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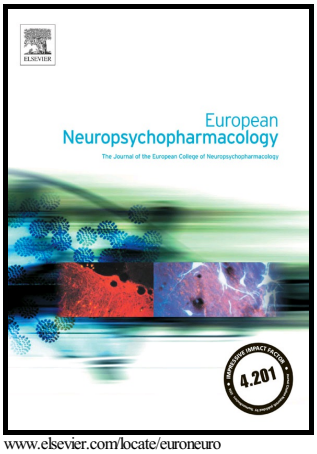

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Modulatory effect of the 5-HT1A agonist buspirone and the mixed non-hallucinogenic 5-HT1A/2A agonist ergotamine on psilocybin-induced psychedelic experience

Thomas Pokorny[1,2], Katrin H. Preller[1,2], Rainer Kraehenmann[1,2], Franz X. Vollenweider[1,2]

[1]Neuropsychopharmacology and Brain Imaging, [2]Heffter Research Center Zurich, Department of Psychiatry, Psychotherapy and Psychosomatics, University Hospital of Psychiatry Zurich, Zurich, Switzerland

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Correspondence to:
Franz X. Vollenweider
Neuropsychopharmacology and Brain Imaging
and Heffter Research Center Zurich
Department of Psychiatry, Psychotherapy and Psychosomatics
University Hospital of Psychiatry Zurich
Lenggstrasse 31
CH-8032 Zurich
Switzerland

e-mail: vollen@bli.uzh.ch

Abstract

The mixed serotonin (5-HT) 1A/2A/2B/2C/6/7 receptor agonist psilocybin dose-dependently induces an altered state of consciousness (ASC) that is characterized by changes in sensory perception, mood, thought, and the sense of self. The psychological effects of psilocybin are primarily mediated by 5-HT2A receptor activation. However, accumulating evidence suggests that 5-HT1A or an interaction between 5-HT1A and 5-HT2A receptors may contribute to the overall effects of psilocybin. Therefore, we used a double-blind, counterbalanced, within-subject design to investigate the modulatory effects of the partial 5-HT1A agonist buspirone (20mg p.o.) and the non-hallucinogenic 5-HT2A/1A agonist ergotamine (3mg p.o.) on psilocybin-induced (170µg/kg p.o.) psychological effects in two groups (n=19, n=17) of healthy human subjects. Psychological effects were assessed using the Altered State of Consciousness (5D-ASC) rating scale. Buspirone significantly reduced the 5D-ASC main scale score for Visionary Restructuralization (VR) ($p<0.001$), which was mostly driven by a reduction of the VR item cluster scores for elementary and complex visual hallucinations. Further, buspirone also reduced the main scale score for Oceanic Boundlessness including derealisation and depersonalisation phenomena at a trend level ($p=0.062$), whereas ergotamine did not show any effects on the psilocybin-induced 5D-ASC main scale scores. The present finding demonstrates that buspirone exerts inhibitory effects on psilocybin-induced effects, presumably via 5-HT1A receptor activation, an interaction between 5-HT1A and 5-HT2A receptors, or both. The data suggest that the modulation of 5-HT1A receptor activity may be a useful target in the treatment of visual hallucinations in different psychiatric and neurological diseases.

Key words: Buspirone; Ergotamine; Psilocybin; Visual hallucinations; 5-HT1A receptor; 5-HT2A receptor

1. Introduction

Serotonergic hallucinogens or psychedelic drugs such as psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine), DMT (N,N-dimethyltryptamine), and LSD (lysergic acid diethylamide) produce an Altered State of Consciousness (ASC) that is characterized by profound changes in sensory perception, emotion, thought, and the sense of self (Geyer and Vollenweider, 2008; Studerus et al., 2011). Psilocybin is the main psychoactive principle of the group of hallucinogenic fungi, commonly known as magic mushrooms (Hofmann, 1968).

Since the 1990s, a series of studies have been conducted in humans to identify the neurophysiological and molecular mechanism of psilocybin-induced ASC, including investigations into the underpinnings of perceptual alterations such as hallucinations, changes in thought, and alterations in the experience of self (Geyer and Vollenweider, 2008; Lebedev et al., 2015; Vollenweider and Geyer, 2001; Vollenweider, 2001). More recent studies have focused on the neuronal substrates of the effect of psilocybin on cognition (Carter et al., 2005; Quednow et al., 2012; Umbricht et al., 2003; Vollenweider et al., 2007), emotion regulation (Bernasconi et al., 2014; Kometer et al., 2011; Kraehenmann et al., 2014; Kraehenmann et al., 2015; Schmidt et al., 2013), and social interaction (Preller et al., 2015), while some studies have begun to re-evaluate the clinical potential of psilocybin for example in the treatment of anxiety and depression in terminally ill patients (Gasser et al., 2015; Grob et al., 2011; Majić et al., 2015; Vollenweider and Kometer, 2010).

In humans, psilocybin is rapidly dephosphorylated into the psychoactive metabolite psilocin (4-hydroxy-N,N-dimethyltryptamine) (Hasler et al., 1997) which acts as an agonist at 5-HT1A, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT6, and 5-HT7 receptors (Nichols, 2004; PDSP database https://pdspdb.unc.edu/html/pdspV2/). There is converging evidence from human and animal studies that the core psychological effects of psilocybin are primarily mediated via 5-HT2A receptor activation, although serotonergic hallucinogens interact with multiple serotonin receptor sites (González-Maeso et al., 2008; González-Maeso et al., 2007; Halberstadt et al., 2011; Vollenweider et al., 1998). Specifically, the 5-HT2A antagonist ketanserin (Carter et al., 2007; Kometer et al., 2012; Vollenweider et al., 1998) blocked the psilocybin-induced subjective effects including hallucinations and the disruption of sensory gating

as indexed by prepulse inhibition (PPI) in humans (Quednow et al., 2012; Vollenweider et al., 2007). Furthermore all serotonergic hallucinogens also induce a head-twitch response (HTR) in rodents that is blocked by highly selective 5-HT2A receptor antagonists (González-Maeso et al., 2007; Halberstadt and Geyer, 2010; Halberstadt et al., 2011; Hanks and González-Maeso, 2013). In contrast to this, non-hallucinogenic 5-HT2A/1A receptor agonists such as ergotamine or R-lisuride do not induce the HTR in rodents (González-Maeso et al., 2007; Hanks and González-Maeso, 2013) and also activate distinct 5-HT2A mediated signalling in cortical neurons. Moreover, R-lisuride blocked the LSD-induced HTR and pyramidal cell activation in somatosensory cortices in mice (González-Maeso et al., 2007).

Although the prevailing view is that 5-HT2A receptor activation is responsible and necessary for many of the psychedelic effects of psilocybin in humans (González-Maeso et al., 2007; Vollenweider et al., 1998), other data suggest that activation of 5-HT1A receptors by serotonergic hallucinogens may also contribute to their subjective and behavioural effects, either directly or through functional interaction with 5-HT2A receptors (Halberstadt et al., 2011; Krebs and Geyer, 1994; Krebs-Thomson and Geyer, 1998). For example, it is well established that the DOI-induced HTR can be blocked by 5-HT1A receptors agonists such as 8-OH-DPAT, buspirone, ipsapirone, and flesinoxan (Dursun and Handley, 1993; Schreiber et al., 1995). Moreover several 5-HT1A agonists including buspirone have been shown to increase PPI in multiple strains of mice (Geyer, 1999), although opposite effects on PPI have also been reported in rats (Geyer et al., 2001). In addition, isobolographic analysis of the locomotion suppressing effects of hallucinogens in rats suggests that at a functional level, 5-HT1A and 5-HT2 receptors interact antagonistically in the modulation of locomotor activity (Krebs-Thomson and Geyer, 1998).

While a number of behavioral paradigms in animals suggest that 5-HT1A receptor agonists produce opposite effects on 5-HT2A receptor mediated behavior induced by hallucinogens, the role of 5-HT1A receptors in psychedelic symptom formation in humans is hardly known. The only human study that has explored the potential contribution of the 5-HT1A receptor system to psychedelic symptom formation reported that manipulation of 5-HT1A receptor system by the partial 5-HT1A receptor antagonist pindolol increased the hallucinogenic effects of DMT about two to three

fold in healthy human subjects (Strassman, 1996). Taken together, the accumulating evidence from these behavioral animal studies suggests that the 5-HT1A receptor system may have a modulatory role on psychedelic symptom formation and proposes that 5-HT1A receptor agonists such as buspirone or non-hallucinogenic 5-HT1A/2A receptor agonists such ergotamine might reduce or block psilocybin-induced psychedelic effects in humans.

To test this hypothesis, we studied whether pre-treatment with the partial 5-HT1A agonist buspirone or the non-hallucinogenic 5-HT2A/1A receptor agonist ergotamine modulates the subjective effects of psilocybin including alterations in perception, emotions, thought, and the sense of self in healthy human subjects. Psilocin binds with high affinity to 5-HT1A (Ki 49-567 nM, human cloned receptor, using 3H-8-OH-DPAT as comparator, Blair et al., 2000) and 5-HT2A receptors (Ki 107nM, human cloned receptor using 3H-Ketanserin, PDSP database https://pdspdb.unc.edu/html/pdspV2). Buspirone is a partial agonist at 5-HT1A receptors (Ki 3.9-77.6, human cloned receptor, using 3H-8-OH-DPAT as comparator, Boess and Martin, 1994) and is clinically used in the treatment of anxiety disorders. Ergotamine binds with high affinity to 5-HT2A (Ki 0.6nM, human cloned receptor, using 3H-Ketanserin as comparator, Bonhaus et al., 1997) and 5-HT1A receptors (Ki 0.1nM, human cloned receptor, using 3H-8-OH-DPAT as comparator, PDSP database https://pdspdb.unc.edu/html/pdspV2) and acts as a non-hallucinogenic agonist at 5-HT2A receptors (Knight et al., 2004), and is used in the treatment of migraine (Silberstein and McCrory, 2003; Tfelt-Hansen et al., 2000). We hypothesized that buspirone reduces some of the psychedelic effects of psilocybin measured with the Altered State of Consciousness (5D-ASC) Rating Scale (Dittrich, 1998), while ergotamine may reduce or even abolish the psychedelic effects of psilocybin in humans.

2. Experimental Procedures

2.1. Subjects

Forty healthy human subjects were recruited through advertisements placed at local universities and were assigned either to the buspirone (n=20) or ergatmine group (n=20). One subject felt queasy after administration of buspirone+psilocybin, and 3

subjects felt dizzy after administration of ergotamine and abstained from completing the study. Thus, 19 participants (10 male subjects, 9 female subjects, mean age 24.89 ± 4.03) completed the study in the buspirone group and 17 participants (8 male subjects, 9 female subjects, mean age 23.82 ±3.70) in the ergotamine group.

The subject's health was confirmed by a physical examination that included electrocardiography, and detailed blood and urine analyses. Pregnant women were identified using urine test and then excluded. The mini-International Neuropsychiatric Interview for DSM-IV (Sheehan et al., 1998), the Expert System for Diagnosing Mental Disorders (Wittchen, 1997), and the John Hopkins Symptom Checklist-90 revised (Derogatis and Unger, 2010) were used to identify subjects with present or antecedent psychiatric disorders or a history of major psychiatric disorders in first-degree relatives, and these subjects were excluded. Urine screening and self-report drug use questionnaire were used to verify the absence of drug dependence.

All participants gave their written consent after having received detailed written and oral information about the aims of the study, and the effects and possible risks of the substances administered. The study was approved by the Ethics Committee of the Department of Public Health of the Canton of Zurich, Switzerland, and the use of psilocybin was authorized by the Swiss Federal Office for Public Health, Department of Pharmacology and Narcotics, Berne, Switzerland.

2.2. Substance and dosing

A double-blind, placebo-controlled, randomized, within-subject design with four experimental drug conditions was applied. All subjects were tested on four different days, each separated by at least 2 weeks with counterbalanced administration of drugs. The four drug conditions were placebo+placebo, buspirone+placebo, placebo+psilocybin, and buspirone+psilocybin. Conditions in the ergotamine group were administered analogously, but instead of buspirone they received ergotamine.

Subjects in the buspirone group received either placebo or buspirone (20mg p.o.) followed by placebo or psilocybin (170µg/kg p.o.) after 1h. Buspirone reaches its maximum plasma peak in 0.8 hours and the mean half-life is about 2.5 hours (Gammans et al., 1986; Mahmood and Sahajwalla, 1999). In the ergotamine group,

subjects received placebo or ergotamine (3mg p.o.), followed by placebo or psilocybin (170µg/kg p.o.) after 100 minutes. Ergotamine reaches its maximum plasma in a large range from 70 minutes up to 2 hours (Silberstein and McCrory, 2003; Tfelt-Hansen et al., 2000). The elimination half-life is 2.7 hours.

All substances were filled in gelatine capsules of identical number and appearance. Blood pressure was measured every 20 minutes. One hour after intake of the second drug all participants underwent a resting state EEG as reported by Kometer et al. (2015). Participants were monitored until the drug effects had worn off.

2.3. Acute subjective drug effects

The Altered State of Consciousness (5D-ASC) Rating Scale (Dittrich, 1998) was used to assess the subjective effects in each drug condition. The 5D-ASC questionnaire is a visual-analogue scale consisting of 94 items assessing five key dimensions of ASC, independent of their etiology (Dittrich, 1998). The 5D-ASC questionnaire consists of five scales, three of which comprise several item clusters. (1) Oceanic Boundlessness (OB), measures derealization and depersonalization accompanied by changes in affect ranging from heightened mood to euphoria and bliss, and alterations in the sense of time. The corresponding item clusters are positive derealization, positive depersonalization, altered sense of time, positive mood, and mania-like experience. (2) Anxious Ego Dissolution (AED) measures ego-disintegration associated with loss of self-control, thought disorder, arousal, and anxiety. The item clusters are anxious derealization, thought disorder, delusion, fear of loss of thought control, and fear of loss of body control. (3) Visionary Restructuralization (VR) includes the item clusters elementary visual hallucinations, complex visual hallucinations, audio-visual synaesthesia, changed meaning of percepts, facilitated autobiographic memory recollection, and facilitated imagination. (4) Auditory Alterations (AA) comprises auditory illusions and auditory (pseudo-) hallucinations. (5) Reduction of Vigilance (VIR) assesses changes in vigilance and alertness. The scales for AA and VIR don't comprise item clusters. The results of the 5D-ASC data are given as percentage scores of maximum absolute scale values. The questionnaire was applied 180 min post-treatment to retrospectively rate subjective experiences after drug intake.

2.4. Statistical analysis

Data were analyzed using STATISTICA 8.0 for Windows (StatSoft). The drug effects on the 5D-ASC main scales were analysed using a repeated measures ANOVA with pretreatment (placebo, blocker), treatment (psilocybin, blocker +psilocybin), and the 5D-ASC main scales (OB, AED, VR, AA, VIR) as within-subject factors, and group (buspirone or ergotamine) as a between-subject factor. For those main scales that can be further divided into item clusters (OB, AED, and VR), item cluster scores (expressed as % of maximum scores) are shown in Table 1. Percentual change scores were calculated as a percentual change in the blocker + psilocybin condition score in relation to the psilocybin score for each item cluster. In case of significant results on the main scales, a repeated-measures ANOVA with pretreatment, treatment and item cluster scores as within-subject factors was conducted to investigate the contribution of specific symptoms. For all analyses, significant effects were followed by Tukey post-hoc tests. The confirmatory statistical comparisons of all data were carried out on a significance level set at $p<0.05$ (two-tailed).

3. Results

Pretreatment with buspirone or ergotamine differently modulated the psilocybin-induced 5D-ASC main scales scores as indicated by the significant interactions "pretreatment x treatment x main scale x group" ($F(4,136)=3.17$, $p<0.01$) and "treatment x main scale x group" ($F(4,136)=2.74$, $p<0.05$), whereas the interaction "pretreatment x main scale x group" ($F(4,136)=0.50$, $p>0.05$) was not significant. Tukey post-hoc tests revealed that buspirone+psilocybin compared to psilocybin significantly reduced the main scale VR ($p<0.001$) and that there were a trend for a reduction in the main scale OB ($p=0.062$), but there were no significant differences in the main scales AED, AA, and VIR (all $p>0.2$) (Fig. 1). Psilocybin increased the 5D-ASC main scales OB, AED, VR, and VIR (all $p<0.05$) but not AA ($p>0.1$) compared to placebo in the buspirone group. Buspirone+psilocybin compared to placebo significantly increased the 5D-ASC main scales OB, VR, AA, and VIR (all $p<0.001$), but not AED ($p>0.5$). Psilocybin significantly differed from buspirone in all 5D-ASC main scales (all $p<0.001$), except for the main scale AA ($p>0.1$). Further there were significant differences between buspirone and buspirone+psilocybin in the 5D-ASC main scales OB, VR, AA, and VIR (all $p<0.05$), but not in the main scale AED ($p>0.4$). In contrast, ergotamine+psilocybin did not significantly modulate any main scale scores compared to psilocybin alone (all $p>0.8$) (Fig.2). Psilocybin increased all five main scales of the 5D-ASC questionnaire compared to placebo in the ergotamine group (all $p<0.01$). In both groups, there were no significant differences between blocker and placebo on the 5D-ASC main scales (all $p>0.9$). In the ergotamine group all five 5D-ASC main scales were significantly different between placebo and ergotamine+psilocybin, ergotamine and psilocybin, and between ergotamine and ergotamine+psilocybin (all $p>0.01$).

Repeated-measures ANOVA investigating the specific contribution of VR item clusters in the buspirone group revealed significant interactions for "pretreatment x treatment x item cluster" ($F(5,90)=5.64$, $p<0.001$), and "treatment x item cluster" ($F(5,90)=6.90$, $p<0.001$), "pretreatment x item cluster" ($F(5,90)=11.42$, $p<0.001$). Tukey post-hoc tests revealed that the following item clusters were significantly reduced in the buspirone+psilocybin condition compared to psilocybin: elementary visual hallucinations, complex visual hallucinations, changed meaning of percepts,

facilitated autobiographic memory recollection, and facilitated imagination (all $p < 0.05$) (Fig. 3).

4. Discussion

The present study was undertaken to clarify whether pretreatment with the partial 5-HT1A receptor agonist buspirone and the non-hallucinogenic 5-HT1A/2A receptor agonist ergotamine modulates, e.g. reduces, the psilocybin-induced psychological alterations in healthy human subjects. In agreement with the results of previous dose-response studies (Hasler et al., 2004; Studerus et al., 2011) we found that at the dose tested psilocybin produced the expected pattern of changes on the five main scales of the 5D-ASC rating scale. Consistent with our hypothesis derived from the results of behavioural studies in animals, the 5-HT1A agonist buspirone significantly reduced the psilocybin-induced scores for Visionary Restructuralization (VR), and trended to reduce the psilocybin-induced scores for Oceanic Boundlessness (OB) including positively experienced derealisation phenomena and a loosening of ego-boundaries, changes in the sense of time, and increased basic emotions ranging from heightened mood to euphoria. In contrast to this and opposite to our hypothesis, the non-hallucinogenic 5-HT2A/1A agonist ergotamine did not significantly modulate any of the psilocybin-induced 5D-ASC main scale scores.

4.1. Buspirone group

The analysis of the VR subscale scores revealed that buspirone markedly reduced the psilocybin-induced VR item cluster scores for elementary and complex visual hallucinations, and to a lesser extent the scores for facilitated autobiographic memory recollection as well as for facilitated imagination and changed meaning of percepts, but had no effect on audio-visual synaesthesia. In addition, although buspirone reduced the OB score only at a trend level ($p<0.06$), it reduced all OB subscale scores including derealisation and depersonalisation phenomena, changes in the sense of time and in basic emotions ranging from heightened mood to euphoria and mania-like experiences to the same extent. Taken together these findings suggest that buspirone reduces psilocybin-induced “excitatory” phenomena (excitation) and particularly visual hallucinations via 5-HT1A receptor activation.

In fact, the ascending serotonergic pathways originating in the dorsal and median raphe nuclei innervate almost every brain structure (Celada et al., 2013b) and release

5-HT which modulates the excitability of cortical neurons and their discharge rate through pre- and postsynaptic 5-HT receptor subtypes, of which the 5-HT1A and 5-HT2A receptor subtypes play a major role (Celada et al., 2013b). The 5-HT1A receptor is the main inhibitory receptor of the serotonergic system and is highly expressed in the human brain in cortical areas, in particular in frontal, cingulate and temporal regions, limbic areas and in the amygdale as well as in the midbrain raphe nuclei (Celada et al., 2004; Saulin et al., 2012). The 5-HT1A receptor is mainly found postsynaptically to 5-HT axon terminals in cortical regions, limbic areas and in the amygdala, but in the raphe nuclei it is also located presynaptically and acts as an autoreceptor, reducing 5-HT neuron activity and 5-HT release (Casanovas et al., 2000; Celada et al., 2013a). The 5-HT2A receptor is the most important excitatory receptor of the serotonin system and highly abundant in cortical areas and to a lesser extent in the limbic system, in the amygdala, and in the basal ganglia (Saulin et al., 2012). Moreover, 5-H1A and 5-HT2A receptors are not only highly abundant in cortical regions including the visual cortex (Lidow et al., 1989; Saulin et al., 2012; Watakabe et al., 2009), they are also co-expressed in about 50% of cortical pyramidal cells (and in 20-30% of GABAergic interneurons) in rodents (Amargós-Bosch et al., 2004; Santana et al., 2004), where they exert opposite effects on neuronal activity (Amargós-Bosch et al., 2004; Puig et al., 2010). That is, activation of 5-HT2A receptors by 5-HT leads to excitation of pyramidal neurons while activation of 5-HT1A receptors leads to inhibition of pyramidal cell activity (Araneda and Andrade, 1991; Celada et al., 2013a; Celada et al., 2013b). Previous studies have shown that the serotonin and particularly the 5-HT2A receptor system plays a critical role in the formation of psilocybin-induced visual hallucinations and more generally in the formation of excitatory symptoms in healthy human subjects (Carter et al., 2005; Kometer et al., 2011; Vollenweider et al., 1998) as well as in various pathological conditions including schizophrenia (González-Maeso et al., 2008; Meltzer, 2012) and Parkinson's disease (Melse et al., 2014; Meltzer et al., 2010). For example, previous studies have repeatedly demonstrated that the selective 5-HT2A receptor antagonist ketanserin completely blocks psilocybin-induced perceptual alterations including visual hallucinations in a dose-dependent manner (Carter et al., 2005; Kometer et al., 2011; Kometer et al., 2013; Vollenweider et al., 1998) while the highly selective 5-HT2A receptor inverse agonist primavanserin was shown to reduce visual hallucinations in Parkinson's disease (Borek and Friedman, 2014; Meltzer et al., 2010). Finally,

psilocybin-induced hallucinations have recently been linked to neuronal hyperactivity in the lateral occipito-parietal cortex (LOC) in humans (Carter et al., 2005; Kometer et al., 2011; Kometer et al., 2013; Vollenweider et al., 1998).

Hence the present result that buspirone reduces psilocybin-induced hallucinations extends these findings by suggesting that the 5-HT1A receptor modulates the extent of psilocybin-induced excitation and hallucinations in humans. Buspirone acts as a partial agonist at postsynaptic 5-HT1A receptors, and a full agonist at presynaptic 5-HT1A receptors (Hjorth and Carlsson, 1982). Given that buspirone acts as a partial agonist at 5-HT1A receptors and that 5-HT1A and 5-HT2A receptors are highly co-expressed across cortical and visual areas such as the LOC (Saulin et al., 2012), it is conceivable that buspirone may reduce hallucinations via a direct stimulation of 5-HT1A receptors or indirectly via an interaction between 5-HT1A and 5-HT2A receptors located postsynaptically on pyramidal cells (Halberstadt and Geyer, 2013; Krebs-Thomson and Geyer, 1998; Puig et al., 2010). This interpretation is well in line with the recent finding that the effect of the hallucinogenic 5-MeO-DMT on low frequency cortical oscillations in prefrontal cortex and somatosensory cortex in rodents was mostly dependent on 5-HT2A receptors, whereas in visual cortex it was dependent on 5-HT1A receptor activation (Riga et al., 2014). Even though both psilocin and buspirone are thought to have partial agonistic activity at 5-HT1A receptors, the blocking effect of buspirone may be due to more efficient inhibitory effect upon pyramidal neurons compared to psilocin or may be based on a different 5-HT1A-mediated transduction mechanisms resulting in different neural activation patterns. On the other hand, it is possible that stimulation of presynaptic 5-HT1A autoreceptors located in the raphe neurons may contribute to the reducing effect of buspirone on psilocybin-induced symptoms (Meltzer and Huang, 2008). In agreement with this view, activation of presynaptic 5-HT1A raphe nuclei autoreceptors by exogenous agonists reduced 5-HT release and 5-HT-dependent neuronal activity in prefrontal cortex (Celada et al., 2013a).

The inhibitory effects of buspirone on the psilocybin-induced hallucinosis is also in accordance with the observation that the HTR induced by the selective 5-HT2A agonist DOI was blocked by 5-HT1A agonsists such as buspirone, gepirone, and 8-OH-DPAT (Dursun and Handley, 1993; Schreiber et al., 1995). Finally, the present finding is also in line with the observation that 5-HT1A agonists increase sensory

gating as indexed by PPI in mice, a central mechanism that is thought to protect the cortex from distracting stimuli and sensory overload (Halberstadt et al., 2011). However, whether 5-HT1A agonists such as buspirone may reduce psilocybin-induced deficits in PPI humans (Quednow et al., 2012; Vollenweider et al., 2007) or rodents warrants further investigations.

Moreover, buspirone also acts as a D2/D3 receptor antagonist (Ki 34nM, Ki 12nm respectively, human cloned) (Loane and Politis, 2012; Protais et al., 1998) indicating that the reduction of psilocybin-induced visual symptoms by buspirone might also be due to D2/D3 receptor antagonism. However, this seems unlikely given that the selective D2 receptor antagonist haloperidol did not reduce psilocybin-induced hallucinations in a comparable study in healthy human subjects (Vollenweider et al., 1998).

4.2. Ergotamine group

The non-hallucinogenic 5-HT2A/1A agonist ergotamine did not significantly affect any of the psilocybin-induced psychological alterations as measured by the 5D-ASC rating scale. Although we found an increase of the VR item cluster audio-visual synaesthesia of 69% after ergotamine plus psilocybin compared to psilocybin alone, this apparent increase was post-hoc statistically not significant using parametric or nonparametric tests (all $p>0.1$). Moreover, an additional analysis revealed that this increase was driven by four subjects not reporting synaesthesia under psilocybin but in the ergotamine plus psilocybin condition."

The lack of effect of ergotamine on psilocybin-induced symptoms is somewhat surprising, given that ergotamine was reported to bind with even higher affinity as psilocin to 5-HT1A and 5-HT2A receptors in various binding assays (Silberstein and McCrory, 2003; Tfelt-Hansen et al., 2000) and to act as agonist at both receptor sites (González-Maeso et al., 2007; Knight et al., 2004; Silberstein and McCrory, 2003; Tfelt-Hansen et al., 2000). A possible explanation for ergotamine's inability to modulate any of the psilocybin-induced psychedelic symptoms may be its very low bioavailability (<1%) (Tfelt-Hansen et al., 1982; Tfelt-Hansen, 2001). Therefore, the administered dose (3 mg p.o.) may not have been high enough to compete with

psilocybin at 5-HT1A and/or 5-HT2A receptor sites. In line with our results, an early pilot study into the putative blocking effects of ergotamine using repeated doses reported that a pretreatment regimen with ergotamine (2 x 2 mg/day p.o.) over 3 to 5 days and an additional ergotamine dose of 2 mg of ergotamine (p.o.) given before and 4 hours after LSD (1.5 µg/kg p.o.) intake on the experimental day (on day 4 or 6) did not affect the LSD-induced subjective effects in healthy human subjects (n=7), although a reduction of simpatico-mimetic effects of LSD such as pupil dilation were observed (Matussek and Halbach, 1964). However, the sample size of this study was rather small and the subjective effects of LSD were not evaluated using standardized rating scales. Therefore, results are not directly comparable.

Ergotamine may also differentially interact with pre- and postsynaptic 5-HT1A and/ or 5-HT2A receptor sites and has lower efficacy at the respective transduction mechanism when compared with classic 5-HT1A agonist such as buspirone or non-hallucinogenic 5-H1A/2A agonists such as S-lisuride which was shown to block psilocybin-induced activation of cortical neurons (González-Maeso et al., 2007). In addition to these pre- and postsynaptic differences, cellular selectivity may also be an important factor when considering the action on postsynaptic 5-HT1A receptors in cortical neurons. For example, it has been reported that systemic administration of low doses of the full 5-HT1A receptor agonists 8-OH-DAPT can lead to a paradoxical increase of pyramidal cell activity presumably via disinhibition of fast-spiking GABAergic interneurons in prefrontal cortex while high doses blocked pyramidal cell activity (Díaz-Mataix et al., 2006; Lladó-Pelfort et al., 2010; Lladó-Pelfort et al., 2012). Whether ergotamine acts as a full or partial agonist at 5-HT1A or 5-HT2A receptors and whether ergotamine displays cellular selectivity is not known. Further mechanistic studies using multiple doses of ergotamine or a different route of application providing higher bioavailability such as i.v. (Silberstein and McCrory, 2003; Tfelt-Hansen et al., 2000) are needed to clarify the action of ergotamine on cortical neurons in rodents and humans.

In conclusion: The present findings indicate that the 5-HT1A receptor plays a crucial role in the (patho)physiology of psilocybin-induced symptom formation including visual hallucinations, affective changes, derealisation, and depersonalisation phenomena and suggest that 5-HT1A agonist such as buspirone abolish psilocybin-

induced positive-like symptoms via activation of 5-HT1A and/or an interaction between 5-HT1A and 5-HT2A receptors. Given that alterations in 5-HT1A receptor density in cortical and limbic regions of schizophrenia patients have been reported (Tauscher et al., 2002; Yasuno et al., 2004) and that 5-HT2A receptors appear to play an important role in the formation of visual hallucinations, novel selective and region specific 5-HT1 agonists may be useful targets for adjunctive treatment of positive symptoms in schizophrenia and visual hallucination in Parkinson's disease to improve the efficacy of current treatments (Meltzer, 2012).

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Figure 1: Scores of the 5D-ASC questionnaire main scales in the buspirone group. Buspirone+psilocybin significantly reduced the scores of the main scale VR compared to psilocybin ($p<0.001$). There was no significant difference between placebo and buspirone (all $p>0.9$). Psilocybin significantly increased the scores of the main scales OB, AED, VR, and VIR (all $p<0.05$), but not AA ($p>0.1$) compared to placebo. Psilocybin significantly increased 5D-ASC main scales (all $p<0.001$), except for the main scale AA ($p>0.1$) compared to buspirone. Buspirone+psilocybin significantly increased the 5D-ASC main scales OB, VR, AA, and VIR (all $p<0.001$), but not AED ($p>0.5$) compared to placebo. Psilocybin significantly differed from buspirone in the 5D-ASC main scales OB, AED, VR, and VIR (all $p<0.001$). Buspirone+psilocybin compared to buspirone significantly increased the 5D-ASC main scales OB, VR, AA, and VIR (all $p<0.05$), but not in the main scale AED ($p>0.4$). Main scales: oceanic boundlessness (OB); anxious ego dissolution (AED); visionary restructuralization (VR); auditory alterations (AA), and vigilance reduction (VIR). Vertical bars indicate mean + SEM, **$p<0.001$.

Figure 2: Scores of the 5D-ASC questionnaire main scales in the ergotamine group. There was no significant difference in the main scale scores between ergotamine+psilocybin and psilocybin (all $p>0.8$). Psilocybin significantly increased all main scales (all $p<0.01$) compared to placebo. Further, 5D-ASC main scales were significantly different between placebo and ergotamine+psilocybin ($p<0.001$), ergotamine and psilocybin ($p<0.001$), and between ergotamine and ergotamine+psilocybin (all $p>0.01$). There was no significant difference between placebo and ergotamine (all $p>0.9$). Main scales: oceanic boundlessness (OB); anxious ego dissolution (AED); visionary restructuralization (VR); auditory alterations (AA), and vigilance reduction (VIR). Vertical bars indicate mean + SEM.

Figure 3: Scores of the item clusters forming the 5D-ASC main scale visionary restructuralization (VR) in the buspirone group. Buspirone+psilocybin significantly reduced the scores of the VR item clusters ele-hall, comp-hall, cha-mean, fac-mem, and fac-fan compared to psilocybin ($p<0.05$). There was no significant difference between placebo and buspirone (all $p>0.05$). Psilocybin significantly increased all VR item clusters compared to both placebo and buspirone (all $p>0.05$). VR Item clusters: elementary visual hallucinations (ele-hall); complex visual hallucinations (comp-hall); audio-visual synaesthesia (synaest); changed meaning of percepts (cha-mean); facilitated autobiographic memory recollection (fac-mem); and facilitated imagination (fac-ima). Vertical bars indicate mean + SEM, *$p<0.05$, **$p<0.001$.

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Author Disclosure

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Conflict of Interest

All authors declare no conflict of interest.

Contributors

TP performed the research and analysed the data, FXV designed the research, TP, FXV, KHP, and RK wrote the paper. All authors have approved the final manuscript.

Highlights

Effects of 5-HT1A and 5-HT1A/2A agonists on psilocybin-induced psychedelic experience

5-HT1A agonist buspirone reduces psilocybin-induced visual hallucinations in humans

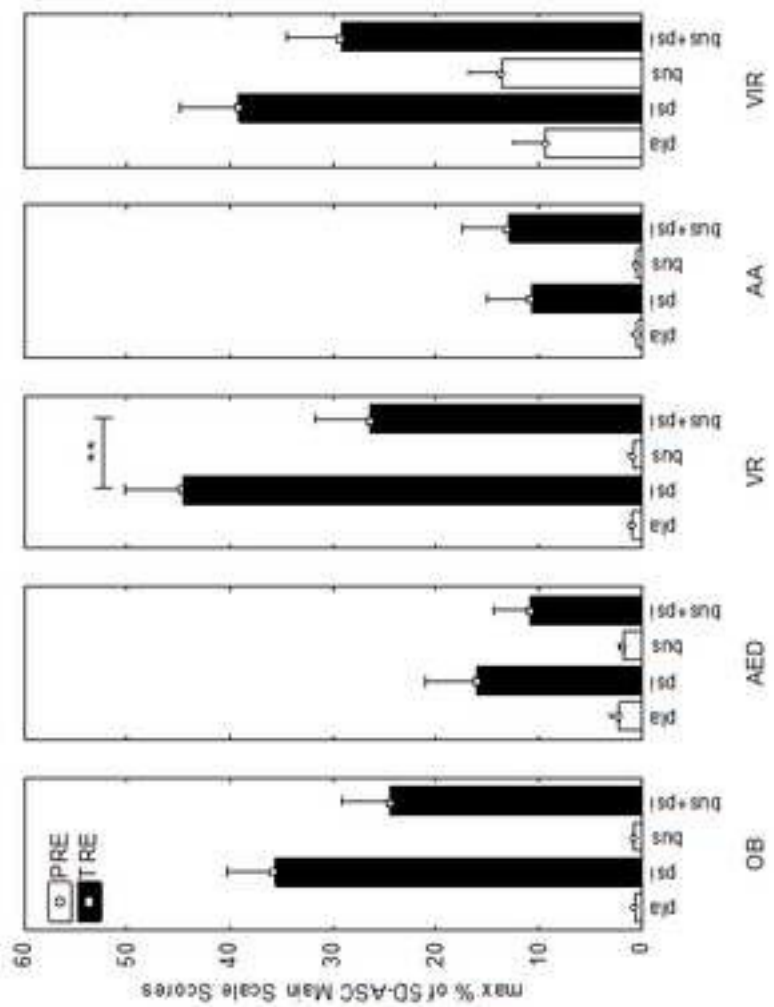
Buspirone but not ergotamine abolishes the subjective effects of psilocybin in humans

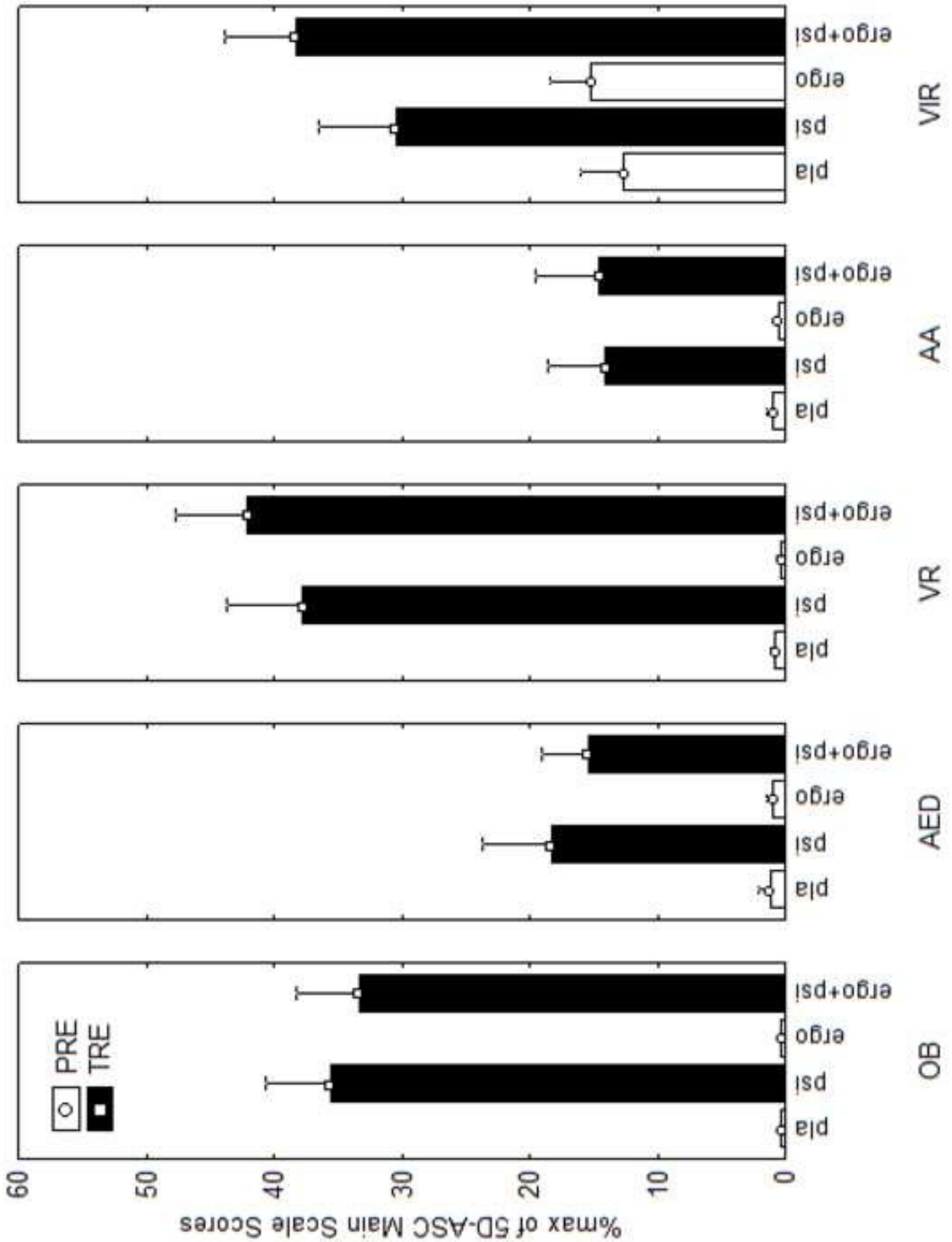
The 5-HT1A receptor may be a useful target in the treatment of visual hallucinations

Table 1: Means (M) and SEM for both groups and all drug conditions of the item cluster scores (express as percent of maximum scores) of the 5D-ASC main scales oceanic boundlessness (OB), anxious ego dissolution (AED), and Visionary Restructuralization (VR). Percentual changes of the mean values were computed between psilocybin and blocker+psilocybin. Minus-sign refers to a percentual reduction, whereas plus-sing refers to a percentual increase in the mean scores of blocker+psilocybin compared to psilocybin alone.

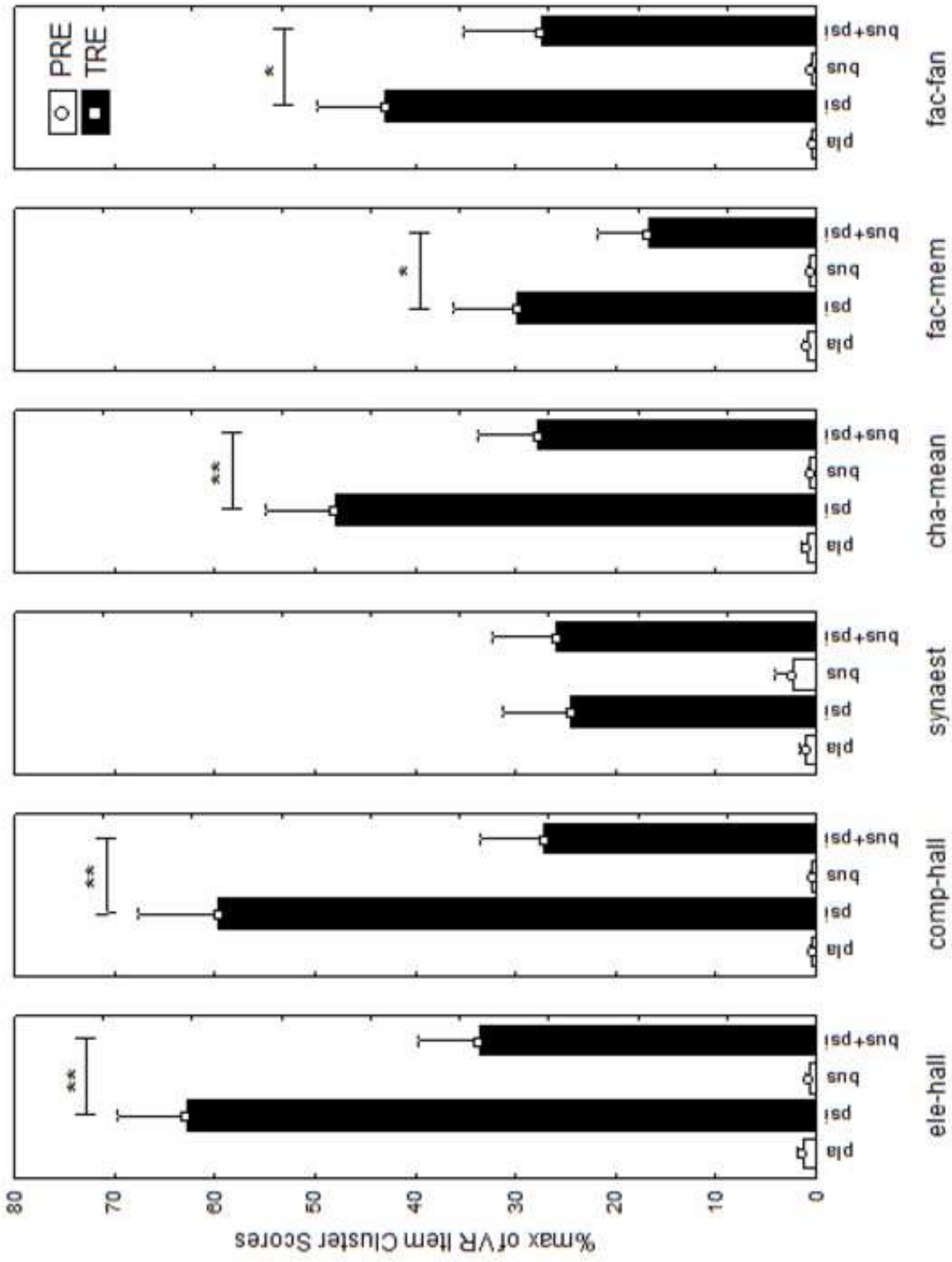
	Buspirone group (n=19)					Ergotamine group (n=17)				
	Placebo M (SEM)	Buspirone M (SEM)	Psilocybin M (SEM)	Busp+Psilo M (SEM)	Percentual change M Psi-(Busp+Psilo)	Placebo M (SEM)	Ergotamine M (SEM)	Psilocybin M (SEM)	Ergo+Psilo M (SEM)	Percentual change M Psi-(Ergo+Psilo)
Item clusters OB										
Positive experienced derealization	0.48 (0.22)	0.52 (0.20)	31.94 (6.32)	25.89 (6.14)	-18.93	0.16 (0.23)	0.14 (0.22)	26.47 (6.68)	30.58 (6.49)	+15.52
Positively experienced depersonalization	0.84 (0.37)	1.17 (0.55)	28.70 (6.58)	21.14 (6.45)	-26.32	0.06 (0.39)	0.26 (0.58)	26.50 (6.95)	27.12 (6.82)	+2.33
Altered sense of time	0.98 (0.47)	0.53 (0.22)	40.72 (7.50)	30.91 (6.89)	-24.08	0.25 (0.50)	0.27 (0.24)	37.61 (7.93)	36.67 (7.28)	-2.50
Positive mood	0.66 (0.30)	0.87 (0.33)	30.76 (5.41)	21.53 (5.73)	-30.00	0.54 (0.32)	0.51 (0.35)	24.54 (5.72)	26.51 (6.06)	+8.03
Mania-like experience	0.56 (0.26)	0.53 (0.23)	26.35 (6.35)	20.66 (6.19)	-21.57	0.18 (0.28)	0.11 (0.24)	24.07 (6.71)	19.59 (6.54)	-18.62
Item clusters AED										
Anxious derealization	3.21 (1.34)	3.50 (1.19)	14.18 (5.80)	9.53 (3.11)	-32.80	2.65 (1.42)	2.30 (1.26)	17.75 (6.14)	11.54 (3.29)	-35.01
Thought disorder	2.39 (0.89)	0.55 (0.44)	27.17 (6.45)	19.89 (4.94)	-26.78	0.85 (0.94)	1.00 (0.47)	23.44 (6.82)	24.46 (5.22)	+4.33
Delusion	0.33 (0.19)	0.75 (0.28)	4.72 (3.81)	5.56 (3.46)	+17.84	0.02 (0.20)	0.12 (0.29)	8.53 (4.03)	6.27 (3.65)	-26.44
Fear of loss of thought control	1.05 (0.42)	0.80 (0.30)	10.36 (4.77)	9.28 (4.75)	-10.42	0.32 (0.45)	0.07 (0.31)	13.26 (5.04)	9.99 (5.02)	-24.72
Fear of loss of body control	3.14 (1.67)	2.01 (0.75)	21.62 (6.48)	17.21 (5.44)	-20.39	0.96 (1.77)	0.47 (0.79)	26.35 (6.85)	24.38 (5.75)	-7.48
Item clusters VR										
Elementary visual hallucinations	1.34 (0.47)	0.64 (0.35)	62.79 (6.70)	33.54 (6.55)	-46.58	0.43 (0.49)	0.59 (0.37)	54.60 (7.09)	56.70 (6.93)	+3.85
Complex visual hallucinations	0.42 (0.26)	0.39 (0.19)	59.63 (7.98)	27.11 (7.08)	-54.54	0.41 (0.28)	0.18 (0.20)	51.51 (8.44)	56.50 (7.49)	+9.67
Audio-visual synaesthesia	0.95 (0.86)	2.30 (1.39)	24.46 (7.23)	25.88 (7.04)	+5.84	1.63 (0.91)	0.27 (1.47)	20.75 (7.64)	35.11 (7.44)	+69.20
Changed meaning of percepts	0.86 (0.40)	0.57 (0.22)	48.03 (6.08)	27.75 (6.31)	-42.22	0.31 (0.42)	0.15 (0.23)	34.90 (6.43)	37.66 (6.67)	+7.92
Facilitated autobiographic memory	0.86 (0.63)	0.60 (0.22)	29.81 (7.15)	16.73 (5.71)	-43.87	1.29 (0.66)	0.12 (0.23)	25.51(7.56)	25.41 (6.03)	-0.40
Facilitated imagination	0.37 (0.41)	0.47 (0.16)	42.92 (6.94)	27.39 (7.16)	-36.17	0.79 (0.43)	0.00 (0.17)	39.31 (7.34)	41.06 (7.57)	+4.45

Figure(s)





Figure(s)



Figure(s)