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ORIGINAL INVESTIGATION

Psilocybin-induced spiritual experiences and insightfulness are associated with synchronization of neuronal oscillations

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Abstract
Rationale During the last years, considerable progress has been made toward understanding the neuronal basis of consciousness by using sophisticated behavioral tasks, brain-imaging techniques, and various psychoactive drugs. Nevertheless, the neuronal mechanisms underlying some of the most intriguing states of consciousness, including spiritual experiences, remain unknown.
Objectives To elucidate state of consciousness-related neuronal mechanisms, human subjects were given psilocybin, a naturally occurring serotonergic agonist and hallucinogen that has been used for centuries to induce spiritual experiences in religious and medical rituals.
Methods In this double-blind, placebo-controlled study, 50 healthy human volunteers received a moderate dose of psilocybin, while high-density electroencephalogram (EEG) recordings were taken during eyes-open and eyes-closed resting states. The current source density and the lagged phase synchronization of neuronal oscillations across distributed brain regions were computed and correlated with psilocybin-induced altered states of consciousness.
Results Psilocybin decreased the current source density of neuronal oscillations at 1.5–20 Hz within a neural network comprising the anterior and posterior cingulate cortices and the parahippocampal regions. Most intriguingly, the intensity levels of psilocybin-induced spiritual experience and insightfulness correlated with the lagged phase synchronization of delta oscillations (1.5–4 Hz) between the retrosplenial cortex, the parahippocampus, and the lateral orbitofrontal area.
Conclusions These results provide systematic evidence for the direct association of a specific spatiotemporal neuronal mechanism with spiritual experiences and enhanced insight into life and existence. The identified mechanism may constitute a pathway for modulating mental health, as spiritual experiences can promote sustained well-being and psychological resilience.

Keywords Psilocybin · Consciousness · Spirituality · Oscillations · Serotonin · EEG · Resting-State · PCC · ACC · Delta

Introduction

Spiritual experiences are rare but highly significant phenomena of consciousness, which have the capacity to promote sustained well-being and resilience (Maselko and Kubzansky 2006; Southwick and Charney 2012). Accordingly, these experiences have been the subject of countless psychological, religious, sociological, and philosophical discussions across human history. Nevertheless, their neuronal correlates are largely unknown, because systematic assessment is hampered by their infrequent and unpredictable occurrence. Questionnaire-based analyses, for example, have revealed that depending on the definition of spiritual experiences, only approximately one third to one half of healthy human subjects ever have an intense spiritual experience over the course of their entire lives (Levin 1993). Therefore, the few systematic neuroscience studies concerning spirituality have

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focused their attention on neuronal features that predispose subjects to a transcendent experience (Urgesi et al. 2010; Tenke et al. 2013; Miller et al. 2014). However, these studies did not address the question, which neuronal processes predominate during a spiritual experience and are therefore likely to be directly associated with this experience?

Interestingly, recent placebo-controlled studies showed that spiritual experiences, referring to profound experiences of awe and connectedness to a superior power, can be dose-dependently induced by the serotonergic hallucinogen psilocybin, often paired with a marked experience of unity, insightfulness, and bliss (Dittrich 1998; Studerus et al. 2010; Kometer et al. 2012). In a recent study, higher doses of psilocybin as used in the present study were found to induce a state that fulfilled according to Stace (1961) all criteria required to qualify for a "complete mystical experience" (Griffiths et al. 2006). At 14-month follow-up, subjects rated these experiences as both authentic (Griffiths et al. 2006) and among the most spiritually significant events of their lives (Griffiths et al. 2008). Thus, psilocybin constitutes a unique research tool that can be used to trigger selected and previously unexplored states of consciousness, including spiritual experiences and associated states, in a controlled experimental setting. In combination with neuroimaging techniques, the drug therefore permits a systematic assessment of neuronal processes behind these altered states of mind.

Neuronal oscillations and their phase synchronization across brain regions may be of particular importance for understanding psilocybin-induced states of consciousness, because neuronal oscillations are thought to represent a key mechanism of neuronal integration (Buzsáki and Draguhn 2004; Womelsdorf et al. 2007; Siegel et al. 2012) that shapes consciousness (Varela et al. 2001; Alkire et al. 2008). In line with this view, anesthesia-induced loss of consciousness is associated with changes in neuronal oscillations, including the appearance of high-amplitude alpha waves in frontal cortical areas (Ching et al. 2010), as well as an increase in the phase synchronization of gamma oscillations between the anterior and posterior cingulate cortices (Murphy et al. 2011). However, despite abundant experimental support for the critical role of oscillations in regulating levels of consciousness, whether neuronal oscillations also mediate specific states of consciousness (Shushruth 2013), as exemplified by spiritual experiences, remains unknown.

Studies exploring the effects of serotonergic hallucinogens on neuronal oscillations would undoubtedly contribute to our understanding of this issue, as serotonergic hallucinogens reliably induce distinctive states of consciousness. Nevertheless, the impact of serotonergic hallucinogens on neuronal oscillations, and particularly the association of these oscillations with identifiable conscious states, is unclear. Initial animal studies performed with the hallucinogenic serotonin (5-HT) 2A/2C agonist, 1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane (DOI), reported a DOI-induced reduction in delta (0.3–4 Hz) and gamma (30–80 Hz) oscillations in the prefrontal areas of the brain (Celada et al. 2008; Puig et al. 2010), in addition to a trend toward an increase in higher frequency (70–90 Hz) oscillations in subcortical structures (Goda et al. 2013). In humans, oscillations decreased across a broad frequency range (up to 20 Hz) during eyes closed resting state after the administration of ayahuasca, a plant brew containing *N*,*N*-dimethyltryptamine (DMT), another naturally occurring serotonergic hallucinogen (Riba et al. 2002; Riba et al. 2004). Furthermore, psilocybin decreased prestimulus-associated parieto-occipital alpha (8–12 Hz) oscillations, which in turn precluded the subsequent visual stimulus-induced modulation of alpha oscillations during visual processing (Kometer et al. 2013). Recently, a magnetoencephalography (MEG) analysis showed that psilocybin decreases the power of all neuronal oscillations of ≤100 Hz during the eyes open resting state (Muthukumaraswamy et al. 2013).

Taken together, the initial evidence provided by the studies described above suggests that the impact of serotonergic hallucinogens on neuronal oscillations is, to some extent, both species- and drug-dependent. However, in humans, serotonergic hallucinogens have a common tendency to decrease the power of lower frequency oscillations, especially alpha oscillations (8–12 Hz). The decrease may not be uniform across cortical areas, may differ in eyes open and eyes closed states, and may have different functional consequences depending on the cortical area of interest. The specific pattern of power decrease could potentially underlie various psilocybin-induced states of consciousness. Finally and most importantly, mounting evidence indicates that phase synchronization of neuronal oscillations plays a key functional role across brain areas in the formation of consciousness (Varela et al. 2001; Melloni et al. 2007; Busch et al. 2009; Dehaene and Changeux 2011; Hipp et al. 2011; Fahrenfort et al. 2012; Steinmann et al. 2014). For this reason, we suggest that not only regional power changes of oscillations but also phase synchronization of oscillations across brain regions may account for some hallucinogen-induced states of consciousness.

To explore this hypothesis, we conducted a double-blind, placebo-controlled study and administered psilocybin to 50 healthy human volunteers to alter consciousness and to induce spiritual experiences. We then used electrophysiological neuroimaging methods to characterize psilocybin-induced alterations in the current source density of neuronal oscillations during eyes-open and eyes-closed resting states. Furthermore, we assessed the dynamic coordination of oscillations across distributed brain regions by computing lagged phase synchronization of neuronal oscillations. Compared with other coordination measures (e.g., instantaneous connectivity), lagged phase synchronization provides a new measure that can capture nonlinear neuronal relationships. Furthermore, lagged phase synchronization is not affected by artifacts deriving from volume

conduction, electromyographic activity, or by concomitant and unrelated power modulation in two regions (Pascual-Marqui et al. 2011). Lastly, we correlated lagged phase synchronization values with the subjective intensity of psilocybin-induced states of consciousness by using nonparametric permutation tests.

Materials and methods

Subjects

Fifty-five healthy human subjects were enrolled. The subjects' physical health was confirmed by a physical examination that included electrocardiography and detailed blood analysis. Pregnant women were identified using a 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 and Pfister 1997), and the Hopkins System Checklist 90-Revised (Derogatis 1994) 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 a self-report drug use questionnaire were used to verify the absence of drug dependence.

Subjects were informed about the procedures of the study and the effects and possible risks of the administered substances. They were further asked to abstain from caffeine and to ingest no other psychoactive substance during the whole experimental days. Moreover, they were not allowed to drink alcohol within 48 h before measurements or to consume any illegal psychoactive substance within 3 weeks before measurements. This procedure was chosen to prevent any effect of this pharmacological substance on neuronal oscillations. All subjects were subsequently asked to give written informed consent to participate. 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 of Public Health, Department of Pharmacology and Narcotics, Bern, Switzerland. Five subjects were excluded from the analysis because artifacts contaminated the majority of data in the psilocybin or the placebo condition. Thus, a total of 50 subjects were included in the statistical analysis (28 males, 22 females, mean age 24.8±4.0 years).

Substance and dosing

Each subject took part in one of three double-blind, placebo-controlled, within-subject, randomized pharmacological studies. In each of these three studies, subjects were tested on four different days, each separated by at least 2 weeks. The four testing sessions were placebo + placebo, placebo + psilocybin, drug 1 + placebo, and drug 1 + psilocybin, where drug 1 represents ketanserin, ergotamine, or buspirone according to the study. In the first study (study 1), the subjects (N=15) received placebo or ketanserin (50 mg peroral (p.o.)) followed by placebo or psilocybin (215 μg/kg p.o.) after 1 h. In the second study (study 2), the subjects (N=18) received placebo or ergotamine (3 mg p.o.), followed by placebo or psilocybin (170 μg/kg p.o.) after 1 h, and in the third study (study 3), the subjects (N=17) received placebo or buspirone (20 mg p.o.) followed by placebo or psilocybin (170 μg/kg p.o.) after 1 h. Thus, each of the 50 subjects received placebo + placebo and placebo + psilocybin on two separate days, and only the data from these two testing sessions were used for the analysis. This large number of subjects will allow to calculate robust correlations between the psilocybin-induced altered states of consciousness and neuronal oscillations. Furthermore, the doses of psilocybin (170 and 215 μg/kg p.o.) are rather moderate compared to some previous behavioral psilocybin studies (Griffiths et al. 2006) because it is conceivable that psilocybin-induced facial muscle tensions at high doses introduce too many EEG artifacts to be properly removed.

Experimental design

On each experimental day, subjects came to the laboratory between 8 and 9 a.m. and confirmed that they had not ingested caffeine that morning. Electroencephalography (EEG) recording took place in a sound-, light-, and electrically shielded room at 60 min post-administration of psilocybin/placebo. Subjects were instructed either to close their eyes (eyes-closed condition) or to keep their gaze fixed on a cross that appeared in the middle of the computer screen (eyes-open condition). This fixation cross was used to reduce eye movements and thus muscle artifacts. These two conditions were conduced twice in a randomized order in study 1 for 2 min each and in studies 2–3 for 2.5 min each. To prevent that subject fall asleep during the experiment, the study principal investigator verbally alerted the subject if any signs of strong drowsiness appeared in the behavior and EEG traces. This procedure was required for two subjects in the placebo condition. The self-reported questionnaire was given after all subjective effects of the drugs disappeared, to retrospectively rate the drug-induced conscious state.

Acute subjective drug effects

The Altered States of Consciousness questionnaire (5D-ASC), a well-validated self-rating scale with 94 visual analogue items, was used to quantify the subjective psychological effects of psilocybin (Dittrich 1998). This questionnaire and its short form OAV are to date the most widely used questionnaires to assess the structure and components of altered states of consciousness, including spiritual experiences (Dittrich 1998). The dimensional structure of the 5D-ASC/OAV was

established in series of experiments and validated based on more than 1000 single trials using various non-pharmacological and pharmacological ASC-inducing methods (Dittrich 1998; Studerus et al. 2010). A confirmatory factor analysis of the 5D-ASC/OAV revealed 11 subscales, which can be measured across drug conditions, settings, and sexes: experience of unity, spiritual experience, blissful state, insightfulness, changed meaning of percepts, disembodiment, impaired control and cognition, anxiety, elementary imagery, complex imagery, audio-visual synesthesia (Studerus et al. 2010). Of particular interest with regard to the current study was the spiritual experience subscale, assessing experiences of awe and being connected with a superior power. This experience is thought to represent the core of spiritual experiences, as almost all definitions of spiritual experiences include this aspect. In addition, related subscales were of interest, including experience of unity, comprising the experience of oneness with the environment and the self, insightfulness, measuring profound insights into life and existence, blissful state, measuring experiences of pleasure, inner peace, and love (Studerus et al. 2010). Importantly, these additional subscales are related to spiritual experience subscale, but confirmatory factor analysis clearly indicate that they cannot be merged into the spiritual experience subscale and should therefore be regarded as separate component of altered states of consciousness.

EEG recordings

EEG data were recorded from 64 scalp electrodes using the BioSemi ActiveTwo electrode system (BioSemi, Netherlands). Additional electrodes were attached to the outer canthus of each eye and both infraorbitally and supraorbitally to the left eye to record the horizontal and vertical electrooculograms, respectively. Electrophysiological signals were sampled at a rate of 512 Hz.

EEG analysis

Preprocessing of EEG data

EEG data were filtered offline with a low cutoff of 0.5 Hz. Artifacts from eye movements, blinks, or muscle tensions were removed using the infomax independent component (ICA) analysis algorithm (Bell and Sejnowski 1995; Lee et al. 1999). Bad channels were interpolated using spherical splines (Perrin et al. 1989). Data were re-referenced to the average and segmented in 2-s epochs. Subsequently, data were carefully inspected by a trained researcher to remove epochs that were contaminated by sweat, technical, or remaining muscle artifacts. The mean±SD number of artifact free epochs per condition was 124±26 for placebo eyes-closed, 124±25 for placebo eyes-open, 121±25 for psilocybin eyes-closed, and 116±28 for psilocybin eyes-open. The number of artifact free epochs did not significantly differ between drug or eyes-open/closed conditions (all Ps=n.s.), as assessed by a repeated measure ANOVA using within-subject factor drug (placebo vs. psilocybin) and condition (eyes-open vs. eyes-closed).

Current source density of neuronal oscillations

Exact low-resolution brain electromagnetic topography (eLORETA; publicly available free academic software at http://www.uzh.ch/keyinst/loreta.htm) was applied to compute the three-dimensional intracerebral current density values ($\mu A/mm^2$) of the scalp-recorded EEG rhythms (Pascual-Marqui et al. 2011). eLORETA is the newest version of LORETA, a linear minimum norm inverse solution that does not require any prior assumptions about the number or position of dipoles underlying the scalp-recorded EEG data (Pascual-Marqui et al. 1994; Pascual-Marqui 2002; Pascual-Marqui et al. 2011). The LORETA inverse solution is based on the assumption that synchronized discharge is required for generating cortical EEG rhythms, an assumption that has been consolidated in numerous intracerebral studies (Buzsáki et al. 2012). LORETA has been applied in almost thousand peer-review publication (Thatcher et al. 2012) and has received considerable cross-modal validation from several studies combining LORETA with more established localizing methods such as functional MRI (Vitacco et al. 2002; Mulert et al. 2004; Mulert et al. 2005; Olbrich et al. 2009; Neuner et al. 2014), structural MRI (Worrell et al. 2000; Babiloni et al. 2011; Babiloni et al. 2013; Vecchio et al., 2015), diffusion spectrum magnetic resonance imaging (Thatcher et al. 2012), or positron emission tomography (Pizzagalli et al. 2004; Horacek et al. 2007). We apply eLORETA, which has no localization bias even in the presence of structured noise (Pascual-Marqui et al. 2011) and, therefore, was found to have a slightly increase localization performance compared to the previous version, called sLORETA (Jatoi et al. 2014).

We used eLORETA with a three-shell spherical head model registered to the digitized MRI version of the Talairach and Tournoux atlas (Brain Imaging Centre, Montreal Neurological Institute). Electrode coordinates were calculated by cross-registration of spherical and realistic head geometry (Towle et al. 1993). The solution space was restricted to cortical gray matter and the hippocampus and included a total of 6239 voxels at 5×5×5-mm spatial resolution. The eLORETA intracranial spectral density was calculated separately for eyes-open and eyes-closed conditions with a resolution of 0.5 Hz for each of eight frequency bands: delta (1.5–4 Hz), theta (4–8 Hz), alpha1 (8–10.5 Hz), alpha2 (10.5–13 Hz), beta1 (13–20 Hz), beta2 (20–30 Hz), gamma1 (30–45 Hz), and gamma2 (55–100 Hz).

Nonparametric mapping was performed by eLORETA software package (Pascual-Marqui et al. 2011; Pascual-Marqui et al. 2014) to statistically assess all frequency bands in both the eyes-open and eyes-closed conditions while

correcting for multiple comparisons across voxels and frequencies. The statistical difference in the three-dimensional current source density between the placebo and psilocybin condition, and the correlation between the current source density in the psilocybin condition and the 11 states of consciousness were evaluated for each frequency band in each condition. To this end, differences in current density values between the placebo and the psilocybin condition for each frequency band were calculated by voxel-by-voxel-dependent *t* tests (two-tailed). Furthermore, the voxel-wise product-moment correlations between current source density in the psilocybin condition and the 11 5D-ASC subscale scores were computed by regression analyses. To determine the cortical voxels with significant effects, we estimated the empirical probability distribution for the maximal statistics under the null hypothesis by 5000 permutations, a procedure that does not rely on Gaussian distribution of dependent variables (Nichols and Holmes 2002; Nichols 2012). The omnibus null hypothesis was rejected if the dependent sample *t* value (two-tailed) of at least one voxel was above the critical threshold for $p=0.05$.

Lagged phase synchronization of neuronal oscillations

The dynamic phase-synchronization of neuronal oscillations across cortical areas was assessed by computing lagged phase synchronization in the eLORETA source localization space (Pascual-Marqui et al. 2011). Lagged phase synchronization is a novel index based on normalized Fourier transforms and is, therefore, related to nonlinear functional connectivity. Lagged phase synchronization measures phase-synchronization between two regions of interests (ROIs) after removing the zero-lag contribution. Thus, it removes the instantaneous component, which is driven by non-physiological effects and intrinsic physical artifacts that occur due to volume conduction and low spatial resolution (Nolte et al. 2004; Stam et al. 2007; Schoffelen and Gross 2009; Pascual-Marqui et al. 2011). Accordingly, lagged phase synchronization has been increasingly used in recent studies (Canuet et al. 2011; Hilty et al. 2011; Canuet et al. 2012; Guggisberg et al. 2014; Kühnis et al. 2014; Olbrich et al. 2014; Ramyead et al. 2014; Steinmann et al. 2014; Elmer et al. 2015; Vecchio et al., 2015) and has received cross-modal validation by studies combining EEG-based lagged phase synchronization measurements with MRI-based diffusion tensor imaging (Vecchio et al. 2015).

To prevent a bias in selecting regions of interest for lagged phase synchronization analysis, we used a whole-brain Broadmann areas (BAs) approach by selecting the centroids of all 42 BAs in each hemisphere as regions of interest and computing lagged phase synchronization between all pairs of regions of interest (Canuet et al. 2011; Pascual-Marqui et al. 2011).

Statistical differences in lagged phase synchronization between placebo and psilocybin conditions were assessed separately for each frequency band and for eyes-closed and eyes-open conditions using dependent samples *t* tests (two-tailed). Randomization strategy with 5000 permutations was used to appropriately correct for multiple comparisons. Finally, the association between lagged phase synchronization and state of consciousness was assessed, firstly by computing the product-moment correlation between lagged phase synchronization values and the scores of the 11 subscales of the 5D-ASC in the psilocybin condition and secondly by using randomization strategy (5000 permutations) to determine the critical probability threshold values for $p=0.05$.

Results

Acute consciousness-altering effects of psilocybin

The subjective effects of psilocybin were assessed by a repeated-measures ANOVA on the Altered States of Consciousness questionnaire (5D-ASC) score with drug (psilocybin, placebo) and 5D-ASC subscale (spiritual experience, experience of unity, blissful state, insightfulness, disembodiment, impaired control and cognition, anxiety, complex imagery, elementary imagery and audio-visual synesthesia, changed meaning of percepts) as within-subject factors and dose (170 and 215 μg/kg p.o) as between-subject factor. There was a significant main effect of drug ($F(1,48)=64.23$, $p<0.00001$) and subscale ($F(10,480)=20.57$, $p<0.00001$), but not of dose ($F(1,48)=0.23$, $p=.63$). The significant interaction between drug×subscale ($F(10,480)=19.90$, $p<0.00001$) and Fischer's LSD post hoc analysis on this interaction revealed that psilocybin significantly increased scores of all subscales (all $p<0.05$), including spiritual experiences ($p<0.00001$), experience of unity ($p<0.00001$), blissful state ($p<0.00001$), and insightfulness ($p<0.00001$). Finally, LSD post hoc analysis on the significant interaction between drug×subscale×dose ($F(10,480)=2.00$, $p<0.05$) revealed that only the subscales elementary hallucinations ($p<0.05$) and blissful states ($p<0.01$) revealed high scores with higher doses. This was expected as the two doses are very similar.

Current source density of neuronal oscillations

In the eyes-closed condition, psilocybin significantly decreased current source density of oscillations in all frequency bands up to 20 Hz ($p_{max}=0.00020$, corrected; Fig. 1), and in the eyes-open condition, psilocybin significantly decreased current source density of oscillations in all frequency bands up to 30 Hz ($p_{max}=0.00020$, corrected; Fig. 2). In both the eyes-open and eyes-closed conditions, there was a consistent, significant psilocybin-induced reduction of current source density across low-frequency bands (<20 Hz) in the PCC

(Brodmann area (BA) 23 and BA31) and the retrosplenial cortex (RSC; BA30) (Figs. 1 and 2). In addition, in both the eyes-open and eyes-closed conditions, there was a significant psilocybin-induced reduction of current source density across most frequency bands in the anterior cingulate cortex (BA24), the precuneus (BA31), the cuneus (BA30), the parahippocampal gyrus (BA27 and BA30), and additional areas of the RSC (BA29) (Figs. 1 and 2). In both the eyes-open and eyes-closed conditions, the psilocybin-induced decrease in current source density in the theta (4–8 Hz) and alpha1 (8–10.5 Hz) frequency bands was more widely distributed than in other frequency bands and included the insular cortex (BA13), the occipitotemporal area (BA37), and parahippocampal regions (BA35 and BA36) (Figs. 1 and 2). In the alpha1 frequency band and partially in the alpha2 frequency band (10.5–13 Hz), the psilocybin-induced decrease in current source density also occurred across large areas of the posterior occipital-parietal cortex (BA7, BA17, BA18, and BA19), particularly in the right hemisphere (Figs. 1 and 2).

In contrast to these strong decreases in low-frequency oscillations, there were no psilocybin-induced effects on current source density in the gamma1 frequency band (30–45 Hz; Figs. 1 and 2). High-frequency oscillations (55–100 Hz) were significantly increased by psilocybin in the left RSC (BA29) during the eyes-closed condition (p_{max}=0.020, corrected; Fig. 1). At a trend level (p=0.1, corrected), this psilocybin-induced increase extended into the parahippocampal gyrus (BA27, BA30). In the eyes-open condition, there was a trend (p_{max}=0.054, corrected) toward a psilocybin-induced increase in current source density in high-frequency oscillations (55–100 Hz) in the RSC (BA29).

Correlation analysis revealed that only the score of insightfulness significantly correlated with the current source density of neuronal oscillations during the eyes-open condition. That is, the current source density in the alpha2 frequency band in very posterior, medial parieto-occipital areas (maximal at x=−10, y=−85, z=40, p=0.012, corrected) in the psilocybin condition correlated with score on the insightfulness subscale of the 5D-ASC (Fig. 3). Interestingly, current source density in the alpha2 frequency band in this area was not reduced by psilocybin administration on a group level (Figs. 1 and 2), in contrast to the surrounding cortical areas, in particular the more anterior areas. This indicates that insightfulness during the eyes-open condition was precluded when the psilocybin-induced decrease in alpha oscillations covered the whole parieto-occipital cortex. There were no correlations between any other subscale of interest in the 5D-ASC and current source density of neuronal oscillations.

Lagged phase synchronization of neuronal oscillations

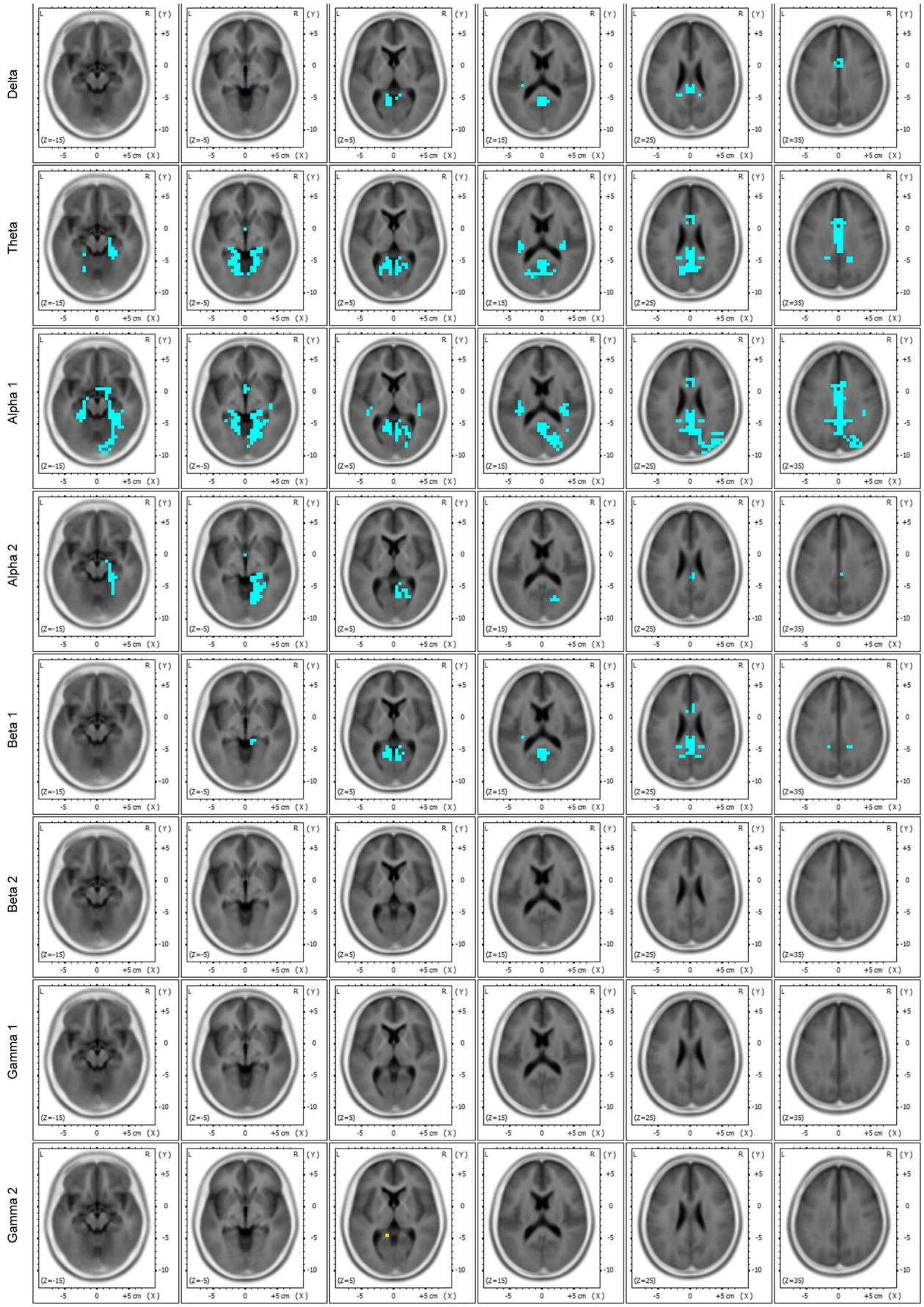
Analysis of lagged phase synchronization revealed that psilocybin slightly increased interhemispheric lagged phase synchronization of delta oscillations (1.5–4 Hz) during the eyes-open condition, reaching significance between right BA 7 and left BA 39 (p_{max}=0.017, corrected). Similarly, there was a trend toward a psilocybin-induced increase in the lagged phase synchronization of delta oscillations during the eyes-closed condition (p_{max}=0.063, corrected). Most interestingly, the extent of lagged phase synchronization within a network of deep cortical structures strongly and positively correlated with score on the insightfulness subscale of the 5D-ASC (p_{max}=0.0028, corrected) and spiritual experiences (p_{max}=0.029, corrected) subscales of the 5D-ASC during the eyes-closed condition. Specifically, the score on the insightfulness subscale of the 5D-ASC correlated with lagged phase synchronization of delta oscillations between BA27 and BA34, BA29 and BA34, and BA28 and BA47, and the score on the spiritual experiences subscale of the 5D-ASC correlated with lagged phase synchronization of delta oscillations between BA28 and BA29, BA34 and BA29, and BA20 and BA41 (Fig. 4). Scores of the remaining nine subscales of the 5D-ASC did not significantly correlate with neuronal oscillations in any frequency band (p_{max}=n.s.), suggesting that the abovementioned correlation between neuronal oscillations and spiritual experiences/insightfulness is highly specific.

Fig. 1 Statistical maps of the voxel-wise effect of psilocybin on neuronal oscillations at 1.5–4 Hz (delta; *top row*), 4–8 Hz (theta; *second row*), 8–10.5 Hz (alpha1; *third row*), 10.5–13 Hz (alpha2; *fourth row*), 13–20 Hz (beta1; *fifth row*), 20–30 Hz (beta2; *sixth row*), 30–45 Hz (gamma1; *seventh row*), and 55–100 Hz (gamma2; *bottom row*) in the eyes-closed condition. *Blue* depicts voxels where neuronal oscillations were significantly decreased by psilocybin (p<0.05, corrected). *Yellow* depicts voxels where neuronal oscillations were significantly increased by psilocybin (p<0.05, corrected) (color figure online)

Discussion

Our data demonstrate that the serotonergic hallucinogen psilocybin decreased ongoing oscillations at 1.5–20 Hz within the PCC, the RSC, the anterior cingulate cortex (ACC), and parahippocampal regions during the resting state. This decrease was spatially most extended in the alpha and theta frequency bands and reached its maximum within the PCC, a key structure of the default-mode network. By contrast, high-frequency oscillations (55–100 Hz) within the RSC were slightly increased by psilocybin. Finally, and most interestingly, lagged phase synchronization of delta oscillations (1.5–4 Hz) within a network comprising the RSC, the parahippocampus, and the lateral orbitofrontal area were associated with spiritual experiences and insightfulness.

In line with the observed decreases in oscillations at 1.5–20 Hz, it has previously been reported that the serotonergic hallucinogenic brew ayahuasca attenuated ongoing oscillations up to 20 Hz, with similar maximum effects in the


Delta
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Alpha 1
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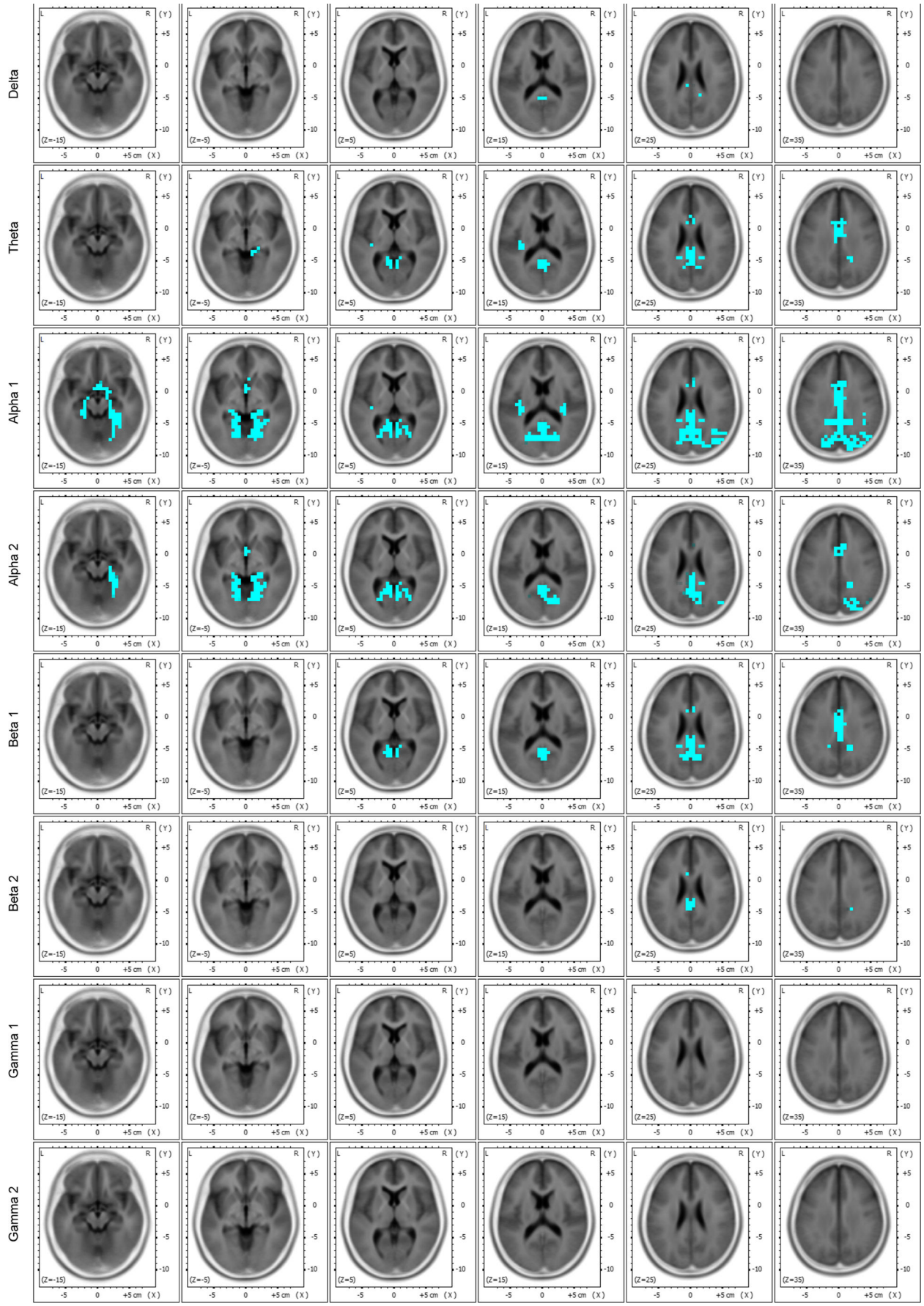
Beta 1
Beta 2
Gamma 1
Gamma 2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◀ **Fig. 2** Statistical maps of the voxel-wise effect of psilocybin on neuronal oscillations at 1.5–4 Hz (delta; *top row*), 4–8 Hz (theta; *second row*), 8–10.5 Hz (alpha1; *third row*), 10.5–13 Hz (alpha2; *fourth row*), 13–20 Hz (beta1; *fifth row*), 20–30 Hz (beta2; *sixth row*), 30–45 Hz (gamma1; *seventh row*), and 55–100 Hz (gamma2; *bottom row*) in the eyes-open condition. *Blue* depicts voxels where neuronal oscillations were significantly decreased by psilocybin ($p<0.05$, corrected) (color figure online)

theta/alpha frequency range (Riba et al. 2002; Riba et al. 2004). Both psilocybin and the main psychoactive compound of ayahuasca, DMT, are thought to induce their psychological effect predominantly by activation of 5-HT2A receptors (Vollenweider et al. 1998; Nichols 2004; Kometer et al. 2012), and activation of these receptors mediated the psilocybin-induced decrease in ongoing alpha oscillations (Kometer et al. 2013). Thus, our findings add to the evidence that a decrease of ongoing oscillations below 20 Hz, particularly theta/alpha oscillations, may be a common mechanism of action of serotonergic hallucinogens such as psilocybin and DMT.

Using source localization, we further revealed that this psilocybin-induced decrease in lower-frequency oscillations was localized within an extended network that included the PCC, the RSC, the ACC, and parahippocampal regions. Interestingly, this network strongly overlaps with the default-mode network (DMN), which has been shown to be modulated by psilocybin in PET and fMRI studies (Vollenweider et al. 1997; Gouzoulis-Mayfrank et al. 1999; Carhart-Harris et al. 2012). Activity within the DMN has been associated with lower-frequency oscillations (Lu et al. 2007) and with altered states of consciousness induced for instance by anesthetics (Boly et al. 2008), serotonergic hallucinogens (Carhart-Harris et al. 2012), and meditation (Brewer et al. 2011). Thus, our findings indicate that psilocybin modulates default-mode functions by decreasing ongoing lower-frequency oscillations within this network, which may contribute to the psilocybin-induced alterations in the state of consciousness. Specifically, lower frequency oscillations, particularly in the alpha range, mediate rhythmic cortical inhibition of neuronal ensembles (Klimesch et al. 2007; Schroeder and Lakatos 2009; Buschman et al. 2012). Thus, the strong decrease in lower-frequency oscillations seen in this study may be indicative of a psilocybin-induced shift of the resting excitation/inhibition balance (E/I balance) toward excitation. This interpretation is also supported by the slight psilocybin-induced increase in high-gamma oscillations because gamma oscillations have been strongly associated with neuronal excitation (Merker 2013). Given the crucial role of lower-frequency oscillations in structuring processes at the cellular level (Haegens et al. 2011), the systemic level (Hanslmayr et al. 2013), and in consciousness (VanRullen and Koch 2003; Schroeder and Lakatos 2009), any profound decrease in lower-frequency oscillations is likely to disrupt the ordinary temporal structure of neuronal processes.

Taken together, these findings suggest that psilocybin elevates the E/I balance and disrupts the temporal structure of neuronal processes by decreasing lower-frequency (<20 Hz) oscillations within the extended DMN. This network has been implicated in self-referential processing (Gusnard et al. 2001); therefore, the increased excitability and disrupted temporal structure of neuronal processes may alter self-referential processes and thereby lead to psilocybin-induced alterations in a state of consciousness such as an increased sense of unity with the environment. However, although these alterations may play a role in altering consciousness, correlation analysis indicated that these alterations are not sufficient to alter consciousness because only the correlation between psilocybin-induced insightfulness and alpha2 (10.5–13 Hz) oscillations in the posterior occipito-parietal region during the eyes-open

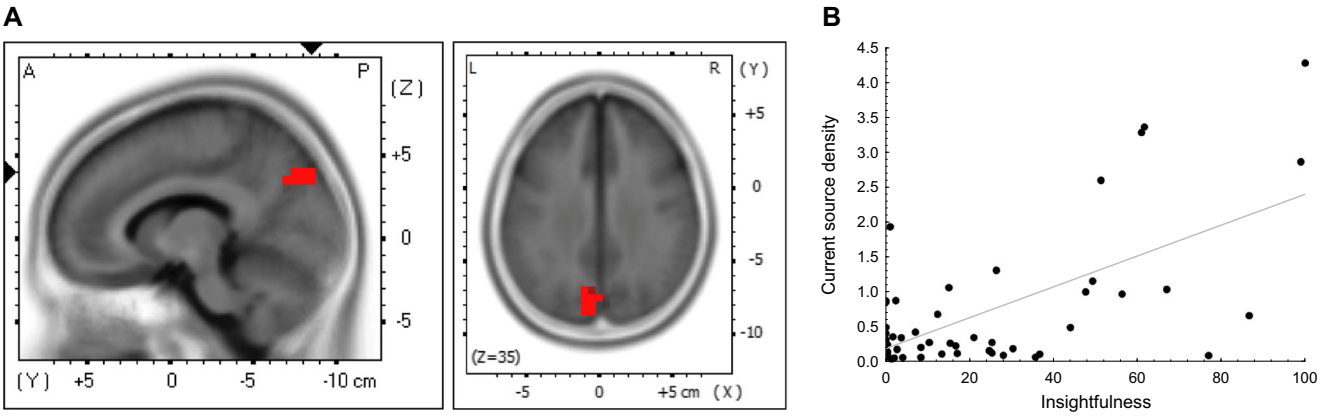

Fig. 3 **a** Statistical maps of the voxel-wise correlation between alpha2 oscillations (10.5–13 Hz) and score on the insightfulness subscale of the 5D-ASC in the eyes-open condition. *Red* depicts voxels where the correlation reached significance ($p<0.05$, corrected). **b** Scatterplot of the relation between the current source density of alpha2 oscillations (10.5–13 Hz) at $x=-10$, $y=-85$, $z=40$ and score on the insightfulness subscale of the 5D-ASC in the eyes-open condition

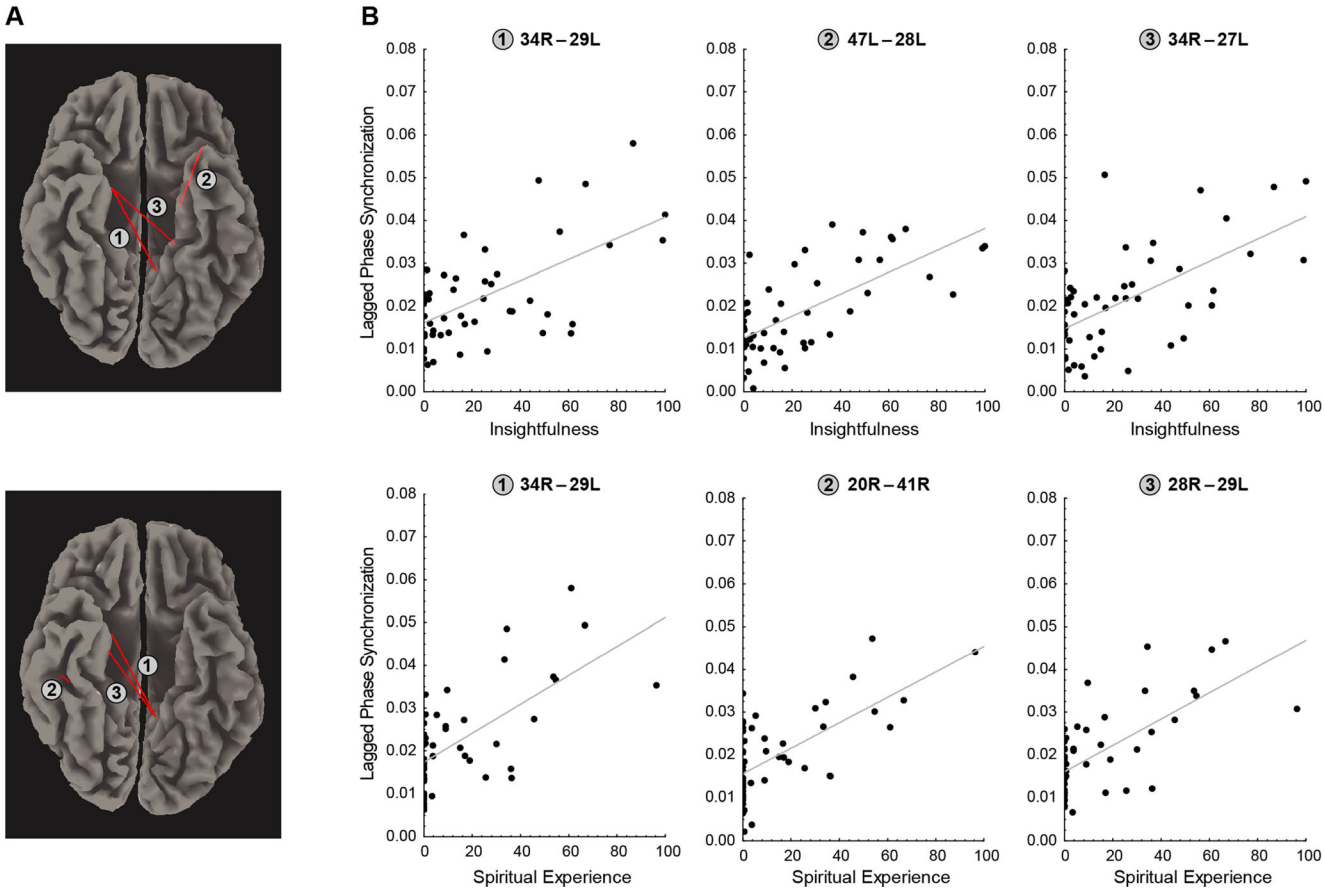

Fig. 4 **a** *Red lines* connects those pairs of Brodmann areas, where the correlations between lagged phase-synchronization values of delta oscillations (1.5–4 Hz) and score on the insightfulness (*top row*) and spiritual experiences (*bottom row*) subscales of the 5D-ASC reached significance during eyes-closed condition ($p<0.05$, corrected). Significant correlations are numbered form one to three to refer to the corresponding scatterplots displayed in **b.** **b** Scatterplots on the significant correlations

condition was significant after correction for multiple comparisons.

In contrast to the weak associations between current source density and state of consciousness, lagged phase synchronization was strongly associated with the psilocybin-induced state of consciousness. Given the crucial role of phase-synchronization in coordinating activity across brain areas (Buzsáki and Draguhn 2004; Siegel et al. 2012), this finding supports the view that neural integration, rather than activity, underlies the state of consciousness (Alkire et al. 2008). Specifically, we found that the intensity of psilocybin-induced insightfulness was associated with lagged phase synchronization of delta oscillations between parahippocampal regions, between parahippocampal regions and the RSC as well as between parahippocampal regions and the lateral orbitofrontal cortex. Because phase synchronization of parahippocampal oscillations in this frequency range has previously been linked to autobiographical memory retrieval (Fell and Axmacher 2011; Foster et al. 2013) and to the attribution of valence in memory (Wallis 2007), our finding suggests that psilocybin-induced insightfulness may be associated with increased retrieval and reattribution of autobiographic memories. In addition, scores of the spiritual experiences subscale of the 5D-ASC questionnaire were associated with increased lagged phase synchronization of delta oscillations between parahippocampal regions and the RSC. The RSC has previously been implicated in coding the location of oneself within a global spatial context (Bar and Aminoff 2003; Vann et al. 2009), and therefore, our finding may suggest that with increasing intensity of spiritual experiences, the self is reorganized within the global spatial context through phase synchronization of delta oscillations.

These interpretations fit well with the phenomenological descriptions of hallucinogen-induced insightfulness and spiritual experiences. Hallucinogen-induced insightfulness is characterized by a deep understanding of personal life and existence (Cott and Rock 2008), which could well explain, why increased autobiographical retrieval and reattribution processes may be present during insightfulness. Furthermore, hallucinogen-induced spiritual experiences include a shift in the perception of one's self and one's existence (Grob et al. 2013) and were defined in our study according to the 5D-

ASC questionnaire as a profound experience of awe and connectedness to a superior power (Studerus et al. 2010). These phenomenological descriptions match well with our interpretation that psilocybin-induced spiritual experiences are associated by a reorganization of the self within the global spatial context mediated by phase synchronization of delta oscillations. Finally, phenomenological studies found that psilocybin-induced insightfulness and spiritual experience often occur together (Studerus et al. 2011), which fits well with our finding that these states are mediated by phase-synchronization in a partially overlapping network.

Interestingly, the revealed network phase-synchronization processes were specifically associated with insightfulness and spiritual experiences, as defined by the 5D-ASC questionnaire, but not with other psilocybin-induced phenomena such as blissful states or disembodiment. Furthermore, after correction for multiple comparison, the correlation was only seen during eyes-closed condition. These findings suggest first that the revealed associations are specific for these two experiences, but likely additional network processes are implicated in a full blown mystical/spiritual experience that fulfills all the criteria by Stace (1961) and is quantified by the SOCQ questionnaires (Griffiths et al. 2006). Second, our results suggest that eyes-closed conditions might be particularly suitable to investigate the neuronal processes associated with insightfulness and spiritual experiences, which is in accordance with the use of eye-shades in some previous phenomenological studies that aimed to specifically investigate psilocybin-induced spiritual experiences (Griffiths et al. 2006).

The neuronal network processes we identified as underlying spiritual experiences and insightfulness may constitute a crucial pathway that can be modulated by serotonergic receptors to regulate mental health. This notion is supported by reports that spiritual experiences promoted sustained well-being and resilience (McClain et al. 2003; Southwick and Charney 2012) and that psilocybin had therapeutic effects in treating mood disorders (Vollenweider and Kometer 2010) and in reducing anxiety in terminal cancer patients (Grob et al. 2011). Thus, in future studies, it will be interesting to test whether lagged phase synchronization between the RSC, the parahippocampus, and the lateral orbitofrontal area can promote mental health through the activation and reattribution of autobiographical memory and the reallocation of the self in a global spatiotemporal context.

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Conflict of interests Prof. Vollenweider is board member of Heffter Research Institute. None of the author has a conflict of interest with regard to this study.

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