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# Psilocybin-assisted mindfulness training modulates self-consciousness and brain default mode network connectivity with lasting effects

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ABSTRACT

Both psychedelics and meditation exert profound modulatory effects on consciousness, perception and cognition, but their combined, possibly synergistic effects on neurobiology are unknown. Accordingly, we conducted a randomized, double-blind, placebo-controlled study with 38 participants following a single administration of the psychedelic psilocybin (315 μg/kg p.o.) during a 5-day mindfulness retreat. Brain dynamics were quantified directly pre- and post-intervention by functional magnetic resonance imaging during the resting state and two meditation forms. The analysis of functional connectivity identified psilocybin-related and mental state–dependent alterations in self-referential processing regions of the default mode network (DMN). Notably, decoupling of medial prefrontal and posterior cingulate cortices, which is thought to mediate sense of self, was associated with the subjective ego dissolution effect during the psilocybin-assisted mindfulness session. The extent of ego dissolution and brain connectivity predicted positive changes in psycho-social functioning of participants 4 months later. Psilocybin, combined with meditation, facilitated neurodynamic modulations in self-referential networks, subserving the process of meditation by acting along the anterior–posterior DMN connection. The study highlights the link between altered self-experience and subsequent behavioral changes. Understanding how interventions facilitate transformative experiences may open novel therapeutic perspectives. Insights into the biology of discrete mental states foster our understanding of non-ordinary forms of human self-consciousness and their concomitant brain substrate.

## 1. Introduction

Psilocybin is a preferential 1A/2A serotonin receptor agonist that dose-dependently induces profound alterations in consciousness (Preller et al., 2017; Preller and Vollenweider, 2018; Vollenweider et al., 1998). Recent research has focused on its potential to facilitate transformative experiences with lasting aftereffects (Griffiths et al., 2011) and treat clinical conditions such as addiction, end-of-life anxiety, and depression (Vollenweider and Kometer, 2010). However, it remains unclear which neuronal underpinnings are associated with those drug-induced experiences and how extra-pharmacological variables known as *set and setting* may shape drug responses. Converging evidence suggests the quality of a psychedelic experience is influenced by context, including mindset, expectations, and environmental factors (Studerus et al., 2012). Traditionally, psilocybin-induced altered states of consciousness were embedded in indigenous rituals and contemplative practices (Nichols, 2004). These setting variables may increase the drug-induced state of self-transcendence resulting from changes in 5-HT-related synaptic signaling and brain network connectivity, which may be a unique therapeutic mechanism in the action of psychedelic drugs (Preller et al., 2018). Therefore, insights into drug-induced neuronal alterations in self-referential processing and conditions facilitating such experiences may foster our understanding of self-consciousness and promote novel therapeutic approaches to improve mental health and well-being.

There are several similarities and possible synergistic interactions between psychedelic-induced and meditative states of consciousness at the levels of both phenomenology and brain dynamics. First, some subjective psilocybin effects resemble the altered modes of perception and cognition occurring in advanced meditation, including self-transcendence (Letheby and Gerrans, 2017). Second, a contemplative

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setting that facilitates mindfulness may also deepen psychedelic experiences (Pahnke, 1969). Third, an increase in mindfulness-related capabilities was recently shown after intake of ayahuasca containing the serotonergic psychedelic *N*,*N*-dimethyltryptamine (Soler et al., 2016), which is chemically related to psilocybin. We thus expect that mindfulness-related capabilities, such as an increased ability to focus and deepen introspection, may have a beneficial impact on outcomes of psychedelic experiences.

Meditation describes a set of mental practices for the cultivation of mindfulness, defined as attentiveness and non-judgmental acceptance of present-moment experience (Bishop et al., 2004). The therapeutic value of mindfulness techniques has been increasingly recognized owing to their proven beneficial effects on psychosomatic health and well-being (Gotink et al., 2015). Scientific studies highlight post-meditation neuroplastic changes, with lasting effects starting after a few days of practice (van Leeuwen et al., 2012). Different neural correlates have been identified during distinct meditative states such as focused attention (FA; sustained attention on a meditation object, e.g., breath) and open awareness (OA; non-reactive monitoring of the content of experience) (Tang et al., 2015). Distinguishing among different styles of meditation provides a useful heuristic for delineating dissociable psychological and neurodynamic effects.

Accumulated evidence highlights common neurobiological signatures for meditative states of self-transcendence (Vago and Silbersweig, 2012) and psychedelic states of ego dissolution (Lebedev et al., 2015), in particular through modulations of activity and connectivity in the default mode network (DMN) (Brewer et al., 2011; Carhart-Harris et al., 2012; Kometer et al., 2015). The DMN (Raichle, 2015) is a large-scale network that functionally integrates distant brain nodes and mediates among other phenomena, such as wakefulness, awareness, and memory, a variety of self-related cognitions (Qin and Northoff, 2011). Abnormalities in the DMN are linked to symptom severity in various psychiatric disorders, with adaptive changes in DMN function following pharmacological treatments (Fox and Greicius, 2010). Accordingly, the DMN was proposed as a biomarker for monitoring the therapeutic effects of meditation (Simon and Engström, 2015). Modulations of the cortical midline network structures involved in higher order mental processes such as self-referential processing (Qin and Northoff, 2011) may facilitate states of self-transcendence, a proposed key treatment mediator in psychedelic-assisted therapies (Garcia-Romeu et al., 2014). Interestingly, a previous study points to the utility of DMN metrics as neural predictors, by demonstrating that a difference in coupling between the medial prefrontal cortex (mPFC) and the posterior cingulate cortex (PCC), two main DMN hubs, predicted behavioral outcomes that rely on self-referential processing (Tompson et al., 2016).

Building upon the above lines of evidence, the present fMRI-based study aimed to investigate changes in functional connectivity as well as experiential and behavioral markers following psilocybin intake during meditation. To this purpose, we administered a single dose of psilocybin to a group of experienced meditators at a 5-day retreat using a randomized, double-blind, placebo-controlled, between-subject design. The effects of psilocybin-assisted meditation were quantified by fMRI the days before and after the retreat (pre-post intervention) during three experimental conditions: 1) resting state (RS, no meditation), 2) FA, and 3) OA meditation. Functional connectivity offers a window into the organization of large-scale, modular, spatially allocated, and functionally linked areas by analyzing linear dependencies (i.e., correlations) between blood-oxygen level-dependent (BOLD) signal fluctuations (Rogers et al., 2007). We hypothesized that drug-induced modulations in brain networks relevant for self-referential processing, particularly within the DMN, mediate acute and lasting retreat outcomes. As psychedelic drugs are known to induce transformative experiences, we hypothesized that the degree of these modulations in the brain may be predictive of long-term adaptive changes in behaviors and attitudes. To our knowledge, this is the first imaging study to investigate the neurodynamics of a potent consciousness-altering drug in a mindfulness retreat setting.

## 2. Materials and methods

### 2.1. Participants

Data from 38 healthy, experienced meditator subjects (23 males, mean age 51.66 ± 8.32) were analyzed. They were matched for age, sex, previous meditation experience, and dispositional mindfulness and randomly assigned to psilocybin or placebo groups. Written consent was obtained prior to study enrollment. After two drop-outs between the randomization and study beginning (one person declined, another was excluded due to a detected exclusion criterium for fMRI) the final active and control groups involved 20 and 18 subjects, respectively. See SM Table 1 for detailed participant characteristics.

### 2.2. Study procedures

All participants followed a structured meditative discipline (known in the Zen tradition as *sesshin*), consisting of a 5-day silent group meditation retreat.

Psilocybin (315 μg/kg body weight; absolute dose, 21.82 ± 3.7 mg) and placebo (lactose) were administered on the fourth day (10:30 a.m.) in a randomized, double-blind placebo-controlled design while the participants maintained daily meditation routines. The day before and after the retreat, pre-post fMRI scans were collected to measure intervention effects. Three 7-min blocks were performed with eyes closed in fixed order, approximating a naturalistic progression of a meditation practice: resting state (RS), focused attention (FA), and open awareness (OA). The order of fMRI measurements was randomly assigned, with pre- and post-scan times differing by no more than 2 h to avoid time-of-day effects. Refer to SM Fig. 1 for details on study flow. The experiment was conducted in accordance with the Declaration of Helsinki. The Cantonal Ethics Committee of Zurich approved the study. The Swiss Federal Office for Public Health, Department of Pharmacology and Narcotics in Bern authorized the use of psilocybin in humans. The specific moderate-to-high dose of psilocybin was chosen based on previous studies, where similar oral doses were successfully applied to induce changes in consciousness and were found physically and psychologically tolerable (Hasler et al., 2004).

### 2.3. Psychometric measures

#### 2.3.1. Five Dimensional Altered States of Consciousness scale (5D-ASC)

The 5D-ASC instrument (Dittrich, 1998) was administered 360 min

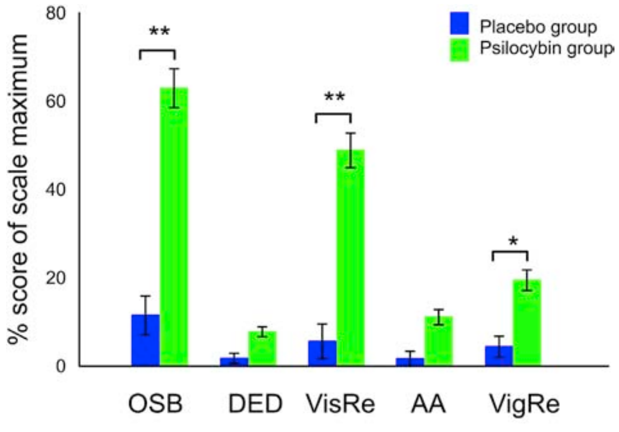

**Fig. 1.** Subjective effects of psilocybin measured along five dimensions of the 5D-ASC scale. Green and blue bars depict psilocybin and placebo groups. Values are means ± SEM; **, $p < 0.001$; *, $p < 0.05$ (Tukey's HSD); $n = 38$. OSB, Oceanic Self-Boundlessness; DED, Dread of Ego Dissolution; VisRe, Visionary Restructuralization; AA, Auditory Alterations; VigRe, Vigilance Reduction.

after placebo/psilocybin intake as a retrospective measure of subjective effects. The scale is a well-validated instrument that measures alterations in consciousness and perception, and it has been applied in previous studies with psilocybin (Studerus et al., 2011). It is composed of 94 visual-analogue items, clustered in five dimensions (scales), rated as percentage scores of the maximum scale value.

#### 2.3.2. Persisting Effects Questionnaire (PEQ)

The PEQ (Griffiths et al., 2011) was administered after 4 months to measure follow-up effects. This questionnaire was developed to evaluate changes in attitudes in psychosocial domain on the basis of previous research on the aftereffects of psychedelic experiences. The 145 items are rated on a 6-point scale from 0 (none) to 5 (extreme) (Griffiths et al., 2006). We used a global change score constructed by taking an overall mean of positive scale scores. The six categories included changes in attitudes about life, attitudes about self, mood changes, social effects, behavior changes, and increased spirituality. The instrument proved sensitive to follow-up changes in studies involving psilocybin and other psychoactive drugs (Griffiths et al., 2011).

### 2.4. MRI data acquisition and scanning parameters

Structural and functional data were recorded using a 3T Philips Achieva MRI scanner with a 32-channel SENSE head coil. High-resolution T1-weighted gradient-echo images were acquired for structural reference at the beginning with a 3D field echo sequence (TR = 9.3 ms; TE = 4.6 ms; FOV = 240 mm; flip angle, = 8°; in-plane resolution = 1 × 1 × 1 mm; 160 sagittal slices). Functional data were recorded with a T2*-weighted echo-planar functional scan (slice thickness = 4 mm (no gap); slices = 32; TR = 2000 ms; TE = 35 ms; FA = 82°). Participant hearing was protected from the scanner noise with earplugs and headphones. Foam pads were used to reduce head motion.

### 2.5. Preprocessing

Spatial preprocessing was performed with SPM v12 (http://www.fil.ion.ucl.ac.uk/spm, Wellcome Department of Imaging Neuroscience, London, UK) and included slice-time correction, realignment, segmentation of structural data, normalization into the stereotactic MNI (Montreal Neurological Institute) template, and smoothing with a 6-mm full-width-at-half-maximum Gaussian kernel. In order to address fluctuations in the magnetic field and spurious correlations from head movements, outliers based on the criterion of >3 standard deviations from the global mean intensity across all functional scans and >1-mm composite measure of total frame-to-frame motion across translation and rotation, were calculated using Artifact Detection Tools (ART, www.nitrc.org/projects/artifact_detect). To increase the precision of the GLM by erasing physiological noise from the signal (i.e., heart rate, respiration), the CompCor strategy (Behzadi et al., 2007) was applied to estimate principal components associated with automatically segmented white matter (WM) and cerebrospinal fluid (CSF), which were entered as nuisance variables along with six realignment parameters (translation, rotation, and their derivatives). These data were captured in a matrix containing the ART-detected outliers and effects of conditions in the subject-level analysis. The applied approach targets most sources of noise without regressing out the global signal, which has been found to generate spurious anticorrelations (Chai et al., 2012; Murphy et al., 2009). The residual signal underwent a linear detrending and was bandpass filtered ($0.009 < f < 0.08$ Hz) to reduce low-frequency drift and high-frequency noise.

### 2.6. Independent component analysis

ICA is a data-driven blind source separation method for generating spatial components using the principle of maximal and statistically grounded independence (Calhoun et al., 2001). Preprocessed fMRI data were decomposed into networks by applying ICA and the Infomax algorithm as implemented in GIFT v3.0a (http://mialab.mrn.org/software/gift). The automatized method of component labeling used multiple spatial regressions with extracted ICs and resting state network templates from a large cohort of healthy adults (Allen et al., 2011). Spatial maps reflect the degree of connectivity between each voxel's time series and the aggregate network time course. The optimal number of components was estimated using the minimum description length criterion (MDL) modified to account for spatial correlations across all the conditions (Li et al., 2007). Prior to the independent component analysis (ICA) procedure, data were pre-normalized by removing timepoint means to deal with the conditioning of the covariance matrix. Independent components were computed using the Infomax algorithm (Bell and Sejnowski, 1995) after a two-step data reduction performed by a principal component analysis (PCA). Infomax, which is commonly used for real-world fMRI data, identifies independent signals by adaptively maximizing the output entropy of a neural network (Calhoun et al., 2013) using a non-Gaussian model with stochastic or natural gradient updates (Amari, 1998) and delivers high signal-to-noise estimates (Correa et al., 2007). GICA was used as a back-reconstruction method. Stability of the IC estimations was ensured by repeating the algorithm 20 times using ICASSO (http://www.cis.hut.fi/projects/ica/icasso) (Himberg et al., 2004). The cluster stability/quality index reflecting the compactness and isolation of a cluster was very high for all 39 ICs ($I_q > 0.9$, range 0.986–0.960). Each subject component image and time course was scaled to represent the percent signal change from the original data. In order to limit the analysis to within-network results and voxels showing consistent activation across subjects, the effects were restricted to the spatial extent of the given component by applying a mask based on the distribution of voxel-wise *t*-statistics. Results were assessed at a FDR-corrected $p < 0.05$ threshold. Anatomical labels are based on the Automated Anatomical Labeling Toolbox (AAL2) for SPM v12 (http://www.gin.cnrs.fr/en/tools/aal-aal2) (Tzourio-Mazoyer et al., 2002).

### 2.7. Region-of-interest analysis with DMN hubs

We centered a 10-mm-radius sphere around the peak voxel of the ICA-derived significant group by time interaction cluster in the mPFC (Fig. 3B, [MNI -6 44–6]) as a region of interest (ROI) in a subsequent hypothesis-driven ROI-to-ROI analysis. Three other main hubs of the DMN, known as the core self-network (Andrews-Hanna et al., 2014) or tripartite self-network (Davey et al., 2016), were defined by the default Conn Toolbox anatomical atlas (Harvard-Oxford Atlas), i.e., the posterior cingulate cortex (PCC, [1–36 30]) and the bilateral angular gyri (AG, right [52 -52 32], left [-50, −56, 30]). This analysis was conducted using Conn Toolbox (version 15.h) (www.nitrc.org/projects/conn) run with Matlab (https://www.mathworks.com). Bivariate correlation coefficients between the denoised mean BOLD signal time course in this ROI and these main hubs of the DMN were computed and subjected to Fisher transformation, what represents a common method for investigating functional connectivity (Rogers et al., 2007). ROI-to-ROI values were extracted for individual subjects for regression analysis.

### 2.8. Statistics

The 5D-ASC data were analyzed with a repeated-measures two-way ANOVA, with group as between- and scales as within-subject factors. A two-sample *t*-test was conducted for PEQ positive global change scores. For ICA maps and ROI-to-ROI analysis, paired *t*-tests, as implemented in Statistical Parametric Mapping (SPM) v12 were used to compare pre-post effects for both groups separately. Group by time interaction effects were calculated in SPM using two-sample *t*-tests on the subject-wise post-pre differences for each of three conditions and components. Brain imaging statistics were assessed at an FDR-corrected $p < 0.05$ threshold. Additional Bonferroni corrections were used to penalize for multiple tests and are reported accordingly. Pearson's correlation coefficients were calculated for OSB (as a measure of alterations in self-experience) with Δ change of significant ROI-to-ROI connectivity and PEQ scores. Finally, a stepwise multiple regression using the forward stepwise model (starting with a null model and adding variables) was conducted with PEQ scores and all ROI-to-ROI connectivity scores (three ROIs, three conditions) to test predictors of follow-up changes. The significance level for linear statistics was $p = 0.05$.

### 2.9. *Data and code availability statement*

Data are available upon direct request.

## 3. Results

### 3.1. *Acute subjective drug effects*

Compared to the placebo, psilocybin significantly altered the scores of the Five Dimensional Altered States of Consciousness scale (5D-ASC) (Dittrich, 1998), as indicated by the significant group by scale interaction ($F_{4,144} = 33.82$, $p < 0.0001$) and main effects of scale ($F_{4,144} = 61.43$, $p < 0.0001$) and group ($F_{1,36} = 102.57$, $p < 0.0001$). A post-hoc Tukey's test of the interaction showed a significant psilocybin-induced increase for Oceanic Self-Boundlessness (OSB), Visionary Restructuralization (VisRe) (both $p < 0.0001$), and Vigilance Reduction (VigRe) ($p < 0.05$; Fig. 1), but not for Dread of Ego Dissolution (DED) ($p = 0.92$) or Auditory Alterations (AA) ($p = 0.43$).

### 3.2. *Identification of DMN components*

To overcome the limitations of model-based approaches, a decomposition method using independent component analysis (ICA) was employed to dissect data into statistically independent spatial and temporal patterns of coherent fMRI signals (Calhoun et al., 2001). ICA is a highly reliable method for identifying the DMN and other brain networks (Beckmann et al., 2005). The optimal number of components was found to be 39. Furthermore, an automatized labeling method based on spatial regression with templates (Allen et al., 2011) additionally informed by visual inspection indicated three networks of interest that best match different divisions of the DMN: posterior DMN (pDMN), antero-ventral DMN (avDMN), and antero-dorsal DMN (adDMN; Fig. 2).

### 3.3. *ICA spatial maps analysis*

Paired *t*-tests (for timepoints 1 and 2) and time by group interactions were calculated separately for each of the three conditions (RS, FA, OA) and networks (pDMN, avDMN, adDMN). Significant interaction effects and pre-post connectivity changes were found in the anterior-cingulate and medio-prefrontal cortex (ACC/MPFC) within the avDMN (Fig. 3). The results remained significant after an additional Bonferroni correction of the *p*-values for the number of tests conducted (by a factor of 9 for interactions and 18 for paired *t*-tests). We found no other statistically significant changes in the adDMN or pDMN at rest or in the other conditions.

### 3.4. *Region-of-interest analysis*

Paired *t*-tests revealed significant decoupling during OA meditation in the psilocybin group only, between the ICA-derived ROI in the mPFC and all three target DMN regions: PCC ($\beta = -0.16$, $t_{19} = -3.81$, $p = 0.003$), right AG ($\beta = -0.12$, $t_{19} = -2.42$, $p = 0.030$), and left AG ($\beta = -0.11$, $t_{19} = -2.34$, $p = 0.030$). A significant treatment group by time interaction was found under OA meditation for the connectivity between the mPFC and the PCC ($t_{36} = -2.65$, $\beta = -0.18$, $p = 0.019$) and left AG ($t_{36} = -2.61$, $\beta = -0.17$, $p = 0.019$), but not the right AG ($t_{36} = -1.47$, $\beta = -0.10$, $p = 0.149$; Fig. 4B). All *p*-values are FDR-corrected for the number of ROIs. After applying a conservative Bonferroni correction for the three interaction tests conducted, the effect was marginally significant (corrected $p = 3 \times 0.019 = 0.057$). However, the high significance of the mPFC-PCC effect withstood the application of the same procedure to control for three *t*-tests (corrected $p = 3 \times 0.003 = 0.009$). We did not find any other statistically significant changes in this analysis for the remaining conditions. There was a significant negative correlation between OSB and pre-post change in connectivity between the mPFC and PCC ($r = -0.595$, $p = 0.006$; $p = 0.018$, corrected for three comparisons with significant ROI-to-ROI connections).

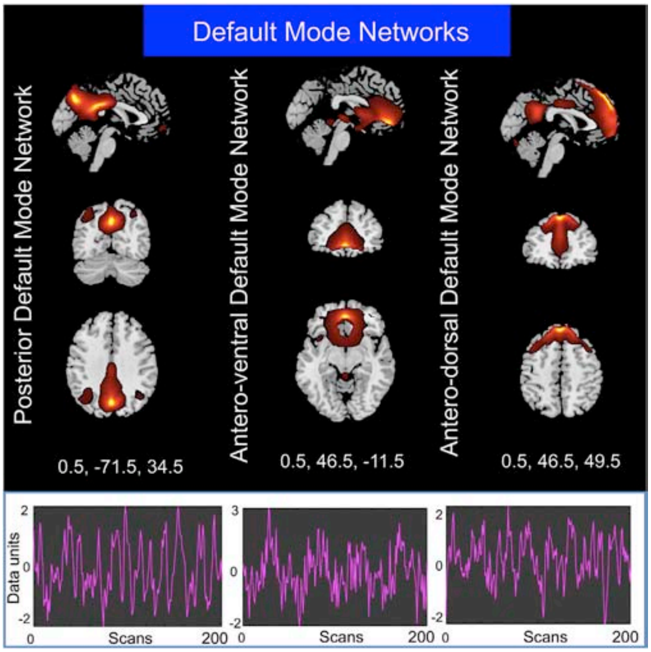

**Fig. 2.** Independent component analysis component maps, with Montreal Neurological Institute (MNI) maximum voxel coordinates and *z*-scored mean time courses, representing three divisions of the default mode networks.

### 3.5. *Positive persistent effects and their predictors*

The psilocybin group scored significantly higher on the mean global positive change score of the Persisting Effects Questionnaire (PEQ) after 4 months ($M = 2.58$, $SD = 1.32$) compared to the placebo ($M = 0.65$, $SD = 0.98$; $t_{36} = 5.05$, $p < 0.0001$). Moreover, these follow-up effects were positively correlated with the acute OSB scores during psilocybin administration ($r = 0.66$, $p = 0.002$; Fig. 5A). Given the hypothesis that psilocybin-related changes in connectivity may predict follow-up effects, a regression analysis with nine DMN ROI-to-ROI connectivity scores (Δ post-pre mPFC-PCC, mPFC-AGr, and mPFC-AGl scores under RS, FA, and OA conditions for the psilocybin group) and persistent effects as the predicted variable was conducted. This revealed a statistically significant model containing two of nine predictors: change in connectivity between mPFC-PCC at rest and mPFC-right angular gyrus for FA. The model accounted for 44% of the variance ($F_{2,17} = 6.79$, $p = 0.007$). An increase in mPFC-PCC connectivity at rest significantly predicted a subsequent positive change in attitudes after the psilocybin-assisted mindfulness retreat ($\beta = 0.41$, $p < 0.05$) as did a decrease in mPFC-AGr connectivity during FA ($\beta = -0.49$, $p < 0.05$).

## 4. Discussion

The effects of a 5-day psilocybin-assisted mindfulness retreat on brain dynamics in experienced meditators aligned with previous findings of altered DMN function during meditation (Brewer et al., 2011; Carhart-Harris et al., 2012) and psychedelic states (Brewer et al., 2011; Carhart-Harris et al., 2012; Palhano-Fontes et al., 2015). We confirmed our

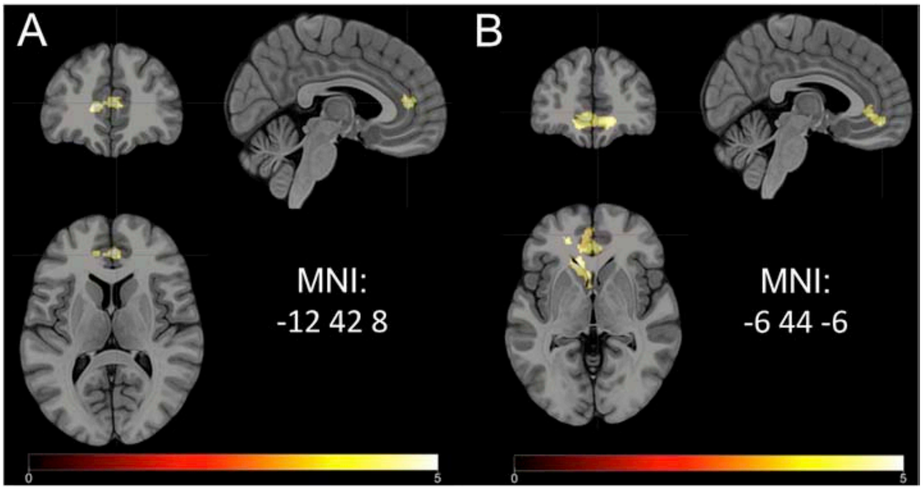

**Fig. 3.** Significant clusters of increased connectivity within the antero-ventral default mode network (avDMN) during resting state, as shown by spatial maps analysis. **(A)** Pre-post-retreat effect ($t_2 > t_1$) in the psilocybin group, as revealed by a paired *t*-test (including anterior cingulate cortex, $t = 5.90$, $k = 144$ voxels). **(B)** Group by time interaction (including left caudate, mediofrontal orbital cortex, and anterior cingulate cortex $t = 5.12$, $k = 1066$ voxels). All statistical brain map results are shown at an FDR-corrected cluster-level threshold of $p < 0.05$ (Bonferroni corrected for number of tests conducted). Montreal Neurological Institute (MNI) coordinates are reported for peak clusters.

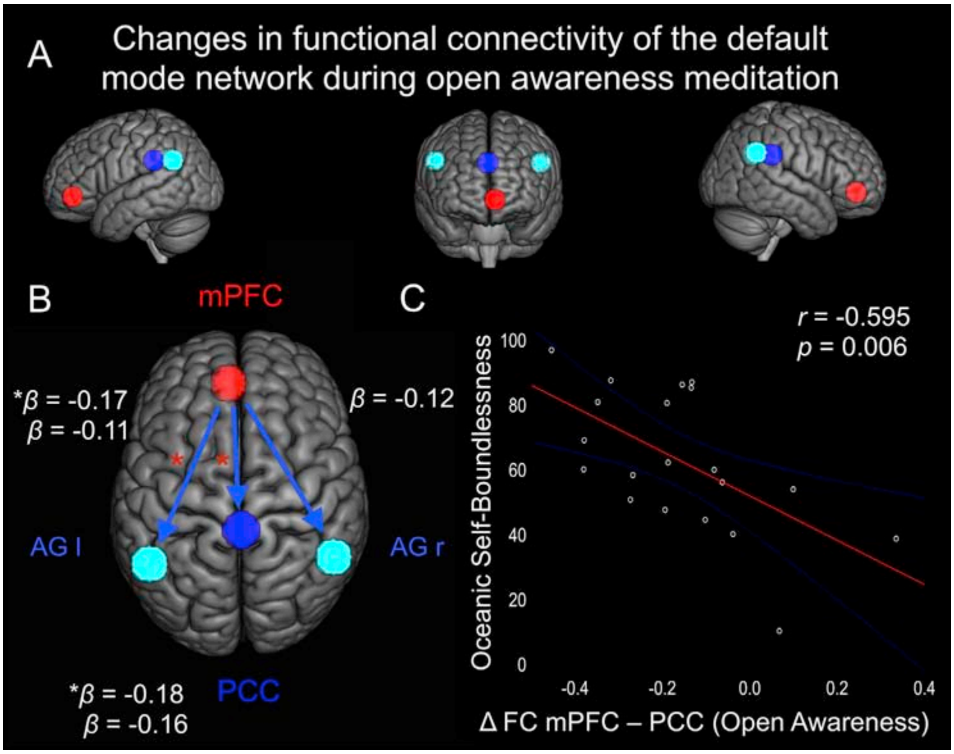

**Fig. 4.** Pre-post-retreat changes in functional connectivity between the main default mode network hubs. **(A)** Volumetric views of the independent component analysis (ICA)-derived seed (in red) and target regions (in blue). **(B)** Group by time interaction (marked with asterisk) and pre-post-retreat contrast showing significant decoupling of antero-posterior DMN connectivity during open awareness meditation in the psilocybin group (FDR-corrected for the number of ROIs within a condition $p < 0.05$; after the additional Bonferroni correction across conditions, the interaction effects were marginally significant ($p = 0.057$), while for the paired *t*-test the corrected *p*-values for the angular gyri and PCC were 0.09 and 0.009, respectively). **(C)** Significant Pearson's correlation coefficients between the psilocybin-induced measure of self-transcendence during acute administration and pre-post-retreat mPFC-PCC change during open awareness meditation in the fMRI scanner (corrected $p = 0.018$; 0.006*3 comparisons). mPFC, medial prefrontal cortex; AG r, right angular gyrus; AG l, left angular gyrus; PCC, posterior cingulate cortex.

hypothesis regarding post-acute psilocybin-specific modulations of functional connectivity during a meditative state in the DMN, a key network for self-referential processes. Psilocybin administered in a mindfulness retreat setting significantly potentiated positively felt states of ego dissolution (i.e., OSB, oceanic self-boundlessness) compared to the placebo. Most notably, OSB was associated with post-retreat decoupling of functional connectivity between anterior (mPFC) and posterior (PCC) regions of the DMN during OA meditation. Antero-posterior DMN connectivity during OA was specifically decreased post-intervention in the psilocybin group but not the placebo group.

Meditation and psilocybin have been shown to share common neural mechanisms of action by affecting brain regions involved in self-awareness such as the DMN (Brewer et al., 2011; Carhart-Harris et al., 2012; Farb et al., 2007; Lebedev et al., 2015). A recent review and meta-analysis of meditation neuroimaging studies found consistent deactivation in DMN hubs (Fox et al., 2016). Notably, changes in DMN activity and functional integrity were also reported under psilocybin, LSD, and ayahuasca (Carhart-Harris et al., 2012; Kometer et al., 2015; Palhano-Fontes et al., 2015; Speth et al., 2016). After intravenous administration of psilocybin and LSD, cerebral blood flow and BOLD activity decreased along with decoupling of functional connectivity between the mPFC and PCC (Carhart-Harris et al., 2012, 2016). Key functions of the PCC include the coordination of mental representations (Cavanna and Trimble, 2006), conceptual self–other distinction (Murray et al., 2015), inward-versus outward-directed mentalizing (Johnson et al., 2006), and maintenance of a unitary sense of self (Johnson et al., 2002). Presumably, when this self-referential processing system collapses, an altered self-experience may emerge. We thus hypothesized that psilocybin-induced states of self-transcendence specifically affect antero-posterior DMN connectivity during meditation.

We found differential effects of psilocybin on resting state brain connectivity and various styles of meditation. Although FA and OA are

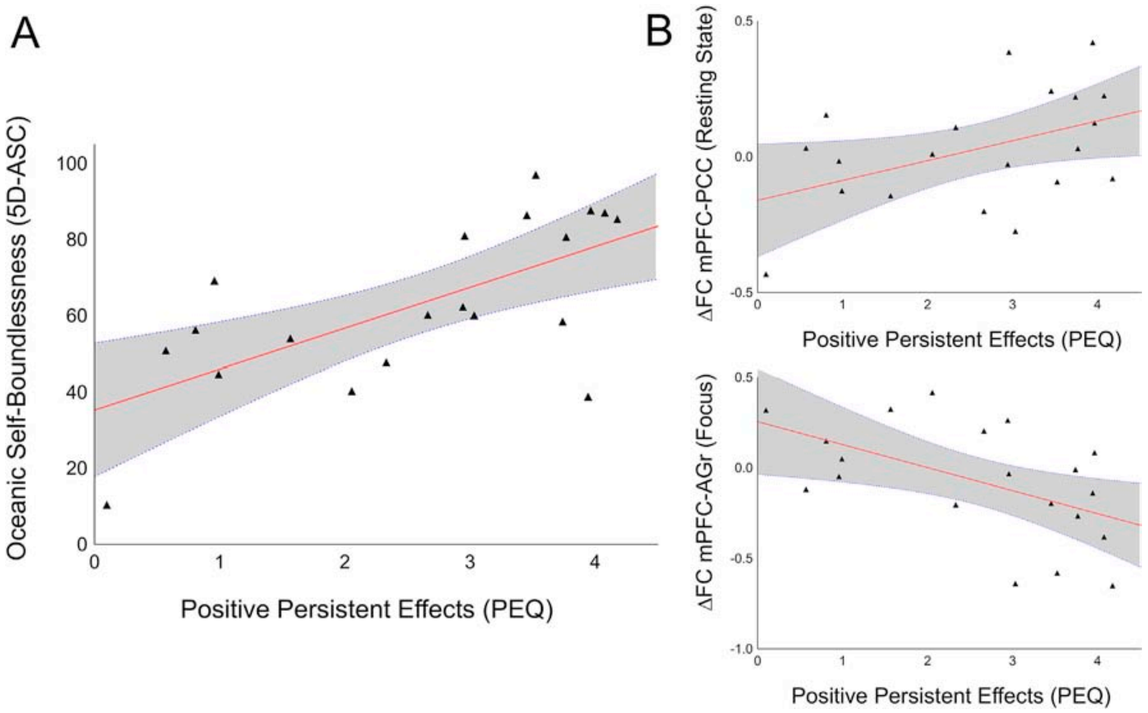

**Fig. 5.** Positive persistent effects following the psilocybin-assisted mindfulness retreat. **(A)** Relationship between psilocybin-induced oceanic self-boundlessness (OSB), as measured by the 5D-ASC instrument, and mean positive changes in attitudes after 4 months ($r = 0.66$, $p = 0.002$). **(B)** Follow-up effects plotted against the pre-post-retreat change in functional connectivity between mPFC-PCC at rest (upper) ($r = 0.45$, $p = 0.046$) and mPFC-AGr during focused meditation (lower) ($r = -0.53$, $p = 0.016$). mPFC, medial prefrontal cortex; AGr, right angular gyrus; PCC, posterior cingulate cortex; $n = 20$.

two common mindfulness practices, they differ in the neural architecture supporting their cognitive processes (Manna et al., 2010). The aim of FA is to stabilize the mind from distraction by maintaining selective attention on a specific object or physiological process (e.g., breath). Conversely, OA promotes a receptive field of non-reactive attitude towards automatic cognitive and emotional interpretations of sensory, perceptual, and endogenous stimuli, developing the scaffolding for a form of meta-awareness (Dahl et al., 2015). Although anterior–posterior DMN connectivity during FA or RS was not found to be reduced in the psilocybin group, the extent of post-intervention antero-posterior DMN disintegration during OA was correlated with decreased self-referential focus (i.e., OSB) under psilocybin. This finding aligns with the experiential quality of OA that resembles psychedelic-induced states of unconstrained cognition and an expanded sense of the self, described as dissolution of ego boundaries (Lebedev et al., 2015). In contrast, FA primarily exploits a narrow attentional focus, a cognitive ability that was less affected post-acute by psilocybin exposure.

In opposition to meditation, the RS represents task-free baseline brain activity when a person is typically engaged in mind wandering (Andrews-Hanna et al., 2014). Psilocybin-related modulations at rest were mainly comprised of higher mPFC/ACC connectivity within the antero-ventral DMN. Notably, the mPFC plays a crucial role in directing the ongoing stream of thought, subserving both integrative and gateway functions and representing a key nexus for self-related cognition and emotion regulation (Bush et al., 2000; Moran et al., 2013; Qin and Northoff, 2011). Although previous studies reported enhanced network efficiency in the ACC following short-term meditation (Xue et al., 2011), we observed no pre-post-retreat changes in anterior DMN connectivity in our placebo group. As long-term meditators show more ACC/mPFC activation and greater functional connectivity within the medio-prefrontal DMN compared to novices (Hölzel et al., 2007), we likely failed to detect any pre-post-retreat changes in anterior DMN in our placebo group owing to the considerable meditation entrainment of our sample (i.e., group mean experience of approx. 5000 h of meditation and 30 retreats).

Psilocybin was previously found to increase the variance and amplitudes of the BOLD signal in the ACC, as a marker of increased synchronization and wider dynamic repertoires of connectivity states (Tagliazucchi et al., 2014). Increases in ACC/mPFC within-network connectivity might result from changes in local network integrity following stimulation of glutamatergic signaling by 5-HT2A receptor activation (Aghajanian and Marek, 2000). This parallels other studies of glucose metabolism (Schreckenberger et al., 1998; Vollenweider et al., 1997) or cerebral blood flow (CBF) after psilocybin administration (Lewis et al., 2017) and ayahuasca intake (Riba et al., 2006) that point to increased activity in mPFC areas that subserve the regulation of mood, cognition, and goal-directed behaviors. These findings are of potential relevance for the understanding of the neural mechanisms underlying psilocybin's putative therapeutic effects, as areas within the anterior-ventral DMN have been directly implicated in treatment outcomes in depression. In particular, such modulations may foster adaptive self-referential processing and help to recalibrate relationships between the default network and task positive networks (Pizzagalli, 2011).

Both meditation- and psychedelic-induced states of transcendence of usual body, space, and time perception may rely on altered communication and large-scale desynchronization between the inferior parietal lobe (IPL) and other nodes of the DMN, such as the mPFC and PCC, comprising a tripartite 'core-self' system (Barrett and Griffiths, 2018; Davey et al., 2016). Hence, we extended our ICA approach and explored the connectivity between the ICA-based hot spot in the anterior DMN (mPFC/ACC) and posterior and parietal DMN regions by ROI-to-ROI analysis. In line with our hypothesis, reduced connectivity of fronto-parietal networks (mPFC/AG) during OA was associated with psilocybin-related loosening of self-reference. Conversely, the activity of the tripartite 'core-self' system was found to be enhanced, with increased levels of self-reference in a dynamic causal modelling study (Davey et al., 2016). Based on a previous study of neural correlates of a self-transcendent state (d'Aquili and Newberg, 1999), d'Aquili and

Newberg proposed “deafferentation” of the posterior parietal lobes from the prefrontal cortex as a neural correlate of mystical-type experiences. Accordingly, the functional elimination of neural input to the brain-orienting system in the parietal lobes can cause a transient blurring of demarcation between self and world, resulting in a state of self-transcendence. Advanced brain-lesion mapping techniques with pre- and post-neurosurgery personality assessments provide further evidence that selective damage to IPL regions induces unusually fast modulations of a stable personality trait related to self-transcendence (Urgesi et al., 2010). Interestingly, a lower ratio of parietal to prefrontal cortical activation was also found to be a signature of meditation characterized by transcendence, but not meditation without transcendence (Barnby et al., 2015). Although we measured only post-acute effects, we propose that psilocybin-assisted mindfulness practice facilitates states of self-transcendence (OSB) and may decrease functional connectivity of the tripartite ‘core-self’ system during OA meditation even two days after drug administration.

Previous attempts to identify neural correlates of the self have focused primarily on the DMN, highlighting its role in ego-identity or the narrative self (Carhart-Harris and Friston, 2010; Qin and Northoff, 2011). In particular, decoupling between the DMN and the medio-temporal lobes (MTL) was hypothesized to be associated with psychedelic-induced ego dissolution (Carhart-Harris and Friston, 2010; Carhart-Harris et al., 2014) and correlated with the dreamlike quality of the experience (Carhart-Harris and Nutt, 2014; Lebedev et al., 2015). Under LSD administration, decreased connectivity between the parahippocampus and retrosplenial cortex (RSC) correlated strongly with ratings of ego dissolution and altered meaning (Carhart-Harris et al., 2016). However, we did not find any modulations of MTL–DMN connectivity two days after psilocybin administration in an additional exploratory analysis of functional connectivity between the PCC and bilateral hippocampi/parahippocampi in our sample (see Supplementary Material). We conclude that changes in MTL–DMN connectivity may be primarily related to distinct aspects of ego dissolution, such as the narrative self and the dreamlike quality of acute drug effects, while post-acute changes in mindfulness-related neurocircuits comprise other nodes of the DMN such as the IPL, PCC, and mPFC.

Transformative effects of psychedelic drugs have been previously reported in healthy volunteers (Griffiths et al., 2011) and in combination with meditation and other spiritual practices (Griffiths et al., 2018). In our study, lasting effects of the psilocybin experience also included subsequent psychological changes at the 4-month follow-up. Specifically, the drug effect of OSB correlated with positively valued mean changes in attitudes about life, self, social behavior, mood, and spirituality. We interpret this as a shift in self-representation, which may act as an organizing principle at different levels of processing (Letheby and Gerrans, 2017). An experience of ego dissolution may further imply cognitive reappraisals, reifications, self-inquiry, or insights and contribute to enduring psychological changes. Our double-blind study presents a notable case because its participants were primarily in middle adulthood and already engaged in meditative practices, and yet the psilocybin-treatment group still reported a significant beneficial effect of the retreat.

Transformative processes might result from drug-induced alterations in functional network connectivity that increase global brain plasticity with lasting behavioral outcomes (Gallimore, 2015; Ly et al., 2018). Several studies point to acute changes in integrity and coupling of resting state networks (Petri et al., 2014; Roseman et al., 2014) and decreased antero-posterior DMN connectivity (Carhart-Harris et al., 2012; Palhano-Fontes et al., 2015) during acute administration of psychedelic drugs, while increases in DMN connectivity have been reported one-day post-treatment with psilocybin (Carhart-Harris et al., 2017) or ayahuasca (Sampedro et al., 2017). We did not find any significant increases in antero-posterior DMN integrity two days after psilocybin administration. However, our regression model revealed that an increase in mPFC-PCC functional connectivity at rest and decrease in mPFC-AGr functional connectivity during FA explained a relatively high proportion of the variance in positive persistent changes after 4 months. These dissociable effects of psilocybin on task-versus-rest and acute-versus-intermediate network dynamics point to a complex, yet behaviorally relevant modulation of DMN function. The psilocybin experience of OSB might increase the meditators' capability of down-regulating DMN integration during OA practice, representing a neural mechanism frequently found during states of self-transcendence. In contrast, higher DMN integration at rest was predictive of lasting behavioral outcomes at the 4-month follow-up. This is consistent with the idea that psychedelics increase context-dependent DMN flexibility, enabling more adaptive allocation of brain resources. Although higher DMN integration in the psilocybin group predicts the long-term transformative impact of the retreat on core life attitudes and behaviors, experienced meditators were still able to down-regulate DMN connectivity during OA to reach states of self-transcendence. Hence, the dynamic repertoire of DMN function may be increased following psychedelic drug administration, which aligns with recently proposed therapeutic mechanisms of “brain resetting” that mediate psilocybin's antidepressant properties (Carhart-Harris et al., 2017).

The present work has some limitations. One of them is a relatively low sample size. Our participants were experienced meditators, restricting generalizability to a larger population, which may be less skilled in handling and integrating the psychotropic effects of psilocybin. The retreat setting with intense meditation practice did not evoke any significant adverse drug reactions such as dysphoric mood, anxiety, or fearful delusions, which may occur when the reference framework of ordinary perception is lost. The participants’ experience in navigating altered states of consciousness through meditation and the supporting environment may have contributed to this positive outcome. A cautionary note should be made on the use of mind-altering drugs in unprepared individuals with uncleared health histories. Potential risks and safety guidelines in human psychedelic research have been outlined by Johnson et al. (2008).

We here report for the first time psilocybin-induced functional connectivity changes in self-referential brain networks in a group of experienced meditators after a mindfulness retreat. Functional imaging markers of different meditative states enabled a comprehensive and state-dependent assessment of these effects. Psilocybin exerted dissociable post-acute effects on DMN integrity with increased anterior DMN connectivity at rest and decreased antero-posterior and fronto-parietal DMN connectivity during OA meditation. Positively felt ego dissolution under psilocybin-assisted meditation was correlated with post-acute changes in DMN connectivity and was predictive of behavioral outcomes 4 months later. Our findings highlight the potential of psilocybin in facilitating dynamic changes in self-referential processing networks with lasting positive outcomes. Moreover, this study motivates further research into the converging effects of mindfulness and psychedelics on brain dynamics and psychotherapeutic change variables in the context of psychedelic-assisted therapy.

## Declaration of interest

The authors declare no conflict of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.04.009.

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