and Geyer, 2010; Ouagazzal *et al*, 2001; Padich *et al*, 1996; Sipes and Geyer, 1995b). However, a more recent study shows that the PPI-disrupting effects of 5-MeO-DMT could possibly be mediated by its agonistic effects at the 5-HT_{1A}R because the PPI-disrupting effects were also abolished by WAY-100635 (Krebs-Thomson *et al*, 2006). Moreover, 5-HT_{1A}R agonists such as 8-OH-DPAT or buspirone also diminish PPI in rats (Sipes and Geyer, 1995a; van den Buuse and Gogos, 2007) and humans (Gogos *et al*, 2006) but this effect seems to be limited to interstimulus intervals (ISIs) longer as 100 ms. In humans, the hallucinogen psilocybin decreases and increases PPI at short (<60 ms) and long ISIs (>120 ms), respectively (Gouzoulis-Mayfrank *et al*, 1998; Vollenweider *et al*, 2007). Consequently, the question arose whether the PPI-disrupting effects of psilocybin in humans could be attributed to its 5-HT_{2A} or to its 5-HT_{1A} agonist properties. Additional evidence from human genetic studies suggests that polymorphisms of the 5-HT_{2A}R (Quednow *et al*, 2008b, 2009), but not the 5-HT_{1A}R (Brauer *et al*, 2009; Quednow, unpublished data), modulates PPI in humans.

The Color Word Stroop Interference Test is an established measure of response inhibition, attentional control, and cognitive flexibility (Barch *et al*, 2009; MacLeod, 1991; Spreen and Strauss, 1998), in which color words written in different ink colors are presented. Participants are told to name the ink color of the words but to ignore its denotation. If ink color and denotation are conflicting, an over-learned process of reading (semantic information) interferes with an intentional process of color naming (contextual information), resulting in increased reaction time (RT) and errors. Performance on this task is linked to the activation of the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC; Botvinick *et al*, 2004; Carter *et al*, 1998; Cohen *et al*, 2000; Mansouri *et al*, 2009; Pardo *et al*, 1990)—regions that are rich in 5-HT_{2A}R (Adams *et al*, 2004; Forutan *et al*, 2002; Pazos *et al*, 1987). In the classical card Stoop Test, schizophrenia patients consistently displayed increased susceptibility to interference effects in RT. In contrast, on trial-by-trial versions of the task, normal RT interference but increased RT facilitation (RT enhancement in congruent trials) and increased error rates and RT in the conflicting trials have been demonstrated (for review see Henik and Salo, 2004). Neuroimaging studies suggested a conflict-related hypoactivation of the ACC during Stroop interference in schizophrenia patients (Melcher *et al*, 2008). Recently, it was shown that sensorimotor gating and performance in the Stroop task are correlated indicating that they may be mediated by common attentional or inhibitory processes (Scholes and Martin-Iverson, 2009).

Acute tryptophan depletion, which transiently depletes brain 5-HT, has been reported to decrease RT interference in the Stroop Test in some (Evers *et al*, 2006; Schmitt *et al*, 2000; Scholes *et al*, 2007) but not all studies (Gallagher *et al*, 2003; Horacek *et al*, 2005; Sobczak *et al*, 2002). Moreover, acute 5-HT release induced by dexfenfluramine or MDMA also did not alter Stroop Test performance (Andrews and Anderson, 1998; Vollenweider *et al*, 1998a). More specifically, early studies found that the preferential 5-HT_{2A}R agonist LSD impaired performance in the Stroop Test in healthy controls as well as in schizophrenia patients (Krus *et al*, 1963; Wapner and Krus, 1960). Recent evidence suggests that the 5-$HT_{2A/1A}$R agonist psilocybin and the 5-$HT_{2A/2C}$R agonist DMT disrupted a similar inhibitory mechanism of attention as measured with the inhibition-of-return (IOR) task, in which performance has been shown to be disturbed in schizophrenia (Daumann *et al*, 2008; Gouzoulis-Mayfrank *et al*, 2002, 2004, 2006a, b, 2007). Finally, cyproheptadine—an antagonist at 5-$HT_{2A/2B/2C}$, 5-HT_{1A}, and 5-HT_7R with high affinity also for histamine and muscarinic receptors (PDSP: http://www.pdsp.med.unc.edu)—improves RT in the conflict condition of the Stroop Test in chronic schizophrenia patients (Chaudhry *et al*, 2002), whereas the partial 5-HT_{1A}R agonist buspirone had no effect on Stroop performance in schizophrenia patients (Piskulic *et al*, 2009). Taken together, these results imply that 5-HT_{2A}Rs are probably involved in controlled inhibitory mechanisms that are needed to accomplish tasks such as the Stroop Test.

Hence, we further investigated the role of the 5-HT_{2A}R in the modulation of automatic (sensorimotor gating) and controlled (Stroop interference) inhibition processes in healthy human volunteers with a placebo-controlled, crossed, counterbalanced, and double-blind design. We examined whether a pretreatment with the 5-$HT_{2A/2C}$R antagonist ketanserin could prevent the inhibition-disrupting effects of psilocybin. Owing to previous studies, we expected that ketanserin pretreatment would reduce psilocybin-induced disruptions of PPI and Stroop interference, while preventing formation of an altered state of consciousness (ASC).

MATERIALS AND METHODS

Participants

A total of 16 healthy subjects (13 males, 3 females; mean age: 29.7 years, age range: 24–39, all were students or academics) were recruited through advertisement from the local universities. Subjects were healthy according to medical history, clinical examination, electrocardiography, and blood analysis. Subjects were screened by the DIA-X

diagnostic expert system (Wittchen and Pfister, 1997), a semi-structured psychiatric interview to exclude those with personal or family (first-degree relatives) histories of major psychiatric disorders, and standard psychometric instruments including the Freiburg Personality Inventory (FPI; Fahrenberg *et al*, 1984), the State Trait Anxiety Inventory STAI (Spielberger *et al*, 1970), and the Symptom Checklist SCL-90R (Derogatis, 1994). As the personality trait factors rigidity and emotional lability predict negative experiences under hallucinogens (Dittrich, 1994), scores two SD above the mean value of normative data in the respective subscales of the FPI (ie, openness and neuroticism) were exclusion criteria. No subject had to be excluded using these criteria. Five of the subjects were occasional smokers, seven subjects reported a sporadic or rare cannabis use in the past (<5 joints/month), one subject had prior experiences with MDMA (two pills lifetime), and two subjects reported experiences with psilocybin (one and two occasions lifetime).

This study was approved by the Ethics Committee of the University Hospital of Psychiatry, Zurich; the use of psilocybin was authorized by the Swiss Federal Office for Public Health, Department of Pharmacology and Narcotics, Bern. All volunteers gave their written consent after being informed by written and oral descriptions of the study and their risks.

Psilocybin

Psilocybin was obtained through the Swiss Federal Office of Public Health, Department of Pharmacology and Narcotics, Berne and prepared as capsules of 1 mg and 5 mg at the Pharmacy of the Cantonal Hospital of Aarau, Switzerland. Psilocybin, ketanserin, and lactose placebo were administered in gelatin capsules of identical appearance.

Study Design

The study was double-blind and placebo-controlled, and included four experimental days. All subjects received placebo, a variable dose of psilocybin (260 μg/kg), a fixed dose of ketanserin (40 mg, Suffrexal), and a combination of both drugs p.o. each on single test days separated by 4-week intervals and in a randomized and counterbalanced order. Because of variations of PPI with menstrual cycle, women were tested in the first 5 days of their follicular phase when PPI is most robust (Swerdlow *et al*, 1997). The five occasional smokers were told to maintain their usual smoking habits to ensure that PPI was not influenced by smoking withdrawal (Kumari and Gray, 1999).

Sessions were conducted in a calm and comfortable laboratory environment. Participants were told to abstain from alcohol the day before each session and not to drink caffeine-containing beverages or to eat 2 h before each session. One hour after arrival, subjects received placebo/ketanserin in capsules (0900 hours) and after another 40 min placebo/psilocybin. Startle measures were obtained 60 min after placebo/psilocybin intake. The Stroop task was conducted 85 min after treatment, while the 5D-ASC rating was conducted about 125 min after treatment. Both measures were assessed during the known plateau of about 50 min of psilocybin response. The peak of the subjective hallucinogenic effects occurs after 70–90 min, while the psilocin plasma peak is reached after 105 min (t_{max}) with a half-life ($t_{1/2}$) of 163 min (Hasler *et al*, 1997, 2002; Passie *et al*, 2002). An oral dose of 40 mg ketanserin shows a $t_{max} = 65$ min and a half-life of $t_{1/2} = 29.2$ h (Persson *et al*, 1987). After the acute effects of psilocybin had subsided completely (about 360 min after treatment), subjects remained in the hospital for another 2 h and were monitored clinically.

Startle Response Measurement

PPI was recorded and analyzed as described in detail previously (Vollenweider *et al*, 1999; Vollenweider *et al*, 2007). In brief, each session began with a 5-min acclimation period of 70-dB background white noise that continued throughout the session consisting of a total of 52 trials presented in a pseudorandom order and separated by intertrial intervals varying between 4 and 22 s (mean 13 s). The session started and ended each with five 115-dB pulse-alone (PA) trials (white noise) of 40 ms duration that were not used for the calculation of PPI. The trials in between these two blocks consisted of three conditions: 12 PA trials; 24 prepulse-pulse (PP) trials consisting of a 20-ms duration prepulse of either 78 dB or 86 dB white noise presented with an ISI of 30 or 120 ms before the PA, yielding four types of PP trials (30 ms_78 dB, 30 ms_86 dB, 120 ms_78 dB, 120 ms_86 dB, six of each type); and 6 no-stimulus trials. The intensity conditions (78 dB or 86 dB) were pooled for further analysis. The entire test session took about 15 min.

Error trials were defined as trials in which no startle response was recorded because of a baseline shift (eg, due to spontaneous or voluntary blinks). Subjects with error trials and/or response rejections $>50\%$ were excluded from data analysis. None the 16 subjects participating in the study had to be excluded from data analysis based on this criterion. As detailed elsewhere (Ludewig *et al*, 2003), the startle measures examined were: (1) startle reactivity = mean amplitude of all PA trials; (2) %habituation = (1−(startle amplitude of 1. PA block/startle amplitude of last PA block) × 100; and (3) %PPI = according to the formula (1−(mean startle amplitude of PP trials/mean startle amplitude of PA trials in the middle block) × 100).

The Altered State of Consciousness Rating Scale

The 5D-ASC rating scale (Dittrich *et al*, 1985; Dittrich, 1998) was used to assess the subjective effects of drug conditions and has been described in detail elsewhere (Vollenweider *et al*, 2007). The 5D-ASC questionnaire is a visual-analogue scale consisting of 94 items assessing three key dimensions of ASC: (1) oceanic boundlessness (OB), (2) anxious ego dissolution (AED), and (3) visionary restructuralization (VR). The subscales of the key dimensions have been described previously (Vollenweider *et al*, 2007).

Stroop Task

A computerized version of the trial-by-trial Color Word Stroop Test was used, as described in detail previously (Vollenweider *et al*, 1998a). Stimuli were presented using MEL Professional 2.0 software (PST Pittsburgh, PA, USA)

and an IBM-compatible PC with a VGA color monitor. The latencies of subjects' spoken responses were collected with millisecond accuracy through a microphone (Labtec AM-22). The stimulus set consisted of the German words OBEN (above), UND (and), WENN (if), KAUM (hardly), BLAU (blue), GRÜN (green), ROT (red), GELB (yellow), and the non-word XXXX presented in the colors blue, red, green, or yellow. Four conditions, corresponding to four types of trials, were included: On congruent trials, words matched colors (eg, the word BLAU written in blue); on conflict trials, words mismatched colors (eg, BLAU written in red); on neutral X trials, the non-word sequence XXXX was presented in one of the four colors; and on neutral W trials, one of the neutral words (OBEN, UND, WENN, KAUM) was presented in one of the four colors (Carter *et al*, 1995). Forty-eight trials of each condition were presented in random order to minimize strategy effects yielding a total of 192 trials. The task was to name the colors of the stimuli as quickly and accurately as possible. Before each stimulus, a fixation cross appeared in the center of the screen for 400 ms followed by the stimulus itself, which remained on the screen until the subject made a verbal response. Completion of the entire task took 10 min.

Facilitation was defined as absolute reduction in RT in the congruent condition compared with the pooled X and W condition (mean congruent RT—mean (X + W/2) RT). Interference was defined as the absolute increase in RT in the conflict condition compared with the pooled X and W condition (mean conflict RT—mean (X + W/2) RT). The total Stroop effect was defined as absolute increase of RT in the conflict condition compared with congruent condition (mean conflict RT—mean congruent RT).

Statistical Analysis

All data were analyzed using STATISTICA 7.1. for Windows (StatSoft). Startle and PPI data were analyzed using repeated measures analyses of variance (ANOVA) with drug (placebo, psilocybin, ketanserin, psilocybin + ketanserin), PP intensity (78 dB, 86 dB), and ISI (30 ms, 120 ms) as within-subject factors. An ANOVA with the repeated measurement factors drug and Stroop condition (word, XXXX, incongruent, congruent) was used to test for significant effects of psilocybin on the Stroop task, while a repeated measurement ANOVA with 5D-ASC dimensions and drug as within-subject factors were used to examine the effect on the 5D-ASC scale. Based on significant main effects or interactions, Tukey's *post-hoc* comparisons were performed. With exception of the 5D-ASC scores under placebo, all dependent variables were normally distributed. Pearson's product moment correlations were conducted to explore the relationship between %PPI and Stroop task. The criterion for significance was set at $p < 0.05$.

RESULTS

Psychological Effects of Psilocybin

As previously reported (Hasler *et al*, 2009; Kometer *et al*, 2011; Vollenweider *et al*, 2007), psilocybin produced an altered state that was characterized by derealization and depersonalization phenomena, affective changes, thought disorder, and perceptual alterations. Psilocybin was well tolerated physically and mentally by all subjects, with none of our subjects reporting persisting residual psychotropic effects in systematic follow-up investigations (Studerus *et al*, 2011).

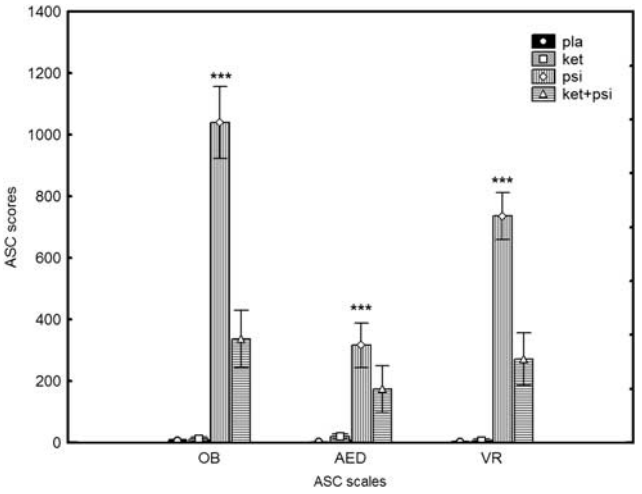

Figure 1 Effects of placebo, ketanserin (40 mg), psilocybin (260 μg/kg), and psilocybin in combination with a pretreatment of ketanserin on the 5D-ASC (altered states of consciousness) in healthy human volunteers. Significant changes compared with placebo are indicted by $^{***}p_{\text{Tukey post hoc}} = 0.001$. Mean scores ± SEM ($n = 16$). AED, anxious ego dissolution; ASC, altered state of consciousness; OB, oceanic boundlessness; VR, visionary restructuralization.

A 2-way ANOVA (drug*5D-ASC dimension) revealed that psilocybin produced significant psychotomimetic effects on all scales (main effect of drug: $F(3, 45) = 48.3$, $p < 0.0001$; *post-hoc* tests psilocybin *vs* placebo, all $p < 0.0002$; Figure 1). There was a significant interaction of drug*5D-ASC dimension because the psilocybin effect was most pronounced on the OB scale ($F(6, 90) = 17.2$, $p < 0.0001$). Ketanserin alone did not induce any symptoms, but significantly reduced the psychotomimetic effects of psilocybin on OB and VR scales (psilocybin *vs* ketanserin plus psilocybin: both $p < 0.0002$), while the reduction in AED was visible but not significant. However, further inspection of the AED subscale scores revealed that ketanserin significantly reduced the psilocybin-induced elevation specifically in the subscales thought disorder ($p < 0.00005$) and fear of losing control over thinking ($p < 0.02$).

Effect of Psilocybin and Ketanserin on Startle Amplitude and Habituation

As shown in Figure 2, a 2-way ANOVA (block*drug) revealed significant effects of the factors block ($F(2, 30) = 79.2$, $p < 0.0001$) and drug ($F(3, 45) = 8.13$, $p = 0.0002$). *Post-hoc* testing showed that psilocybin alone (NS) did not affect startle response, whereas ketanserin ($p < 0.0015$) and ketanserin plus psilocybin ($p < 0.015$) significantly reduced startle reactivity. The lack of a significant drug*block interaction ($F(6, 90) < 1$, NS) indicates no differences in habituation between drug conditions.

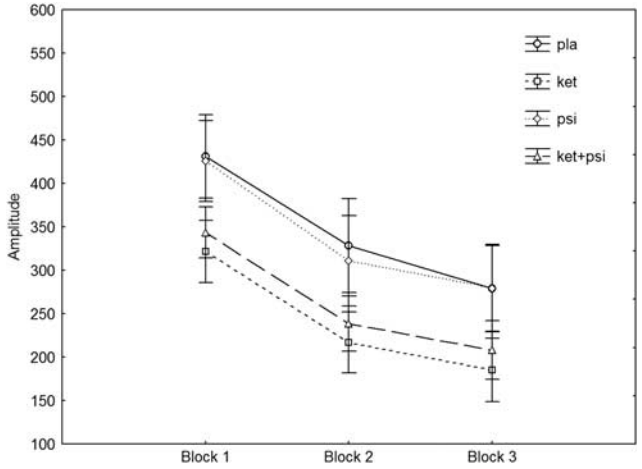

Figure 2 Effects of placebo, ketanserin (40 mg), psilocybin (260 μg/kg), and psilocybin in combination with a pretreatment of ketanserin on startle amplitude and habituation across three blocks of pulse-alone trials in healthy human volunteers. Mean scores ± SEM ($n = 16$).

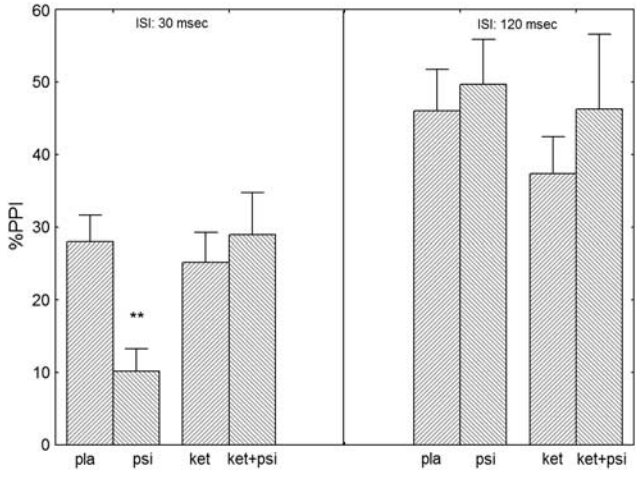

Figure 3 Effects of placebo, ketanserin (40 mg), psilocybin (260 μg/kg), and psilocybin in combination with a pretreatment of ketanserin on prepulse inhibition (PPI) of the acoustic startle response in healthy human volunteers. Significant differences compared with placebo are indicated by $^{**}p_{\text{Tukey post hoc}} = 0.01$. Mean scores ± SEM (pooled prepulse intensities, $n = 16$). ISI, interstimulus-interval; ket, ketanserin; ket + psi, ketanserin + psilocybin; pla, placebo; psi, psilocybin.

Effect of Psilocybin and Ketanserin on Percent PPI

An initial 4-way ANOVA (pretreatment×treatment×intensity×ISI) revealed an interaction of pretreatment×treatment and ISI ($F(1, 15) = 4.21$, $p < 0.05$) reflecting differential effects of the drugs on ISI conditions (Figure 3). *Post-hoc* tests showed that psilocybin decreased %PPI in the 30 ms condition ($p < 0.008$) and that this effect was reversed by ketanserin (NS). At the long ISI of 120 ms, psilocybin slightly increased %PPI, whereas ketanserin slightly decreased %PPI, but these effects were not significant. As expected the factors intensity ($F(1, 15) = 43.4$, $p < 0.0001$) and ISI ($F(1, 15) = 36.7$, $p < 0.0001$) were significant. Introduction of smoking status as a covariate did not affect these results.

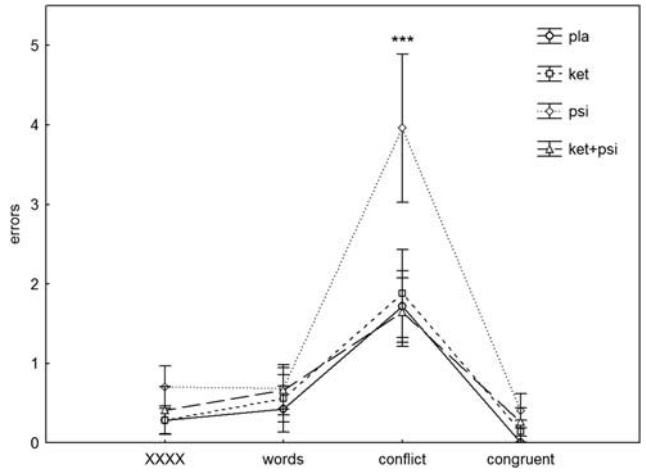

Figure 4 Effects of placebo, ketanserin (40 mg), psilocybin (260 μg/kg), and psilocybin in combination with a pretreatment of ketanserin on errors in the Stroop Test in healthy human volunteers. Mean scores ± SEM ($n = 16$). Significant changes compared with placebo are indicted by $^{***}p_{\text{Tukey post hoc}} = 0.001$. XXXX represents a non-word sequence.

Effect of Psilocybin on Stroop Test

A 2-way ANOVA (drug×Stroop condition) of the errors showed significant effects of drug ($F(3, 45) = 6.26$, $p < 0.001$), condition ($F(3, 45) = 17.9$, $p < 0.0001$), and their interaction ($F(9, 135) = 2.39$, $p < 0.015$). In *post-hoc* tests, psilocybin increased error rates in the conflict condition ($p < 0.0001$), which was reversed by ketanserin ($p < 0.0001$). Ketanserin alone did not alter Stroop error rates (NS; Figure 4).

A similar analysis of the RT showed significant effects of drug ($F(3, 45) = 9.51$, $p < 0.0001$), condition ($F(3, 45) = 61.6$, $p < 0.00001$), and their interaction ($F(9, 135) = 3.62$, $p < 0.0005$). In contrast to the errors, psilocybin increased RT in all conditions (all $p < 0.00003$), which was substantially reduced by ketanserin (all $p < 0.00003$). Again, ketanserin alone did not alter RT (Figure 5).

As shown in Table 1, psilocybin significantly increased Stroop interference and Stroop effect compared with placebo and ketanserin. This effect was neutralized by the combination of psilocybin and ketanserin. Psilocybin alone did not change facilitation but in combination with ketanserin facilitation was enhanced. Ketanserin alone did not alter interference, Stroop effect, or facilitation.

Relationships between PPI, Stroop Test, and Altered States of Consciousness

To explore the relationship between PPI and clinical symptoms in psilocybin states, data obtained during the peak effects of psilocybin and psilocybin plus ketanserin were pooled ($n = 32$), and correlation analyses between PPI change scores (psilocybin—placebo and of psilocybin/ketanserin—placebo) and the 5D-ASC scale change scores or Stroop measures were performed. The change in PPI obtained at the 30 ms lead interval correlated significantly with OB ($R = 0.47$, $p < 0.01$) and VR scores ($R = 0.40$, $p < 0.05$), but not with any change scores of the Stroop task performance. In other words, the higher the reduction in

%PPI in psilocybin or psilocybin plus ketanserin condition, the more OB or VR symptoms occurred. Subsequent analyses of the OB and VR subscale scores revealed that these correlations were driven by derealization phenomena, mania-like symptoms and changed meaning in percepts (data not shown). However, a similar analysis of the pooled 5D-ASC change scores and the Stroop RT revealed that the change in AED score correlated significantly with the Stoop interference obtained in the neutral X ($R = 0.40$, $p < 0.05$) and W condition ($R = 0.35$, $p < 0.05$). Analyses of the AED subscale scores showed that this correlation was driven by thought disorder and loss of control over thinking and body (data not shown).

DISCUSSION

The present study demonstrated that the 5-$HT_{2A/2C}$R antagonist ketanserin abolished the disrupting effects of the 5-$HT_{2A/2B/2C/1A}$R agonist psilocybin on automatic (sensorimotor gating) and controlled (Stroop interference) inhibition processes. Moreover, we again replicated our previous findings that most of the subjective hallucinogenic effects of psilocybin are substantially neutralized by ketanserin (Carter *et al*, 2005, 2007; Vollenweider *et al*, 1998b).

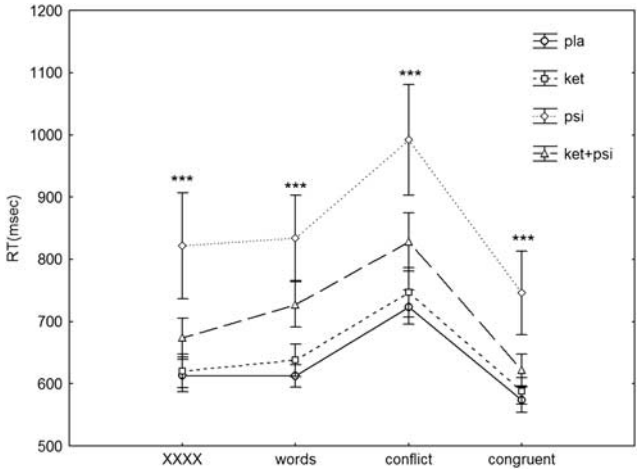

Figure 5 Effects of placebo, ketanserin (40 mg), psilocybin (260 μg/kg), and psilocybin in combination with a pretreatment of ketanserin on response time (RT) in the Stroop Test in healthy human volunteers. Mean scores ± SEM ($n = 16$). Significant changes compared with placebo are indicted by $^{***}p_{\text{Tukey post hoc}} = 0.001$. XXXX represents a non-word sequence.

In a previous study, we found that psilocybin reduced PPI at short (30 ms), had no effect at medium (60 ms), and increased PPI at long (120 and 240 ms) ISIs (Vollenweider *et al*, 2007). We found a similar pattern in the present study, although the increase of PPI in the 120 ms ISI condition was not significant. The lacking significance regarding the increase at 120 ms might be due to the fact that a somewhat higher dose of psilocybin was used in the present study (260 μg/kg) compared with the dose with which we found the significant effect in our previous study (215 μg/kg), and that the response in the 120 ISI condition appears to follow an inverse-U relationship (no significant increase at 315 μg/kg, Vollenweider *et al*, 2007). Moreover, indirect stimulation of all 5-HT receptors by SSRI has also shown no effect on PPI at 60 and 120 ms ISIs in previous studies (Jensen *et al*, 2007; Oranje *et al*, 2011; Quednow *et al*, 2004), which is in line with our present results. We previously hypothesized that the reduction of PPI at short ISIs is caused by the 5-HT_{2A}R agonist action of psilocybin, whereas the increase at long ISIs might be due to its 5-HT_{1A}R agonist action (Vollenweider *et al*, 2007). The present results strongly suggest that the psilocybin-induced PPI disruption at short ISIs is generated by the action of psilocybin at 5-HT_{2A}Rs. This finding further supports the assumption that PPI deficits in schizophrenia might be induced by 5-HT_{2A}R changes (Quednow *et al*, 2008b, 2009). Moreover, as demonstrated in two previous studies, psilocybin again showed no significant effect on startle reactivity or habituation (Gouzoulis-Mayfrank *et al*, 1998; Vollenweider *et al*, 2007).

Furthermore, we found a slight and non-significant reduction of startle reactivity by ketanserin, which is partly in line with a previous study reporting that the same dose of ketanserin (40 mg) significantly reduced startle amplitude (Graham *et al*, 2002). In contrast, Graham *et al* (2002) also described that ketanserin disrupts PPI—a finding that we

Table 1 Performance in the Stroop Test under Placebo, Ketanserin, Psilocybin, and Psilocybin + Ketanserin ($n = 16$, Mean and Standard Error of Means of Change in Response Time (RT) in millisecond are Shown)

Condition	Placebo	Ketanserin	Psilocybin	Psilocybin+Ketanserin	F	df	p
Interference							
(Conflict RT – pooled XXXX and word RT)	110.1 (19.3)	118.0° (24.3)	188.7* (52.8)	127.3 (23.6)	4.04	3, 45	0.01
Facilitation							
(Congruent RT – pooled XXXX and word RT)	−35.5 (16.2)	−63.4 (26.5)	−43.8 (9.7)	−96.7** (25.9)	5.50	3, 45	0.003
Stroop							
(Conflict RT – congruent RT)	148.7 (14.6)	158.6°°° (22.6)	245.4*** (35.6)	205.7 (23.5)	8.29	3, 45	0.0002

Tukey's HSD *post-hoc* test *vs* placebo: *$p < .05$, **$p < .01$, ***$p < .001$.
Tukey's HSD *post-hoc* test *vs* psilocybin: °$p < .05$, °°°$p < .001$.

could not replicate. However, the PPI-disrupting effects reported by Graham *et al* (2002) might be the result of the strong reduction in startle amplitude found in their experiment (Csomor *et al*, 2008). Although, Graham's and our experimental setups were similar, the different results may have been because of some specific parametric differences in prepulse durations, trial sequences, and the lack of startle-alone trials before assessing PPI. Furthermore, it appears unlikely that an effect of ketanserin on startle amplitude influenced our main findings because the inclusion of startle amplitude as a covariate did not change our results.

Our results are partly in line with the finding that selective 5-HT_{1A}R agonists decrease PPI only at ISIs >100 ms (Gogos *et al*, 2006; van den Buuse and Gogos, 2007). However, the psilocybin-induced increase of PPI at 120 ms seen in the present and our previous experiment (Vollenweider *et al*, 2007) seems not to be caused by the 5-HT_{1A}R agonistic properties of the compound. This effect might be induced by an interaction between the 5-HT_{1A}, 5-HT_{2A}, or 5-HT_{2C}R because ketanserin did not block the small PPI enhancing effect of psilocybin at 120 ms. To investigate the contribution of 5-HT_{1A}, 5-HT_{2A}, and HT_{2C}Rs on the PPI-changing effects of psilocybin, further studies should incorporate a blockade of these receptor types in combination with a variety of short and long ISI ranging from 30–240 ms.

Psilocybin significantly increased RT and error rates particularly in the conflict condition of a computerized trial-by-trial Stroop Test, a pattern of results that is similar to that reported for schizophrenia patients (Henik and Salo, 2004). Ketanserin prevented these deficits in the conflict condition, suggesting that the 5-HT_{2A}R agonist action of psilocybin disturbed processes that influence performance in the conflict condition of the Stroop Test. Performance in the Stroop Test is based upon mechanisms that involve the active selection and maintenance of an appropriate task rule, including working memory, attentional control, conflict monitoring, and inhibition processes (Barch *et al*, 2009). We have previously demonstrated that psilocybin impairs attentional processes (Carter *et al*, 2005; Vollenweider *et al*, 2007), while working memory is less affected (Carter *et al*, 2005; Wittmann *et al*, 2007). Furthermore, the psilocybin-induced disturbance of attentional tracking ability could not be blocked by ketanserin, suggesting a primary involvement of 5-HT_{1A}R in this effect (Carter *et al*, 2005). In addition, it was shown that psilocybin also impairs performance in the IOR Task, which is supposed to reflect an automatic inhibitory mechanism of attention (Gouzoulis-Mayfrank *et al*, 2002). Taken together, these findings suggest that the effect of psilocybin on the performance in the conflict condition of the Stroop Test might rather be explained by a dysfunction of conflict monitoring and/or inhibition processes than by an effect on working memory or attention *per se*.

The different interactions of psilocybin and ketanserin on various cognitive functions might be explained by the fact that immunohistochemical studies have demonstrated that 5-HT_{1A}Rs are colocalized with 5-HT_{2A}Rs receptors in cortical pyramidal cells (Martin-Ruiz *et al*, 2001), where both receptor subtypes displayed opposing effects when they were stimulated (Araneda and Andrade, 1991). Specifically, studies in rats have shown that 5-HT_{1A} and 5-HT_{2A}Rs in the medial prefrontal cortex (mPFC) exert opposite action on attentional functioning and aspects of executive functioning (Carli *et al*, 2006). Thus, the results of Carter *et al* (2005) are not necessarily in conflict with the present findings.

Our data are consistent with two early studies showing that performance on the classical card version of the Stroop Test is disrupted by the 5-$HT_{2A/2B/2C}$, 5-$HT_{1A/1B/1D}$, and 5-$HT_{6/7}$R agonist LSD. However, LSD also affected the performance in the congruent conditions (cards A and B), even though the effect was most pronounced in the conflict condition (card C; Krus *et al*, 1963; Wapner and Krus, 1960). That the 5-HT system is crucially involved in processes involved in the performance of the Stroop Test has been shown by several studies: (1) acute tryptophan depletion reduces RT interference in the Stroop Test (Evers *et al*, 2006; Schmitt *et al*, 2000; Scholes *et al*, 2007); (2) performance in the conflict condition of the Eriksen Flanker Task (Reuter *et al*, 2007) as well as in congruent conditions of the Stroop Test (Osinsky *et al*, 2009) depends on a promoter polymorphism of the tryptophan-hydroxylase 2 gene (TPH2 –703 G/T), which has an impact on 5-HT synthesis (Invernizzi, 2007); and (3) Stroop interference was correlated with the 5-HT transporter density within the DLPFC measured with [^{11}C]DASB positron emission tomography (PET; Madsen *et al*, 2011). Based on the present findings, we speculate that deficits in conflict monitoring and response inhibition in schizophrenia might be caused by changes in 5-HT_{2A}R—an assumption that might be supported by the finding that the 5-$HT_{2A/2B/2C}$, 5-HT_{1A}, and 5-HT_7R antagonist cyproheptadine improved RT in the conflict condition of the Stroop Test in chronic schizophrenia patients (Chaudhry *et al*, 2002), whereas the partial 5-HT_{1A}R agonist buspirone had no effect on Stroop performance in a comparable patient population (Piskulic *et al*, 2009).

Given that ketanserin blocks not only the 5-HT_{2A} but also to a lesser extend the 5-HT_{2C}R, one might speculate that the 5-HT_{2C}R might also be involved the psilocybin-induced impairments of PPI and Stroop performance seen in this study. An involvement of 5-HT_{2C}R in the effects of hallucinogens has recently proposed based on the observation that 5-HT_{2C}R knock-out mice display a 50% reduction of DOI-induced head-twitch response—a proposed animal model of human hallucinosis (Canal *et al*, 2010). However, the psilocin-induced impairments of automatic and controlled inhibition reported here is unlikely to be caused by 5-HT_{2C}R agonism for several reasons: (1) the selective 5-HT_{2C}R agonist WAY-163909 reverses MK-801- and DOI-induced PPI deficits and does not change or rather increase PPI when given alone (Grauer *et al*, 2009; Marquis *et al*, 2007), (2) the selective 5-HT_{2C}R antagonist SDZ SER-082 does not block DOI-induced PPI deficits (Sipes and Geyer, 1995b), and (3) 5-HT_{2C}R agonists enhance while 5-HT_{2C}R antagonists impair behavioral inhibition in rodents (Fletcher *et al*, 2007; Navarra *et al*, 2008; Robinson *et al*, 2008; Winstanley *et al*, 2004).

In contrast to a previous study, we did not find a significant correlation between Stroop Test performance and PPI (Scholes and Martin-Iverson, 2009). However, Scholes and Martin-Iverson used an attentional modulation

gating paradigm and calculated PPI by an uncommon technique (non-linear regression fit of mean peak response), which might be not comparable with our approach. Earlier studies employing similar PPI techniques as in the present study also did not find associations between PPI and Stroop Test performance (Swerdlow *et al*, 1995a, b). Thus, although PPI and Stroop interference are obviously modulated by similar 5-HT_{2A}R mechanisms, the inhibitory processes engaged in each of the tasks might tap into different regional 5-HT_{2A}R populations. Animal research has shown that a DOI application in the ventral pallidum disrupts PPI and that this effect was blocked by highly selective 5-HT_{2A}R antagonists (Sipes and Geyer, 1997). Thus, psilocybin-induced PPI deficits at short ISIs may depend primarily on 5-HT_{2A}R stimulation located in more basic modulatory structures of the startle circuit such as the striatum or the thalamus (Vollenweider *et al*, 2007). In contrast, Stroop interference depends on activation of the ACC and DLPFC (Carter *et al*, 1998; Cohen *et al*, 2000; Pardo *et al*, 1990). These regions display a high density of 5-HT_{2A}R (Adams *et al*, 2004; Forutan *et al*, 2002; Pazos *et al*, 1987), and [^{18}F]fluorodeoxyglucose PET studies revealed that psilocybin strongly increases regional glucose metabolism in these areas during resting state, especially in the ACC (Gouzoulis-Mayfrank *et al*, 1999; Vollenweider *et al*, 1997). Finally, preliminary data from our lab have shown that 5-HT_{2A}R occupation in the ACC and mPFC measured with [^{18}F]altanserin PET was correlated with the intensity of the hallucinogenic action of psilocybin (Hasler *et al*, 2009; Quednow *et al*, 2010). Thus, although PPI-disrupting effects of psilocybin might be mediated rather by striatal 5-HT_{2A}R, the effect on Stroop interference might be explained by overstimulation of 5-HT_{2A}R in the prefrontal cortex and the ACC. 5-HT_{2A}R changes in different brain areas might therefore contribute to diverse alterations in several stages of information processing found in schizophrenia.

To our knowledge, this is the first study investigating the automatic and controlled inhibition processes as well as the psychopathological symptoms via challenge with a hallucinogenic drug in healthy human volunteers. The present study suggests that a stimulation of 5-HT_{2A}R disrupts sensorimotor gating and Stroop interference, and that these processes likely depend on different regional 5-HT_{2A}R populations. We therefore propose that 5-HT_{2A}R changes in cortical and subcortical brain regions might contribute to varied inhibitory deficits of schizophrenia patients.

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DISCLOSURE

The authors declare no conflict of interest.

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