Psilocybin induces aberrant prediction error processing of tactile mismatch responses – a simultaneous EEG-FMRI study

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Abstract

As source of sensory information, the body provides a sense of agency and self/non-self-discrimination. The integration of bodily states and sensory inputs with prior beliefs has been linked to the generation of bodily self-consciousness. The ability to detect surprising tactile stimuli is essential for the survival of an organism and for the formation of mental body representations. Despite the relevance for a variety of psychiatric disorders characterized by altered body and self-perception, the neurobiology of these processes is poorly understood. We therefore investigated the effect of psilocybin (Psi), known to induce alterations in self-experience, on tactile mismatch responses by combining pharmacological manipulations with simultaneous EEG-fMRI recording. Psi reduced activity in response to tactile surprising stimuli in frontal regions, the visual cortex, and the cerebellum. Furthermore, Psi reduced tactile mismatch negativity EEG responses at frontal electrodes, associated with alterations of body- and self-experience. This study provides first evidence that Psi alters the integration of tactile sensory inputs through aberrant prediction error processing and highlights the importance of the 5-HT_{2A} system in tactile deviancy processing as well as in the integration of bodily and self-related stimuli. These findings may have important implications for the treatment of psychiatric disorders characterized by aberrant bodily self-awareness.

Introduction

The skin, as the body's largest organ, is our first contact point with the environment and is central to the processing of boundaries and Self/Non-Self discrimination (Allen et al. 2016; Kahl and Kopp 2018). The body, as a source of sensory information, is considered the starting point of our self-awareness and provides a sense of agency and ownership (Tsakiris 2017). Furthermore, affective and cognitive processes are deeply rooted in the body's interaction with the environment (Wilson 2002; Damasio and Carvalho 2013). However, any disruption in this complex system of multisensory processing and integration of sensory signals has an effect on our bodily self-awareness (Tsakiris 2017). Altered bodily self-perception is a core symptom of many psychiatric disorders, such as schizophrenia (Sakson-Obada et al. 2018), depression (Fuchs and Schlimme 2009) or anorexia nervosa (Gadsby 2017).

The ability to react to novel or surprising environmental stimuli is essential for survival as well as for the mental and physical health of an organism (Riva 2018). In general, surprising stimuli imply higher motivational importance. At the same time, our prior expectations affect our subjective perception (Clark 2013). Being able to detect and discriminate surprising stimuli from habituated ones and to adapt by forming new memory traces or updating mental representations fulfill an important role in the maintenance of a homeostatic level (Damasio 2012; Craig 2009; Riva 2018).

The predictive coding account offers a framework for understanding processes underlying the bodily self and their importance in psychiatric disorders (Friston 2005; Seth 2013; Allen 2020a; Allen et al. 2020; Owens et al. 2018; Allen et al. 2019). The brain learns to model and predict incoming sensory input to minimize surprise across different body representations. Discrepancy between the predicted and the actual incoming bottom-up content produces a predictions error (PE) signal. Subsequently, this PE is minimized by updating the mental model (Friston 2005; Seth 2013; Tsakiris 2017). It is suggested that the integration of bodily states and sensory inputs

with prior beliefs underlies the generation of self-awareness (Seth 2014; Tsakiris 2017; Lenggenhager et al. 2007).

The mismatch negativity (MMN) is an event-related brain potential (ERP) that provides an index for the neural processes underlying the initial response to unpredicted stimuli (Wacongne, Changeux, Dehaene 2012) and has been linked to perceptual learning and neuroplasticity (Garrido et al. 2009). The MMN can be elicited by a novel stimulus called the "deviant" after presentation of repeated habituated stimuli called the "standards" (Näätänen et al. 2014). The occurrence of an MMN is independent of the level of attention towards the stimuli and has been reported across different sensory modalities (Kekoni et al. 1997; Näätänen et al. 2007; Pazo-Alvarez, Cadaveira, Amenedo 2003; Allen et al. 2016). Clinical studies have linked a reduced MMN amplitude to aberrant perceptual learning, e.g. in patients with alterations of sensory information processing such as schizophrenia (Umbricht and Krljes 2005; Baldeweg et al. 2004). Interestingly, these disorders are also characterized by disturbances in body image and self-experiences (Sakson-Obada et al. 2018).

Serotonergic psychedelics, such as psilocybin (Psi) or lysergic acid diethylamide (LSD) exert their psychological effects primarily via 5-HT_{2A} receptor activation (Vollenweider et al. 1998; Halberstadt and Geyer 2011; Preller et al. 2017) and are valuable tools to study brain mechanisms of consciousness, cognition, and emotion. Furthermore, recent results indicate the therapeutic potential of psychedelic-assisted therapy as effective treatment option for various psychiatric disorders (Carhart-Harris et al. 2018; Grob et al. 2011; Bogenschutz et al. 2015; Rucker et al. 2016; Bogenschutz and Ross 2018). Psi produces a dose-dependent altered state of consciousness and induces transient and reversible alterations in body and self-perception which are closely linked to each other (Preller and Vollenweider 2018; Studerus et al. 2011; Vollenweider and Kometer 2010).

Recent studies have investigated the effects of serotonergic psychedelics on the MMN in the auditory domain. However, results have been inconsistent (Bravermanová et al. 2018; Schmidt et al. 2012; Umbricht et al. 2002; Umbricht et al. 2003).

The impact of psychedelics on the processing of tactile mismatch responses has not been investigated so far. Given that psilocybin induces alterations in self/body boundaries, feelings of oneness, and disembodiment, previously associated with changes in frontal glucose metabolism (Vollenweider 1997), investigating tactile deviancy processing after the administration of Psi offers the unique opportunity to gain valuable insights into the neurobiological processes that give rise to the formation of bodily awareness and self-experience. Leveraging simultaneous EEG-fMRI data acquisition furthermore allows us to investigate neuroanatomical substrates as well as computational mechanisms underlying these processes.

This study therefore investigated the impact of Psi on the processing of tactile mismatch responses induced by a tactile oddball paradigm during simultaneous EEG-fMRI measurement (Allen et al. 2016). We hypothesized that Psi compared to placebo (Pla) 1) induces changes in the BOLD signal in brain regions previously found to be involved in tactile deviancy processing (Allen et al., 2016; Fardo et al., 2017; Ostwald et al., 2012), 2) reduces the EEG-MMN amplitude, and that 3) these changes are correlated with subjective alterations in self and body experience. Collectively, this pharmacological neuroimaging study demonstrates that Psi-induced alterations in body and self-perception are related to changes in the neural response to surprising tactile vs. habituated stimuli in particular in frontal brain regions, indicating alterations in the integration of tactile sensory inputs through aberrant PE processing and potentially reduced memory trace formation of tactile information.

Materials and Methods

Participants

Participants were recruited through advertisements placed at local universities. Before admission to the study, participants underwent a screening visit. All included subjects were aged between 20 – 40 years and healthy according to medical history, physical examination, blood analysis and electrocardiography. The Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al. 1998), the DSM-IV self-rating questionnaire for Axis-II personality disorders (SCID-II) (Fydrich et al. 1997) and the Hopkins Symptom Checklist (SCL-90-R) (Franke 1995) were used to exclude subjects with present or previous psychiatric disorders or a history of major psychiatric disorders in first-degree relatives. Participants were asked to abstain from the use of any prescription or illicit drugs for a minimum of two weeks prior to the first test day and for the duration of the entire study, and to abstain from drinking alcohol for at least 24 h prior to test days. To verify the absence of drug and alcohol use, urine tests and a self-report questionnaire were used at the beginning of each test day. Urine tests were also used to exclude pregnancy. Furthermore, participants were required to abstain from drinking caffeine during the test day and to abstain from smoking for at least 60 mins before MRI assessment. Further exclusion criteria included history of head injury or of neurological disorders, cardiovascular disease, history of alcohol or drug dependence, left-handedness, poor knowledge of the German language, any exclusion criteria for MRI studies (including claustrophobia), and previous significant adverse reactions to a hallucinogenic drug.

The initial sample consisted of 24 healthy participants. To ensure interpretability of the data, participants with excessive head movement in the fMRI (>3mm in any direction) or poor EEG data quality (<50% clean segments in the ERP analysis) were excluded from data analysis. Six participants were excluded due to poor EEG or fMRI data quality in at least one of the sessions.

Additionally, three participants were excluded because of malfunctioning equipment for delivering the electrical stimulation. Therefore, the final sample consisted of 15 participants (*n* = 10 men and *n* = 5 women; mean age = 26.86 years).

Before participating, all participants provided written informed consent after having received detailed written and oral descriptions of the study procedures, as well as details regarding the effects and possible risks of Psi administration in accordance with the Declaration of Helsinki. The study was approved by the Cantonal Ethics Committee of Zurich (KEK), and the Swiss Federal office of Public Health (BAG) authorized the use of Psi in humans. The study was registered at clinicaltrials.gov (NCT03736980). No substantial side effects were recorded during the study. One participant reported transient sleep disturbances for one night and three participants reported mild transient headaches after drug administration. No further side effects were recorded.

Study design and procedure

This study employed a double-blind, randomized, placebo-controlled, crossover design. At two different occasions at minimum two weeks apart, each participant received either:

1) Placebo (179 mg mannitol and colloidal silicon dioxide [Aerosil; Evonik Resource Efficiency GmbH, Essen, Germany] 1 mg orally; Pla condition)
2) Psilocybin (0.2 mg/kg body weight, orally; Psi condition)

The Roving Somatosensory Oddball Task (RSOT) was conducted 85 minutes after Psi/Pla administration during the plateau of peak subjective Psi effects. Subjective drug effects were assessed using the Five-Dimensional Altered States of Consciousness Rating Scale (5D-ASC) (Dittrich 1998; Studerus, Gamma, Vollenweider 2010) 360 min after each drug treatment to retrospectively assess the subjective experience after drug intake.

Roving somatosensory oddball task

Stimuli of the RSOT consisted of somatosensory electrical stimulation (50 ms pulse duration) on the median nerve of the left forearm at about twice the individual perceptual threshold. To induce tactile mismatch responses, trains of stimuli switched randomly between high and low intensity after a variable number of 3 to 7 repetitions (Allen et al. 2016). Low intensity trains consisted of single pulses separated by 2000 ms intervals. High intensity trains consisted of two pulses delivered in a rapid sequence (100 ms stimulus onset asynchrony) followed by 2000 ms interstimulus intervals.

The first stimulus of each new train was modelled as the "deviant (D)" and each third repetition in a train as "standard" (S). For the high intensity condition, the S stimulus was modelled as the onset of the second pulse of the third repetition. Trains of stimuli varying from 3 to 7 repetitions were uniform randomly sampled to generate an unpredictable stimulus sequence. Two test versions (A and B) were developed and administered in a counter-balanced randomized order to the subject on the two experimental days. Participants received a total of 320 stimuli in each session of which 69 stimuli were D and 69 stimuli were S. The duration of the task was approximately 13 mins. All stimuli were delivered using a MR-safe electrode and a constant current stimulator (Digitimer, 7SHVA; for an overview of the experimental setup see **Supplementary Methods, Fig. S1**).

The individual perceptual threshold was determined immediately prior to scanning in each drug condition using an adaptive staircase procedure (adapted from (Allen et al. 2016), **Supplementary Methods, Table S2**). The staircase procedure consisted of a one-up/three down procedure. Step size was reduced every two reversals until reaching the individual threshold. After the individual threshold was reached, the intensity was doubled and then reduced until participants did not perceive it as uncomfortable. The participants reported the

sensation as a mild "pinching", but not painful. Thresholds and intensities are reported in **Table S2**. The mean of the participant's individual perceptual threshold differed significantly between Pla and Psi conditions ($p = 0.017$), however, there was no significant difference for the mean of the participant's final intensities between treatments ($p > 0.1$). Participants were instructed to pay attention (Allen 2020b) to each single stimulus. After the thresholding procedure and a short practice version of the oddball task, the main experiment started after each participant confirmed that they had fully understood the task.

FMRI data acquisition and preprocessing

Magnetic resonance data were acquired on a Philips Achieva 3.0T whole-body scanner (Best, The Netherlands). A 32-channel receive head coil and MultiTransmit parallel radio frequency transmission was used. Images were acquired using a whole-brain gradient-echo planar imaging (EPI) sequence (repetition time = 2,430 ms; echo time = 27 ms; slice thickness = 3 mm; 45 axial slices; no slice gap; field of view, 240 × 240 mm^2; in-plane resolution, 3 × 3 mm; sensitivity-encoding reduction factor, 2.0). Additionally, high-resolution anatomical images (voxel size, 0.7×0.7×0.7 mm^3) were acquired using a standard T1-weighted 3D magnetization prepared rapid-acquisition with gradient echo sequence. Images were analyzed using SPM12 (www.fil.ion.ucl.ac.uk). Preprocessing consisted of slice time correction, realignment, spatial normalization to the standard EPI template of the Montreal Neurological Institute (MNI), and spatial smoothing using a Gaussian kernel of 8-mm FWHM to meet the statistical requirements of the general linear model (GLM). For the detection and repair of artefacts due to movement during scanning the ArtRepair toolbox was used (http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html).

FMRI data analysis

fMRI images were analyzed using a general linear model (GLM) implemented in SPM12. To identify BOLD responses to tactile surprising stimuli represented by the deviants we applied a standard summary statistic approach. At the first level, we modelled deviants (D, first stimuli of each new train) and standards (S, the third repetition following each D) as separate event-related regressors convolved with the canonical hemodynamic response function. The remaining repetition trials (S2 und S4-S7) were not modelled, i.e., they were left as "implicit baseline". For a second analysis modelling the final stimulus of each train as standard, see **Fig. S2**. The contrast D > S was computed for each participant.

To identify brain regions sensitive to deviancy processing the contrast D > S was entered into a second-level random-effects group analysis using a paired t-test for the comparison between drug treatment conditions (Pla > Psi, Psi > Pla) with a threshold of $p < 0.05$ cluster level family-wise-error (FWE) corrected with a cluster-defining primary threshold of $p < 0.001$ to meet the requirements of random field theory. All brain coordinates are reported in the MNI atlas space.

EEG aquisition and preprocessing

Simultaneous EEG-fMRI was recorded using an MR-compatible EEG system (64 Channels BrainAmp MR Plus; Brain products GmbH, Germany). The Fz electrode served as recording reference, the AFz as ground and two electrocardiogram (ECG) electrodes for the cardioballistogram correction (CBC). The EEG signal of all electrodes was recorded with a sampling rate of 5000 Hz (DC). Data were lowpass filtered with a cut-off of 250 Hz for scalp electrodes and 1000 Hz for ECG channels. Impedances were kept below 30 kΩ. To minimize gradient residuals occurring during simultaneous EEG-fMRI recordings the EEG system was synchronized to the scanner clock (Philips Achieva 3.0T) (Mandelkow et al. 2006).

Data were analyzed by using Brain Vision Analyzer 2.1 software (Brain Products GmbH). Preprocessing consisted of the following steps: MR gradient artefact removal using

implemented sliding average subtraction (Allen et al., 2000), visual inspection and manual exclusion of periods with major artefacts, topographic interpolation, ballistocardiogram correction, ocular and residual ballistocardiogram artefacts were removed using independent component analysis (ICA; (Bell and Sejnowski 1997), re-referencing to the average reference (Lehmann and Skrandies 1980), band-pass filtering between 0.1 and 30 Hz (notch filter 50 Hz), automatic artifact removal of artefacts exceeding +/-100µV.

EEG-ERP analysis

Stimulus locked EEG segments were created based on the marker position of the D and S stimuli types (epochs from -100 ms prestimulus to +700 ms poststimulus, averaging type-wise) per condition. After artefact rejection, at least 63 S stimuli (mean S = 63.53, i.e. more than 92%) and 64 D stimuli (mean D = 64.01, i. e. more than 92%) were available for the Pla condition. For the Psi condition at least 53 S stimuli (mean S = 53.7, more than 78 %) and 55 D stimuli (mean D = 55.3, more than 80%) were available after artefact rejection. The EEG segments were baseline corrected using the -100 to 0 ms prestimulus interval as baseline.

The time interval for the ERP analysis was defined based on inspection of the global field power (GFP), a measure of global field strength (Lehmann and Skrandies 1980), computed over the grand average of D and S stimuli types for each condition. Visual inspection of the highest GPF mean amplitudes of the grand average for each drug condition and D and S stimuli types defined the interval 216 – 414 ms as time window for the ERP analyses (see **results section, Fig. 2**).

The mean amplitudes of this time window (216 – 414 ms) were calculated for each condition (Pla and Psi) and stimulus type (S and D) for the frontal electrodes (Fp1, Fp2 and AF2). The selection of the electrodes was based on the visual inspection of the topographical maps of activity for standard and deviant stimuli during this time interval defined by the GFP and the literature based somatosensory MMN electrodes clusters (Strömmer, Tarkka, Astikainen 2014).

A repeated measures analyses of variance (ANOVA) was performed to compare mean amplitudes between stimulus type (S, D), electrodes (Fp1, Fp2, AF2) and condition (Pla, Psi) as within subject factors. Analyses were conducted using Brain Vision Analyzer 2.1 and IBM SPSS Statistics 23 software (IBM, Chicago, Illinois, USA).

Subjective drug effects: Five-Dimensional Altered States of Consciousness Questionnaire (5D-ASC)

The 5D-ASC is a standardized questionnaire that comprises 94 items that are answered on visual analogue scales. Scores were calculated for 11 validated second order scales (Studerus, Gamma, Vollenweider 2010): experience of unity, spiritual experience, blissful state, insightfulness, disembodiment, impaired control and cognition, anxiety, complex imagery, elementary imagery, audiovisual synesthesia, and changed meaning of perception. The 5D-ASC second order scales were analyzed using a repeated-measures ANOVA with condition (Pla, Psi) and scale as within-subject factors.

Correlations between subjective drug effects, fMRI and EEG effects

An exploratory analysis was conducted to investigate the relationship between subjective drug-induced alterations in body perception and the EEG and fMRI responses to the Psi-induced changes in the processing of tactile surprising stimuli. We therefore correlated the 5D-ASC scores “experience of unity” and “disembodiment” in the Psi condition with the tactile MMN response (i.e., the subtraction of the mean amplitude in response to the S stimulus from the amplitude of the D stimulus) averaged across participants at the frontal electrodes (Fp1, Fp2 and AF2) for the time window 216 – 414 ms in the Psi condition, and the first eigenvariate of clusters showing a significant difference of D > S in the Pla condition compared to Psi in the fMRI data. Analyses were conducted by using IBM SPSS Statistics 21 Software (IBM, Chicago, Illinois, USA) and carried out with a significance level of $p < 0.05$ (two-tailed).

Results

Psilocybin changes Deviant-Standard discrimination in the frontal and visual cortex and the cerebellum

Results for the D > S contrast in the Pla condition are reported in the **Supplementary Material, Table S1.** Comparing the Pla vs. Psi condition for the D > S contrast revealed a significantly reduced BOLD signal in the ventromedial prefrontal cortex (vMPFC) (peak: x = -9 y = 56 z = 29, k = 53, T = 5.44), dorsomedial prefrontal (dMPFC) (peak: x = 0 y = 35 z = 53, k = 40, T = 5.04) (**Fig. 1A**), primary visual cortex (V1) (peak: x = -3 y = -94 z = -7, k = 40, T = 4.57) (**Fig. 1B**) and the cerebellum (peak: x = 30 y = -61 z = -31, k = 42, T = 5.86) (**Fig. 1C**) (all $p < 0.05$, FWE corrected). Beta values are displayed in **Fig. 1D**. No significant Psi-induced increases in BOLD signal for the D > S contrast were observed ($p < 0.05$, FWE corrected).

The analysis of the subjective drug effects assessed with the retrospectively administered 5D-ASC questionnaire with a repeated measures ANOVA (condition*scale) revealed a significant main effect for treatment ($F(1, 14 = 37.3$, $p < 0.001$) and scale ($F(10, 140) = 7.821$, $p < 0.001$) and a significant condition*scale interaction ($F(10, 140) = 7.103$, $p < 0.001$). Bonferroni corrected simple main effect analyses showed that Psi increased all 5D-ASC scores compared to Pla (all $p < 0.05$) except for “spiritual experience” and “anxiety” ($p > 0.05$, **Fig. 1E**).

Fig. 1. fMRI results and subjective effects. Significant differences in BOLD signal for *Placebo* > *Psilocybin* in the *Deviant* > *Standard* contrast at **(A)** vMPFC (peak: x = -9 y = 56 z = 29) and dMPFC (peak: x = 0 y = 35 z = 53), **(B)** V1 (peak: x = -3 y = -94 z = -7), **(C)** cerebellum (peak: x = 30 y = -61 z = -31) (all $p < 0.05$, FWE corrected); Blue shades represent a Psi-induced decrease in BOLD signal. Colorbars indicate t-values. **(D)** Comparison of the Beta values between conditions for significant clusters. Data are displayed as mean and standard error of the mean. **(E)** Subjective drug effects of the Pla and Psi condition expressed as percent of the scale maximum. Retrospectively assessed with the 5D-ASC questionnaire 360 min after drug administration. Psi significantly increased all scale scores compared to Pla except for spiritual experience and anxiety. Data are expressed as mean and standard error of the mean. Asterisks indicate significant differences between Psi and Pla conditions, *$p < 0.05$, Bonferroni corrected, *n* = 15 participants. VMPFC, ventromedial prefrontal cortex; dMPFC,

dorsomedial prefrontal cortex; V1, primary visual cortex; D, deviant; S, standard; Psi, Psilocybin; Pla, Placebo.

Psilocybin changes GFP mean amplitude in the time window 216 - 414 ms

We computed the GFP over the grand average per condition and stimuli type to define the time interval for the ERP analysis (see below). Comparison of GFP mean amplitudes between condition and stimuli types in the time window 216 – 414 ms showed higher amplitudes for D compared to S stimuli in the Pla condition. In the Psi condition the opposite pattern appeared, with S stimuli showing higher GFP mean amplitudes than D. Visual inspection of the mean amplitudes between the conditions points towards higher overall GFP mean amplitudes in the Psi compared to Pla condition for both stimuli types.

Fig. 2. Global Field Power of the grand average waveforms. (A and B) GFP for standard and deviant stimuli in the Pla **(A)** and Psi **(B)** conditions. Red backgrounds indicate the stimulus onset and duration. Grey backgrounds indicate the 216 - 414 ms time window after stimulus onset. GFP represents the global field strength for the potential fields of the grand average waveforms. **(C and D)** Topographical maps of activity for standard and deviant stimuli during the second time window (216 – 414 ms) defined by the GFP for Pla **(C)** and Psi **(D)**. Topographical maps illustrate the potential field distribution over the whole scalp. **(E)** GFP mean amplitude for each condition (Pla and Psi) and stimuli type (S and D) in the time window 216 – 414 ms after stimulus onset **(F)** GFP mean amplitude for the difference of standard and deviant (S minus D) for each condition (Pla and Psi). $n = 15$. GFP, global field power; μV, microvolt; ms, millisecond; Pla, placebo; Psi, psilocybin; S, standard; D, deviant.

Psilocybin induces changes in the somatosensory EEG-MMN response

The ERP analysis was based on the time window (216 – 414 ms) as identified above. The selection of the electrodes was based on visual inspection of the topographical maps of activity for standard and deviant stimuli during this time interval (216 – 414 ms) defined by the GFP as well as on previous studies investigating somatosensory MMN (Strömmer, Tarkka, Astikainen 2014). A repeated measures ANOVA (electrode*condition*type) of the mean amplitudes of the

frontal electrodes (Fp1, Fp2, AF2) during the time interval 216 - 414 ms revealed a significant main effect for electrodes ($F(2, 28) = 11.607$, $p < 0.001$) and a trend for the interaction of type*condition ($F(1, 14) = 3.636$, $p = 0.077$). Furthermore, there was a significant interaction for type*condition for the electrodes Fp2 ($F(1,14) = 4.824$, $p = 0.045$) and AF2 ($F(1, 14) = 5.129$, $p = 0.040$). Simple main effect analyses revealed a significant difference between S and D in the Pla condition for Fp1 $t(14) = 2.328$, $p < 0.035$) and AF2 ($t(14) = 2.433$, $p < 0.029$) and a trend for Fp2 ($t(14) = 2.138$, $p = 0.051$). There was no significant difference in the Psi condition between S and D ($p > 0.28$) at these electrodes (Fp1, Fp2, AF2) (see **Fig. 3).** To investigate the influence of Psi on early sensory components, the mean amplitude during the time interval 0 – 50 ms was analyzed analogously. This analysis did not reveal any significant main effects or interactions (all $p > 0.05$).

Fig 3. Grand mean average waveforms at frontal electrodes Fp1, Fp2, AF2 (A) ERPs at 216 - 414 ms (grey background) after stimuli onset (red background) of S and D per condition Pla (above) and Psi (below), **(B)** Box plots for mean amplitudes at frontal electrodes (Fp1, Fp2, AF2) elicited for S and D per condition showing median, quartiles and range. Asterisks indicate significant differences in mean amplitudes. **(C)** Tactile MMN (D – S waveforms) at frontal electrodes for Pla and Psi in the time window 216 – 414 ms (grey background) after stimuli onset (red background) at frontal electrodes. *$p < 0.05$; n = 15. Pla, placebo; Psi, psilocybin; μV, microvolt.

Correlations between subjective alterations in body perception and tactile MMN responses

To investigate for associations between Psi-induced subjective alterations in body and self-perception and tactile MMN responses, we correlated the 5D-ASC scores "experience of unity" and "disembodiment" in the Psi condition with the tactile MMN response (i.e., the subtraction of the mean amplitude in response to the S stimulus from the amplitude of the D stimulus) averaged across participants at the frontal electrodes (Fp1, Fp2 and AF2) for the time window 216 – 414 ms in the Psi condition, and the first eigenvariates of clusters showing a significant difference of D > S in the Pla condition compared to Psi in the fMRI data. A significant positive Pearson correlation was found between the 5D-ASC scale "disembodiment" and tactile MMN responses in the Psi condition ($r = 0.630$, $p = 0.012$, **Fig. 4A**.). Furthermore, we found a positive relationship between the 5D-ASC scale "experience of unity" and tactile MMN responses at AF2 in the Psi condition ($r = .578$, $p = 0.024$, **Fig. 4B**.). Both 5D-ASC scales "disembodiment" and "experience of unity" were positively correlated ($r = 0.698$, $p = 0.004$). No significant correlations were observed for other electrodes (all $p > 0.05$). Furthermore, the first eigenvariates of clusters showing a significant decrease of BOLD signal in the Psi condition compared to Pla for the contrast D > S (**Fig. 1D)** did not correlate significantly with Psi-induced disembodiment, experience of unity, or tactile MMN responses at frontal electrodes in the Psi condition (all $p > 0.05$).

Fig 4. Correlations between subjective alterations in body perception and tactile MMN responses (mean amplitude of the difference wave (D – S)) in the Psi condition. (A) Positive association between the 5D-ASC scale disembodiment and tactile MMN responses at AF2 in in the Psi condition ($r = 0.63$, $p = 0.012$). **(B)** Positive association between the 5D-ASC scale experience of unity and tactile MMN responses at AF2 in the Psi condition ($r = 0.58$, $p = 0.024$). Data points are color coded for each individual and rank-ordered according to their difference wave value. Grey background in scatterplots indicates the 95% confidence interval. *n* =15. MMN, mismatch negativity; DE, disembodiment; EU, experience of unity; Psi, psilocybin.

Discussion

This study provides first evidence that stimulation of the serotonin (5-HT) receptor system with Psi alters the processing of tactile mismatch responses by combining pharmacological manipulation with simultaneous EEG-fMRI recording. For this our results show the advantage of fMRI for the spatial resolution as well as the temporal resolution of the EEG. Our results show that Psi compared to Pla 1) decreases the BOLD signal in response to surprising tactile stimuli vs. habituated stimuli in brain regions previously found to be involved in tactile deviancy processing (Allen et al. 2016), 2) reduces the EEG-MMN amplitude and 3) produces robust perceptual alterations of bodily awareness and self-experience which are associated with tactile MMN responses at the frontal AF2 electrode in the Psi condition.

Psilocybin reduces the BOLD signal in frontal and visual areas in response tactile surprising stimuli

Psi significantly reduced the BOLD signal in response to tactile surprising vs. habituated stimuli in the vMPFC, dMPFC, V1 and the cerebellum. Therefore, our fMRI data reveal that Psi alters deviancy processing and points towards an important role of the serotonin system in perceptual tactile processing and the ability to discriminate tactile deviant stimuli from habituated ones. Our results are in line with previous studies showing that the medial prefrontal cortex (MPFC) is involved in salience processing (Seeley et al. 2007) and represents a key region for the integration of self-related information (Schmitz and Johnson 2007). Stimulation of the 5-HT_{2A} receptor has been shown to induce alterations in self/other boundaries (Vollenweider et al. 1998; Quednow et al. 2012; Kometer et al. 2012) and self-relevance processing associated with altered activity of the MPFC (Preller et al. 2017; Preller and Vollenweider 2018). Furthermore, the MPFC is crucial in the construction and maintenance of a coherent self (Vollenweider 2001). Our results showing that Psi alters activity primarily in frontal brain areas but not somatosensory brain regions during tactile deviancy processing are also in line with recent

formulations of the Global Neuronal Workspace Theory suggesting that higher-level areas such as the PFC play a key role for global broadcasting of information and amplifying and sustaining relevant stimuli (Whyte and Smith 2020; Liu et al. 2019; Mashour et al. 2020).

Activation of V1 during deviancy processing in the Pla compared to Psi condition may reflect the impact of visual processing on tactile perception (Kuehn and Pleger 2018). Vision can exert a top-down influence on the integration and localization of tactile information. Previous studies showed that the ability to discriminate tactile stimuli is enhanced when the body part is viewed. Furthermore, other studies using the of the rubber hand illusion demonstrated that visual illusions can affect the experience of body ownership (Welch and Warren 1980; Press et al. 2008; Tsakiris 2017; Botvinick and Cohen 1998). The visual top-down influence on tactile information processing may be altered in the Psi condition where we found reduced activation in the V1 compared to Pla in the D > S contrast. Psi has been shown to induce aberrant visual sensory integration and to alter the visual perceptual experience, potentially due to an increase in internal-driven excitability of the visual network via serotonergic modulation (Kometer et al. 2013; Preller and Vollenweider 2018). Furthermore, Psi-induced visual illusions have been linked to the emotion system and changes in the meaning of percepts (Preller and Vollenweider 2018). Psi-induced visual experiences and aberrant visual integration may therefore change top-down processing of tactile sensory information as well as bodily self-awareness (Tsakiris 2017). Additionally, the cerebellum has been proposed to play a critical role in generating predictions concerning upcoming sensory information (Courchesne and Allen 1997) and is also involved in perceptual and cognitive processes (Schmahmann 1997).

Psilocybin induces a reduction of tactile MMN responses associated with subjective alterations in body perception

In the Pla condition, we found the expected MMN response in line with previous findings on the somatosensory MMN, i.e. negativity after D compared to S stimuli over frontal electrodes

(Strömmer, Tarkka, Astikainen 2014). The mean amplitudes in the Pla condition differed significantly between D and S stimuli, showing more negativity in response to D at frontal electrodes – a results that is in line with significantly increased BOLD signal in frontal brain regions in the D > S contrast in the Pla condition. In the Psi condition, however, mean amplitudes at frontal electrodes between D and S did not differ significantly. Psi therefore reduced MMN responses to tactile surprising stimuli compared to Pla. This is also in line with our fMRI results showing that Psi decreased the differential activation of frontal brain regions in response to D vs. S stimuli. Furthermore, comparison of GFP mean amplitudes between conditions indicates higher mean amplitudes for S stimuli in the Psi compared to the Pla condition, whereas within the Pla condition D stimuli revealed higher mean amplitudes compared to S stimuli. Additionally, visual inspection of the GFP mean amplitudes between the conditions points towards an increase in overall GFP activity in response to all stimuli in the Psi condition indicating a heightened sensitivity in response to all stimuli regardless of habituation. This suggests a reduced adaptation mechanism that could be caused by difficulties in forming new memory traces, potentially due to a hypersensitivity to all incoming inputs. This may lead to aberrant salience processing making it difficult to discriminate between D and S stimuli. This finding is in line with another recent study showing increased neural response to S stimuli and less divergence between S an D stimuli in an auditory oddball task under LSD (Timmermann et al. 2018). Furthermore, changes in subjective alterations in disembodiment and experience of unity were positively correlated with the tactile MMN amplitude at the frontal AF2 electrode in the Psi condition. This indicates an association between altered self and body perception with changes in the negativity response after a tactile mismatch stimuli corroborating the hypothesis that tactile sensory processing may underlie bodily self-perception (Tsakiris 2017).

Contrary to previous studies reporting no significant reduction of the auditory MMN amplitude after Psi administration (Schmidt et al. 2012; Bravermanová et al. 2018; Umbricht et al. 2003; Umbricht et al. 2002), we found a significant reduction of tactile MMN responses under Psi but no evidence of an impact on early sensory components before the expected MMN. Tactile deviancy processing is potentially more directly related to the sensory integration of bodily and self-related stimuli in the body's multisensory system to construct our sense of self (Tsakiris 2017). Stimulation of the 5-HT_{2A} receptor therefore seems to play an important role in the disruption of the integration of self-related stimuli and interferes with the formation of a coherent self-experience.

Psilocybin induces aberrant prediction error processing

Adaptation of bodily representations is a constantly ongoing process during the processing of sensory inputs. These representations remain plastic and are constantly shaped through the integration of our experiences with our expectations (Apps and Tsakiris 2014). In terms of predictive coding these representations and its predictions depend on top-down prior expectations that are constantly updated based on PE signals that are produced by unexpected sensory information (Friston 2005).

Psi induced effects on the bodily self-experience can be explained in terms of predictive coding (Friston 2005; Apps and Tsakiris 2014), specifically its effects on bottom-up and top-down processing. Psychedelics have been suggested to alter bottom-up processing via increased thalamo-cortical connectivity (Preller et al. 2018). Increased excitatory connections from the thalamus following 5-HT_{2A} stimulation could lead to a sensory overload resulting in a heightened bottom-up "surprise" signal (Preller et al. 2019). This sensory overload in the cortex affects top-down processing and may led to a break-down of sensory integration (Vollenweider 2001). Top-down predictions and the updating of internal models may not be possible as the incoming information is not predictable. It has also been suggested that the brain may relax the

precision weighting of prior beliefs in the psychedelic state while the bottom-up flow of sensory information is increased (Carhart-Harris and Friston 2019). A previous auditory oddball study (Timmermann et al. 2018) found that the presentation of deviant tones elicits an increase in intrinsic connectivity which represents the strength of memory formation due to discrepancy between predicted and actual sensory input. After administration of LSD, this intrinsic connectivity was reduced. In line with this, our study showed less divergence between the D and S stimuli responses in the Psi condition potentially resulting from reduced adaptation and maybe aberrant salience processing. Furthermore, aberrant salience processing and alterations in matching incoming tactile stimuli with the sensory memory under Psi could affect schema-related learning in the vMPFC which has been proposed to be a critical node for schema memory (Gilboa and Marlatte 2017). Future studies investigating different sensory modalities are needed to determine if psychedelics specifically impact tactile processing, or if the effects reported here represent a more generally altered mechanism of saliency detection, adaption, and learning.

Limitations

A limitation of the study is the small sample size. Further studies with larger sample sizes are needed to extend our knowledge about the serotonergic neurochemical mechanisms that underlie tactile deviancy processing as well as its association with bodily awareness and self-experience. Furthermore, it needs to be noted that the somatosensory MMN amplitude as well as the time window of its occurrence can vary depending on body parts stimulated and the type, repetition frequency, and interstimulus interval of stimulation (Shen et al. 2018b; Shen et al. 2018a; Shinozaki et al. 1998; Spackman, Boyd, Towell 2007; Kekoni et al. 1997). Future studies should therefore extend the current results by including stimulation of other body parts and different stimulation protocols. Additionally, it is possible that Psi induced greater inter-

individual variability in the EEG-responses compared to Pla. Further studies which are well powered to investigate inter-individual variability are needed to test this hypothesis.

Conclusions

This study investigated the impact of the preferential 5-HT2A agonist Psi on the processing of tactile deviancy processing and its relation to the formation of bodily and self- awareness. The sense of touch is not raw and direct but rather constructed with reference to internal body representations that contain prior expectations (Haggard, Taylor-Clarke, Kennett 2003). We show that Psi alters the integration of tactile sensory inputs via aberrant PE processing and potentially reduced memory trace formation of tactile information. Furthermore, our results point towards an association between Psi-induced reduced responses to surprisingly stimuli and alterations in subjective body and self-experience.

Our findings therefore highlight the role of the serotonin and in particular the 5-HT_{2A} system in the disruption of multisensory processing of self- and body-related sensory inputs and perceptual tactile learning. This findings may be important for the treatment of many psychiatric disorders which involve aberrant recall or integration mechanisms of bodily self-representations, such as body dysmorphic disorder (Hrabosky et al. 2009), anorexia nervosa (Gadsby 2017) or depression (Fuchs and Schlimme 2009).

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Author contributions

PD, FXV, and KHP designed the research. PD, TN, and PS performed the research. PD, SB, GFG, MA, and PZ analyzed the data. PD and KHP wrote the manuscript. All authors revised the manuscript.

Conflict of Interest

All authors declare no conflict of interest. KHP is an employee of F.Hoffmann-La Roche AG.

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Figure Legends

Fig. 1: fMRI results and subjective effects. Significant differences in BOLD signal for *Placebo* > *Psilocybin* in the *Deviant* > *Standard* contrast at **(A)** vMPFC (peak: x = -9 y = 56 z = 29) and dMPFC (peak: x = 0 y = 35 z = 53), **(B)** V1 (peak: x = -3 y = -94 z = -7), **(C)** cerebellum (peak: x = 30 y = -61 z = -31) (all $p < 0.05$, FWE corrected); Blue shades represent a Psi-induced decrease in BOLD signal. Colorbars indicate t-values. **(D)** Comparison of the Beta values between conditions for significant clusters. Data are displayed as mean and standard error of the mean. **(E)** Subjective drug effects of the Pla and Psi condition expressed as percent of the scale maximum. Retrospectively assessed with the 5D-ASC questionnaire 360 min after drug administration. Psi significantly increased all scale scores compared to Pla except for spiritual experience and anxiety. Data are expressed as mean and standard error of the mean. Asterisks indicate significant differences between Psi and Pla conditions, $*p < 0.05$, Bonferroni corrected, $n = 15$ participants. VMPFC, ventromedial prefrontal cortex; dMPFC, dorsomedial prefrontal cortex; V1, primary visual cortex; D, deviant; S, standard; Psi, Psilocybin; Pla, Placebo.

Fig. 2. Global Field Power of the grand average waveforms. (A and B) GFP for standard and deviant stimuli in the Pla **(A)** and Psi **(B)** conditions. Red backgrounds indicate the stimulus onset and duration. Grey backgrounds indicate the 216 - 414 ms time window after stimulus onset. GFP represents the global field strength for the potential fields of the grand average waveforms. **(C and D)** Topographical maps of activity for standard and deviant stimuli during the second time window (216 – 414 ms) defined by the GFP for Pla **(C)** and Psi **(D)**. ~~Topographies~~ Topographical maps illustrate the potential field distribution over the whole scalp. **(E)** GFP mean amplitude for each condition (Pla and Psi) and stimuli type (S and D) in the time window 216 – 414 ms after stimulus onset **(F)** GFP mean amplitude for the difference

of standard and deviant (S minus D) for each condition (Pla and Psi). *n* = 15. GFP, global field power; μV, microvolt; ms, millisecond; Pla, placebo; Psi, psilocybin; S, standard; D, deviant.

Fig 3: Grand mean average waveforms at frontal electrodes Fp1, Fp2, AF2 (A) ERPs at 216 - 414 ms (grey background) after stimuli onset (red background) of S and D per condition Pla (above) and Psi (below), **(B)** Box plots for mean amplitudes at frontal electrodes (Fp1, Fp2, AF2) elicited for S and D per condition showing median, quartiles and range. Asterisks indicate significant differences in mean amplitudes. **(C)** Tactile MMN (D – S waveforms) at frontal electrodes for Pla and Psi in the time window 216 – 414 ms (grey background) after stimuli onset (red background) at frontal electrodes. *$p < 0.05$; n = 15. Pla, placebo; Psi, psilocybin; μV, microvolt.

Fig 4: Correlations between subjective alterations in body perception and tactile MMN responses (mean amplitude of the difference wave (D – S)) in the Psi condition. (A) Positive association between the 5D-ASC scale disembodiment and tactile MMN responses at AF2 in in the Psi condition ($r = 0.63$, $p = 0.012$). **(B)** Positive association between the 5D-ASC scale experience of unity and tactile MMN responses at AF2 in the Psi condition ($r = 0.58$, $p = 0.024$). Data points are color coded for each individual and rank-ordered according to their difference wave value. Grey background in scatterplots indicates the 95% confidence interval. *n* =15. MMN, mismatch negativity; DE, disembodiment; EU, experience of unity; Psi, psilocybin.