Finding the Self by Losing the Self: Neural Correlates of Ego-Dissolution Under Psilocybin

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Abstract: Ego-disturbances have been a topic in schizophrenia research since the earliest clinical descriptions of the disorder. Manifesting as a feeling that one's "self," "ego," or "I" is disintegrating or that the border between one's self and the external world is dissolving, "ego-disintegration" or "dissolution" is also an important feature of the psychedelic experience, such as is produced by psilocybin (a compound found in "magic mushrooms"). Fifteen healthy subjects took part in this placebo-controlled study. Twelve-minute functional MRI scans were acquired on two occasions: subjects received an intravenous infusion of saline on one occasion (placebo) and 2 mg psilocybin on the other. Twenty-two visual analogue scale ratings were completed soon after scanning and the first principal component of these, dominated by items referring to "ego-dissolution", was used as a primary measure of interest in subsequent analyses. Employing methods of connectivity analysis and graph theory, an association was found between psilocybin-induced ego-dissolution and decreased functional connectivity between the medial temporal lobe and high-level cortical regions. Ego-dissolution was also associated with a "disintegration" of the salience network and reduced interhemispheric communication. Addressing baseline brain dynamics as a predictor of drug-response, individuals with lower diversity of executive network nodes were more likely to experience ego-dissolution under psilocybin. These results implicate MTL-cortical decoupling, decreased salience network integrity, and reduced inter-hemispheric communication in psilocybin-induced ego disturbance and suggest that the maintenance of "self"or "ego," as a perceptual phenomenon, may rest on the normal functioning of these systems. *Hum Brain Mapp 36:3137–3153, 2015.*   © 2015 **Wiley Periodicals, Inc.**

Key words: consciousness; psychedelics; sense of self; ego-disturbances; ichstörungen; fMRI; connectivity; graph theory; medial temporal lobe; psychosis

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INTRODUCTION

The concept of the self has been a topic of debate in philosophy and science since ancient times. It is at the center of some of the most influential theories on the nature of the human mind [Freud, 1924], including theories on the origins of modern human consciousness [Jaynes, 1976].The self is a pivotal feature of normal waking human consciousness, as demonstrated by the prevalence of personal and possessive pronounssuch as "I," "me," and "mine" in everyday speech. Indeed, the ubiquity of "self" in waking consciousness invites the assumption that it is a permanent feature of that consciousness. Certain altered states of consciousness reveal the self to be vulnerable however. Examples of states in which the "dissolution" of the self can be observed include: acute psychosis [Bleuler, 1911], temporal lobe epilepsy auras [Schenk and Bear, 1981], and putatively nonpathological states such as spiritual or mystical-type experiences [Hood, 1975]. Importantly, self- or ego-dissolution can also be experimentally induced by the neurobiological action of so-called "psychedelic" drugs, such as psilocybin [Griffiths et al., 2011], LSD [Goodman, 2002; Lyvers and Meester, 2012], and dimethyl-tryptamines or "DMT" [Trichter et al., 2009].

"The self" is perhaps best viewed as an "umbrella" [Fleming et al., 2012] or "constellation" [Seth, 2013] construct that subsumes a broad range of mental phenomena, including: self-awareness, self-monitoring, self-recognition, self-identity, self-control, sense of agency and ownership, theory-of-mind, subject-object differentiation, reality-testing, and even focused attention or goal-directed cognition [Carhart-Harris and Friston, 2010]. Indeed, that the self is such a broad construct explains why it is so difficult to define. The term "the self," in its broadest sense, is synonymous with "the ego" as traditionally described in psychology [Freud, 1924].

Studying a broad range of states associated with altered sense of self (later called "ego-disturbances" [Schneider, 1959]), Karl Jaspers [Jaspers, 1913] distinguished several domains of ego-consciousness, which may be useful for understanding the phenomenon that is the focus of the present article. These domains include: (i) ego-vitality ("awareness of existence"), (ii) ego-activity ("awareness of one's own performance" or "sense of self-agency"), (iii) ego-consistency ("multimodal phenomena being perceived as integrated experience"), (iv) ego-demarcation ("differentiation of the self from the outside world"), and (v) ego-identity ("Me" as a narrative or a story that I can tell about myself). These five domains, being incorporated into the ego pathology inventory [Scharfetter, 1981], have been successfully used in studies of psychedelic [Vollenweider et al., 1997] and psychotic [Rohricht and Priebe, 2004] states.

It is also worth mentioning that recent work has made an effort to further conceptualize classic psychodynamic ideas [Freud, 1924] in the context of Bayesian brain and free-energy minimization principle, describing the self/ego not just as a sensation, but also as a system with functions, such as reality-testing, subserved by hierarchically higher brain circuits that function to suppress the free-energy ("prediction error") of the lower ones [Carhart-Harris and Friston, 2010]. Thus, an alternative approach to studying the ego might be to focus on specific functions, such as reality-testing, and to use corresponding behavioral measures [Carhart-Harris et al., 2014a]. In the present study, however, we have chosen to examine the ego primarily from the phenomenological standpoint, as a complex sensory *experience of being "me,"* as being *coherent in mental acts* and *distinct from the outside world*.

Psilocybin is the prodrug of psilocin, a classic psychedelic substance and an indolealkylamine. Indolealkylamines are relatives of 5-hydroxytryptamine (5-HT, also known as serotonin), an endogenous neuromodulator that plays a crucial role in the regulation of mood, sleep and cognition [Canli and Lesch, 2007; Cowen and Sherwood, 2013; Monti et al., 2008]. Most psychedelics are serotonin receptor agonists and although their pharmacology is non-selective, their characteristic psychoactive effects appear to depend on stimulation of the serotonin 2A receptors. Psychedelics can produce experiences that are similar in some respects to those seen in acute psychotic states [Vollenweider et al., 1998; Vollenweider et al., 1999] and their effects are blocked by atypical antipsychotics and 5HT-2A antagonist, ketanserin [Carter et al., 2007; Vollenweider et al., 1998]. These observations put psilocybin forward as a tool for studying certain aspects of psychotic states [Carhart-Harris et al., 2013; Vollenweider et al., 1999]. Conceptually, one can think of drug-induced psychedelic states as "psychotic experiences", since they often feature severe distortion of perception and ego-functions. Indeed, serotoninergic psychedelics have been found to alter a broad range of cognitive functions related to the self, including goal-directed behavior [Kometer et al., 2012], reality-testing [Carhart-Harris et al., 2014a], and time perception [Wittmann et al., 2007].

There is very limited knowledge of the neural correlates of the self and its disturbances but there are reasons to think that medial temporal lobe (MTL) circuitry is important. Electrical stimulation of MTL regions has been found to produce visual hallucinatory phenomena similar to those reported under psychedelics [Rangarajan et al., 2014], as well as so-called "dreamy states" (i.e. sensations of dreaming, déjà vu, and depersonalization-like experiences) [Bancaud et al., 1994; Bartolomei et al., 2012; Lee et al., 2013]. Exploratory depth recordings in patients administered psychedelics in the mid-20th century found abnormal activity that was most conspicuous in limbic regions including the MTLs [Monroe and Heath, 1961; Schwarz et al., 1956]. These findings have recently been supported by fMRI work demonstrating increased signal variance/amplitude in the MTLs [Tagliazucchi et al., 2014] and decreased MTL to default-mode network (DMN) functional connectivity under psilocybin [Carhart-Harris et al., 2014b]. Interestingly, the former result correlated

positively with ratings of the "dreamlike" quality of the experience [Carhart-Harris and Nutt, 2014]. Rodent fMRI work with a DMT-related drug found an "activating" effect on the MTLs in the context of a generalized "deactivating" effect on the cortex [Riga et al., 2014]. Depth electrophysiological [Heath and Mickle, 1960; Sem-Jacobsen et al., 1955; Sherwood, 1962] and later neuroimaging work [Friston et al., 1992; Gordon et al., 1994; Liddle et al., 1992] have also implicated the MTLs in psychotic states, with converging evidence supporting the involvement of parahippocampal regions in schizophrenia and schizophrenia-like psychotic states [Acioly et al., 2010; Allen and McGuire, 2014; Bodnar et al., 2011; Friston et al., 1992; Prasad et al., 2004]. This has also been supported by in silico simulations demonstrating that disruption of parahippocampal cortex from other MTL regions results in memory deficits that mimic those seen in schizophrenia [Talamini et al., 2005]. Finally, depersonalization (a state of altered self-awareness at the psychotic level equivalent to ego-disturbances [Burgy, 2011; Sass et al., 2013]) has been linked to abnormal function of the MTL regions [Lambert et al., 2002; Lemche et al., 2013].

One of the key MTL regions, the parahippocampal cortex (PHC) is a multimodal hub that plays an important role in contextual processing, familiarity detection, memory retrieval, and associative memory [Aminoff et al., 2013]. It is also known as the "gateway to hippocampus" [Watrous et al., 2013] mediating its connectivity with major brain network hubs subserving higher cognition, such as the posterior cingulate (default mode network, DMN), superior parietal (attention/control network), and dorsomedial prefrontal (salience network) areas [Jones and Witter, 2007; Kondo et al., 2005; Ward et al., 2014; Watrous et al., 2013]. Recent work has revealed an anterior-posterior functional segregation within the PHC, with the anterior part (aPHC) more involved in higher cognition and the posterior part contributing to spatial processing [Aminoff et al., 2013; Baldassano et al., 2013; Weniger and Irle, 2006]. Interestingly, binding of the 5-HT2A receptors is reduced in this area in patients with schizophrenia [Burnet et al., 1996]. Finally, it is specifically the a PHC that is most closely associated with "dreamy" state experiences [Bartolomei et al., 2012; Guedj et al., 2010; Illman et al., 2012; Spatt, 2002; Takeda et al., 2011; Vignal et al., 2007]. Based on these findings, we predicted that decoupling of the PHC from the neocortex would correlate positively with ego-dissolution [Carhart-Harris, 2007; Carhart-Harris and Friston, 2010; Carhart-Harris et al., 2014b], consistent with the loss of a contextual "feed" into the ongoing stream of cognition.

Previous attempts to identify neural correlates of the self or ego have tended to focus primarily on the DMN [Carhart-Harris and Friston, 2010; Qin and Northoff, 2011]. Several studies have found increased activation in the DMN during self-referential processing [Buckner et al., 2008] and other high-level cognitive functions related to the construct of "the self," such as theory-of-mind [Li et al., 2014], mental time travel [Ostby et al., 2012], and moral decision-making [Reniers et al., 2012], clearly implicating the DMN in "ego-identity" (see above) or the "narrative self." Our previous fMRI and MEG studies have found decreased cerebral blood flow, functional connectivity, and oscillatory power within the DMN [Carhart-Harris et al., 2012; Carhart-Harris et al., 2014b; Muthukumaraswamy et al., 2013] following administration of psilocybin. In addition, alpha desynchronisation in the posterior cingulate cortex (PCC) node of the DMN correlated positively with ratings of psilocybin-induced ego-disintegration [Carhart-Harris et al., 2014b]. Based on these studies, we predicted that ego-dissolution would correlate positively with altered DMN connectivity (e.g. reduced DMN integrity) and regions belonging to it (e.g. altered PCC diversity) under psilocybin.

The salience network and its component nodes have also been a focus of research of neural correlates of the self [Craig, 2009; Seth, 2013]. Interestingly, this network is very rich in the von Economo neurons that are hypothesized to contribute to the brain mechanisms of self-awareness, higher cognition, and are specific for socially complex animals like great apes and macaques [Allman et al., 2010; Allman et al., 2011; Cauda et al., 2013; Evrard et al., 2012]. Compromised function of the salience network has previously been linked with empathy deficits in frontotemporal dementia [Seeley, 2008; Seeley, 2010], impaired self-awareness in patients with traumatic brain injury [Ham et al., 2014] and has also been implicated in psychosis and the aberrant salience model of positive psychotic symptoms [Krishnadas et al., 2014; Manoliu et al., 2014; Palaniyappan and Liddle, 2012; Palaniyappan et al., 2013; Pu et al., 2012; White et al., 2010]. It is worth noting that the functions most strongly associated with the salience network fall under the construct of the "minimal self" comprising ego-vitality, activity, consistency, and demarcation (see Jaspers' domains of ego-consciousness, above), but not under the "narrative" aspect of the self (ego-identity) which are perhaps more related to the DMN and its interactions with the MTLs.

It has previously been proposed that the psychedelic state offers ideal experimental means of perturbing the self or ego so that it can be studied scientifically [Carhart-Harris et al., 2014b], as well as to aid studies of some psychotic states [Carhart-Harris et al., 2013]. Ego-disturbances have been a central focus of schizophrenia research and its diagnostic criteria since the earliest clinical descriptions of the disorder [Bleuler, 1911; Feinberg, 2011; Fuentenebro and Berrios, 1995; Kircher and David, 2003; Nelson et al., 2012; Sass et al., 2013; Schneider, 1959] and their severity at admission have been demonstrated to substantially influence treatment outcome [Rohricht et al., 2009; Rohricht and Priebe, 2004]. All of the above supports the relevance of psychedelic research for understanding brain dynamics underlying a very broad range of altered states of consciousness, including both drug-induced and endogenously occurring psychotic states.

TABLE I. Two-factor structure of the psychedelic experience

Subjective ratings	PC1 ("ego-loss")	PC2 ("affective valence")
I lost all sense of ego	0.842	0.014
My imagination was extremely vivid	0.841	−0.282
The experience had a spiritual or mystical quality	0.811	0.161
I experienced a loss of separation from my environment	0.756	−0.129
I saw geometric patterns	0.725	0.240
It felt like I was floating	0.725	−0.250
I felt like I was merging with my surroundings	0.717	0.526
The experience had a supernatural quality	0.693	0.649
I felt afraid	0.675	−0.271
I feared loosing control of my mind	0.665	0.074
My thoughts wandered freely	0.661	0.470
I saw events from my past	0.637	0.049
The experience had dreamlike quality	0.589	−0.251
Things looked strange	0.533	−0.503
I felt a profound inner peace	0.463	0.476
Sounds influenced things I saw	0.406	0.244
I felt unusual bodily sensations	0.402	−0.728
My sense of time was distorted	0.276	−0.183
My thinking was muddled	0.247	−0.705
My sense of size and space was distorted	0.189	−0.193
I felt suspicious and paranoid	0.186	−0.346
I felt completely normal	0.055	0.338
Intensity of the experience	0.74	−0.189
% Of variance explained (cumulative)	36.37%	50.33%

Values are Pearson correlation coefficients (r) representing associations between first two principal components and corresponding subjective ratings.
36.37% 13.97% of the variance (50.33% cumulative)

In the present article, methods of large-scale network analysis were employed to test our hypotheses. These methods have previously been used to inform our understanding of brain dynamics underlying higher cognitive functions [Sporns, 2010]; however, to the best of our knowledge, they have never been used to investigate the neural correlates of drug-induced ego-dissolution.

METHODS

Design and Participants

This was a within-subjects, counterbalanced-order, placebo-controlled design. The study was approved by an NHS research ethics committee. Fifteen volunteers (13 males, 2 females, aged 32 [±8.9] years) with previous psychedelic experience were scanned on two occasions: (1) receiving saline injection ("placebo," PCB-session), 12 min task-free fMRI scan, eyes closed, and (2) 2 mg psilocybin infusion ("psilocybin," PSI-session), midway through 12 min fMRI scan. All subjects underwent health screens prior to enrolment. Inclusion criteria were: age >21 years, no personal or immediate family history of a major psychiatric disorder, drug dependence, cardiovascular disease, and no history of a significant adverse response to a hallucinogen. All of the subjects had used psilocybin at least once before (mean number of uses per subject = 16.4, SD = 27.2) but not within 6 weeks before the study started. A standardized physical examination, including electrocardiogram, blood tests, urine test for drugs of abuse and pregnancy were carried out. Experienced clinicians at Bristol Royal Infirmary conducted a psychiatric assessment, during which the participants disclosed their drug use histories, and medical record was taken. The participants also completed the State Trait Anxiety Inventory and the Beck Depression Inventory.

Subjective Behavioral Measures

Twenty-two visual analogue scale (VAS) items were completed by the volunteers shortly after they exited the scanner. The complete list of items can be found in the Table I. All items had a bottom anchor of "no more than usually" (referring to normal waking consciousness) and a top anchor of "much more than usually," consistent with the format of Dittrich's altered states of consciousness questionnaire [Dittrich, 1998]. Ratings ranged from zero to 100. In order to reduce the dimensionality of these data, Principal Component Analysis (PCA) was performed, yielding a first principal component (i.e. the item "I lost all sense of ego") which was then used as a subsequent

measure of interest (see Table I and Fig. 2). For the present analysis, VAS ratings completed at the end of the psilocybin session were used. Pearson correlation coefficients were computed between relevant biological measures and principal component scores. This was done after performing a Shapiro-Wilk test for normality.

Ethics

The study was approved by a National Health Service research ethics committee. All subjects gave consent to participate in the study after the procedures had been explained in details.

MRI

Image acquisition

MR images were acquired in Cardiff University's Brain Research Imaging Centre on a 3T Siemens Trio Tim MRI scanner (Siemens Healthcare, Erlangen, Germany) using a 32-channel head coil. Anatomical reference images were acquired using the ADNI-GO MPRAGE protocol: 1 mm isotropic voxels, TR = 2300 ms, TE = 2.98 ms, 160 sagittal slices, 256 × 256 in-plane resolution, flip angle = 9 degrees, bandwidth = 240 Hz/pixel, GRAPPA acceleration = 2. Two hundred and forty (240) T2*-weighted echo planar images were acquired during each session using a standardized sequence: 3 mm isotropic voxels, TR = 3000 ms, TE = 35 ms, field-of-view = 192 mm, flip angle = 90°, 53 axial slices per one TR, parallel acceleration factor = 2, 64 × 64 acquisition matrix.

Image preprocessing

For the present analysis, a standardized pipeline combining functions from SPM-8 (http://www.fil.ion.ucl.ac.uk/spm) and FSL-5.0 was implemented, largely based on the Data Processing Assistant for Resting-State fMRI: Advanced Edition (DPARSFA, version 3.0) [Chao-Gan and Yu-Feng, 2010], installed on the MATLAB environment [MATLAB, 2013]. The raw EPI images subsequently underwent steps for spatial realignment, slice-timing correction, linear [Jenkinson et al., 2002], and nonlinear [Andersson et al., 2007] registrations to high-resolution native and standardized MNI spaces, correspondingly. Spurious variance was reduced by regressing-out signal from the white matter and cerebrospinal fluid together with Friston's extended 24-parameter motion correction model that includes current and past position of each of 6 head motion parameters along with their squares [Friston et al., 1996]. Next, the images were band-pass filtered to eliminate biologically nonrelevant signals [Lowe et al., 1998] and smoothed with 6 mm Gaussian kernel. The resulting low-frequency fluctuations, extracted using standardized parcellation schemes (see below), were used in the subsequent network analysis [Rubinov and Sporns, 2010].

Parcellation schemes

For the graph analysis, we used Craddock's atlas [Craddock et al., 2012] covering 200 regions-of-interest (ROIs). Based on prior hypothesis, 4 ROIs including the left and right anterior parahippocampal (aPHC, MNI coordinates: L [−31 −3 −33], R [36 −11 −27]), posterior cingulate (PCC, MNI coordinates: [1 −37 31]), and retrosplenial cortex (RSC, MNI coordinates: [1 −51 14]) were used to assess changes in diversity coefficients related to ego-dissolution at the first step of the analysis (hypothesis-driven part). The results were further replicated employing the extended 600-ROI version of this atlas. Finally, for the analysis of within-network integrity, Craddock's 200-ROI parcellation was masked by each of the 7 networks from the Yeo's scheme [Yeo et al., 2011] in order to calculate within-network mean clustering coefficients (one per each network).

After the preprocessing had been finished, the "psilocybin" data was split into 2 subsets: 5-min prepsilocybin and 5-min postpsilocybin.

Outlier detection

Outlier detection was done by a visual assessment of the first two principal component scores extracted from the subjective measures and imaging data (functional connectivity matrices) separately. No outliers were found.

Analysis of head motion

In order to further rule-out possible contribution of motion-related artifacts to our results, we also performed analysis of head movements (6-parameter model), comparing averaged standard deviation and first principal component scores extracted from the motion time-series: 1–prepsilocybin vs postpsilocybin, 2–placebo vs postpsilocybin, as well as their associations with our measure of interest: "ego-loss" composite score: first principal component extracted from the subjective measures (see **Results**). Among all comparisons, only one was significant: mean SD of head motion was slightly higher in the postpsilocybin as compared to prepsilocybin state (p_{uncorr} = 0.015). Head motion (SD, first PC) did not demonstrate significant impact on any of the network measures extracted from the motion-corrected data. Likewise, "ego-dissolution" scores did not correlate with motion or motion differences.

Assessment of temporal signal-to-noise ratio (tSNR)

To rule out the possibility that tSNR could account for the differences between conditions, a corresponding set analyses was performed measuring mean BOLD signal from a ROI divided by its standard deviation. Critically, neither of the SNR measures (for PCB, prepsilocybin, postpsilocybin conditions), nor their differences, correlated with ego-dissolution phenomena. For graph metrics
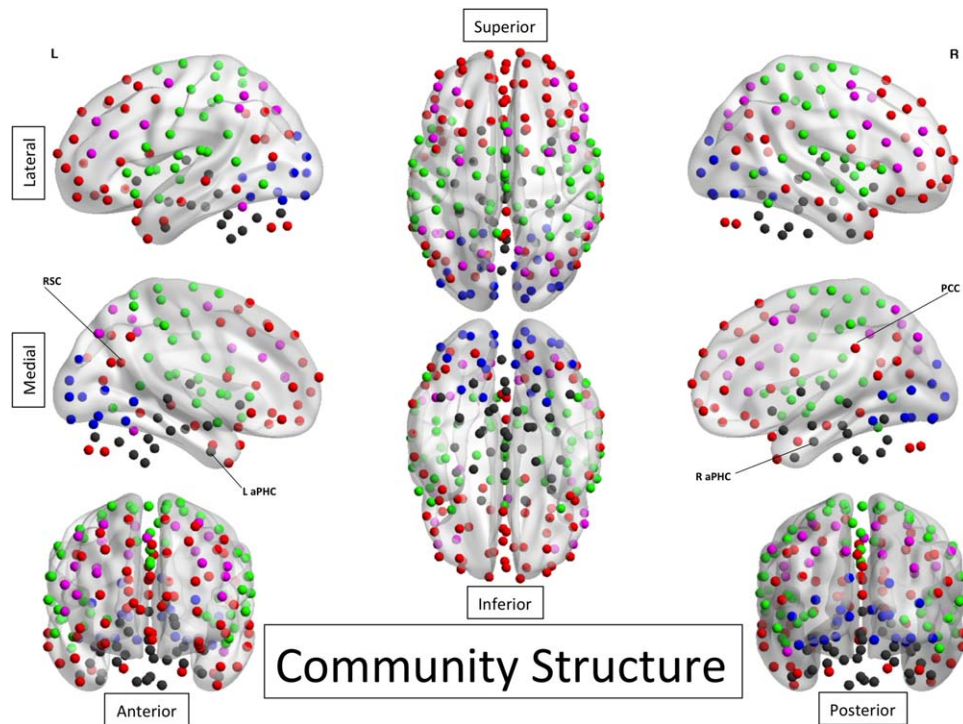
Figure 1.

Communities (estimated for 12-min placebo scan). L/R aPHC–Left/Right anterior Parahippocampal Cortex; PCC–Posterior Cingulate Cortex (midline region); RSC–Retrosplenial Cortex (midline region); **Colors (communities): Blue**–Visual. **Green**–Somatosensory+Salience. **Red**–DMN + Prefrontal ["Higher Cognition"]. **Purple**–Control **Dark Gray**–Subcortical/MTL. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

measured, only changes in tSNR and diversity coefficients of the RSC demonstrated strong negative relationship ($r = -0.71$, $P < 0.005$) (for the filtered data only), meaning that tSNR reductions (presumably associated with reduced activity) in RSC were associated with increases in the diversity of its connections.

Measure preparation

Adjacency matrices were constructed using Pearson correlation that represented functional connectivity (edges) between 200 ROI (nodes) as defined in the Craddock's parcellation scheme [Craddock et al., 2012].

Extraction of graph measures was carried out using Brain Connectivity Toolbox (BCT, http://www.brain-connectivity-toolbox.net) [Rubinov and Sporns, 2010].

Community structure and diversity coefficients

At the first stage, community structure was estimated using placebo data employing fine-tune modularity algorithm [Rubinov and Sporns, 2011]. Five communities were estimated from the placebo data and labeled according to

their localization and known functions: 1–Visual, 2–Somatosensory+Salience, 3–"Higher Cognition" community, 4–Control Network, 5–Subcortical/Temporal (See Fig. 1). Then, diversity coefficient was calculated for all 200 ROIs for the pre- and postpsilocybin-infusion datasets as well as the entire placebo dataset. Diversity coefficient is a Shannon entropy-based measure, defining how a particular ROI is connected to different communities (how "diverse" a particular region is in its connections). When the diversity coefficient is high, it implies more diffuse connectivity and when it is low it implies more restricted connectivity. For more detailed explanations and formal definition, see Supporting Information. The relationship between the diversity coefficients for the selected ROIs (i.e. the aPHC and PCC) and "ego-dissolution" were analyzed first, followed by an exploratory analyses using all 200 ROIs (with correction for multiple tests using the false discovery rate, FDR). Diversity coefficients for "post-psilocybin", "pre-psilocybin" vs. "post-psilocybin" (difference between two states) and "pre-psilocybin" were calculated. In addition, the last two parts of the analyses were repeated using placebo data instead of pre-psilocybin in order to test the robustness of the findings.
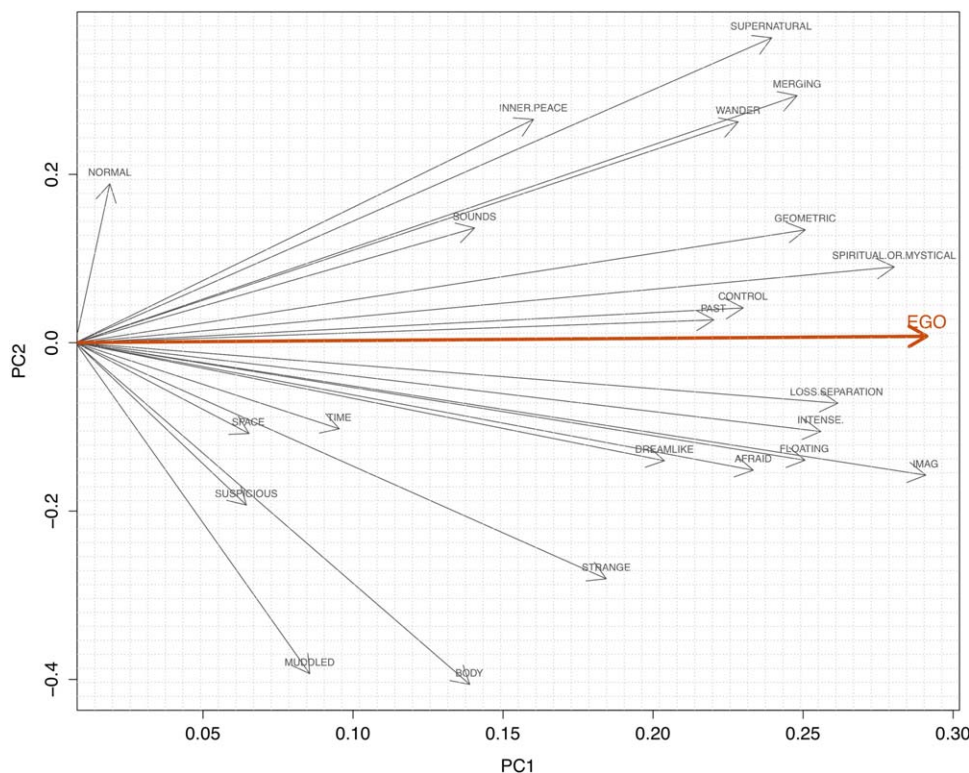
Figure 2.

First two principal components extracted from the raw subjective measures. PC 1 (1st Principal Component): ego disintegration phenomena; PC2 (2nd Principal Component): perhaps bestrelates to the "emotional valence" of the experience; Component scores were normalized at the range. [Color figure can be viewed in the online issue, which is available at wileyonline library.com.]

Within-network clustering coefficient

Within-network integrity was assessed by calculating mean clustering coefficient for each of 7 networks from the Yeo's atlas. Next, intensity of the ego-dissolution phenomena was analyzed as a function of mean clustering coefficient for each network in the same order as for other analyses (1–post-psilocybin, 2–pre-psilocybin vs. post-psilocybin, 3–post-psilocybin).

Hypothesis-free analysis of the between-ROI functional connectivity

For this part, the analysis of ego-dissolution phenomena was conducted by looking at bivariate correlations between 200 ROIs, as implemented in the Network Based Statistics toolbox (NBS: https://sites.google.com/site/bctnet/comparison/nbs). This method employs nonparametric framework (permutation testing for each graph component clustered in a topological space) to control for the family-wise error (FWE) rate.

Statistical analysis

Data analysis was conducted using R programming language, version 3.1(13) [R Core Team, 2014] and NBS toolbox [Zalesky et al., 2010] with linear modeling and correction for multiple comparisons (FDR and FWE, correspondingly).

Visualization

Results visualization was carried out using BrainNet-viewer [Xia et al., 2013], version 1.43.

RESULTS

Subjective Behavioral Measures

The first principal component explained 36.37% of the data variance and was strongly associated with ego-dissolution phenomena (see Table I and Fig. 2) measured by a VAS that read: "I lost all sense of ego" ($r = 0.82$). The
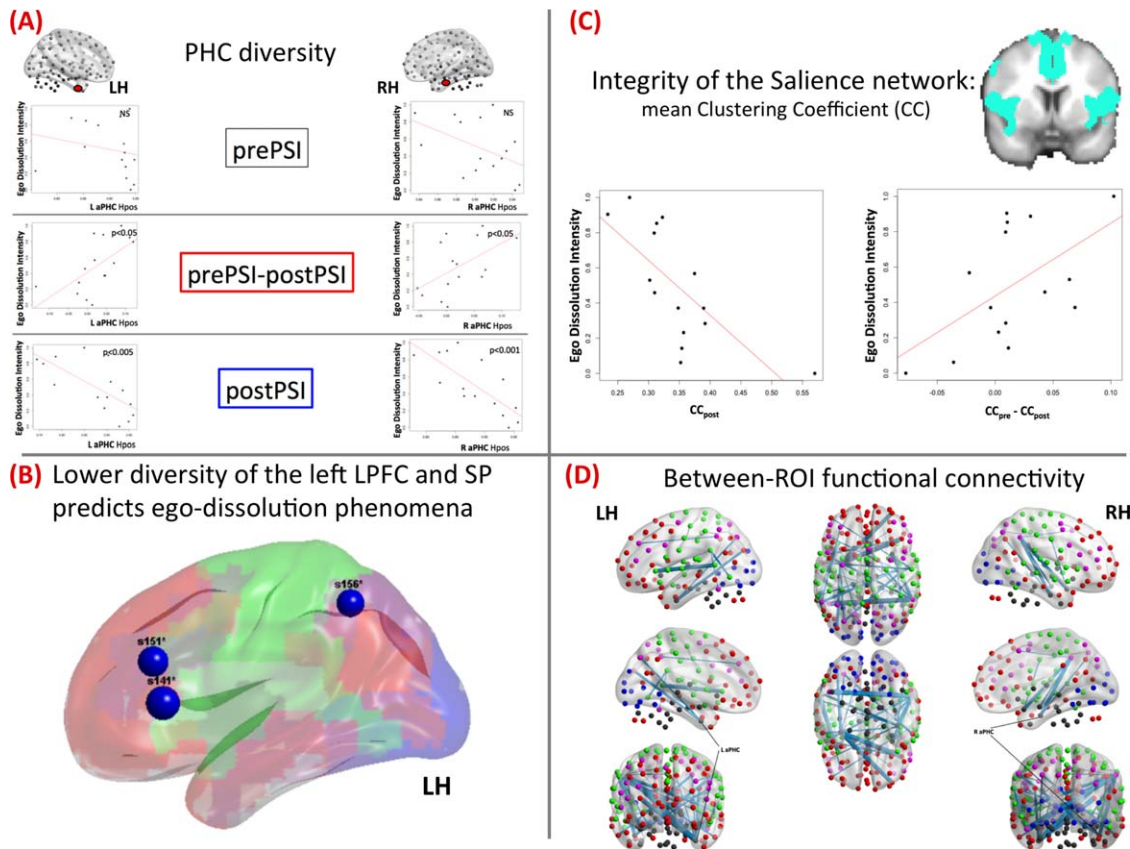
Figure 3.

Neural correlates of psilocybin-induced ego-dissolution. **(A)** Ego-dissolution correlates with decreased diversity of the anterior parahippocampal (aPHC) connections under psilocybin; **(B)** Lower diversity of the Left Dorsolateral Prefrontal (regions 141 and 151 in Craddock's atlas) and superior parietal (region 156) regions at baseline predicted ego-disintegration phenomena under the drug. **(C)** Decreased integrity of the salience network correlates with ego-dissolution: scatter plots (LEFT: after the psilocybin administration, RIGHT: difference between baseline and psilocybin-induced states); results were significant at $P < 0.05$ (FDR-corrected); brain template is color-coded accord-ing to the baseline community structure (see Methods). **(D)** Ego-dissolution is associated with psilocybin-induced connectivity reductions between specific nodes, e.g. those crossing the two hemispheres and particularly those including medial temporal areas. Results were significant at $P < 0.05$ (FWE-corrected); nodes are color-coded according to the community structure (see Methods). **Blue**–Visual; **Green**–Somatosensory + Salience; **Red**–DMN + Prefrontal; **Pink**–Control; **Dark Gray**–Subcorti-cal/MTL. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

first principal component also showed associations with other VAS items related to ego-dissolution, such as: "I experienced a loss of separation from my surroundings" ($r = 0.76$) and "It felt like I was merging with my environment" ($r = 0.72$) and, interestingly, with "the experience had a spiritual/mystical quality" ($r = 0.81$) and "the experience had a supernatural quality" ($r = 0.69$) (see Table I and Fig. 2). Values for the first component were scaled and became our primary measure of interest.

The second component explained 13.97% of the variance (50.33% cumulative) and may be related to the emotional valence of the psychedelic experience. Higher scores in the second component were positively associated with "the experience had a spiritual/mystical quality" (0.65) which can be construed as being emotionally positive, whereas negative scores were associated with "my thinking was muddled" ($r = -0.7$), which relates to the psychotic symptom of thought-disorder and "I experienced unusual bodily sensations" ($r = -0.73$).

Diversity Coefficients

As described above, this analysis included a hypothesis-driven and whole-brain, exploratory part. The hypothesis-

TABLE II. Ego-dissolution phenomena and diversity coefficients

Region (ROI #)	postPSI	prePSI – postPSI	prePSI	PCB	postPSI-PCB
R aPHC (87)	−0.76 (<0.001)****	0.53 (0.04)*	−0.47 (0.08)'	0.01 (0.96)	0.6 (0.017)*
L aPHC (27)	−0.69 (0.004)***	0.62 (0.01)**	−0.21 (0.44)	0 (1)	0.64 (0.01)**
RSC (58)	0.28 (0.31)	−0.41 (0.13)	−0.04 (0.88)	0 (1)	−0.4 (0.14)
PCC (46)	−0.17 (0.53)	−0.2 (0.47)	−0.34 (0.21)	−0.17 (0.54)	−0.04 (0.89)

Pearson r (P-value)
'$P < 0.1$; *–$P < 0.05$; **–$P < 0.01$; ***$P < 0.005$; ****– $P < 0.001$
R/L aPHC–Right/Left Anterior Parahippocampal Cortex
RSC–Retrosplenial Cortex
PCC–Posterior Cingulate Cortex
prePSI–prepsilocybin; postPSI–postpsilocybin; PCB–placebo

driven analysis revealed a strong negative correlation between the intensity of the ego-dissolution phenomena and the diversity of the aPHC connections (See Table II and Fig. 3A), meaning that experiencing ego-dissolution was associated with reductions in functional connectivity or "communication" between the aPHC and the (mostly) cortical communities under the drug. To test the robustness of this result, we also looked at the ROI-based connectivity between the hippocampal formation and major brain networks (see Supporting Information) and an association between ego-loss and reduced MTL-cortical connectivity was confirmed using this approach.

It was somewhat surprising not to find any associations between the posteriomedial cortex (i.e. the PCC and the RSC) and ego-dissolution, given that previous work has supported this. However, there was a strong association between the second principal component that related to emotional valence of the experience (see Table I and Fig. 2) and posteriomedial (retrosplenial) cortex diversity (See Table III), for both conditions: before and after the psilocybin administration. Specifically, larger diversity of the retrosplenial area was associated with an increased likelihood of rather unpleasant experiences like muddled thinking, unusual bodily sensations and paranoid ideas.

Diversity Coefficients: Hypothesis-Free Part

In the hypothesis-free diversity coefficient analyses, only the baseline state (prepsilocybin) revealed regions where there were significant negative associations with ego-dissolution that survived adjustment for multiple tests (see Fig. 3B): left inferior frontal gyrus (belonging to the "higher cognition" community), left middle frontal gyrus and superior parietal lobule ("control network"). This means that lower diversity of the left frontoparietal regions (at baseline) was predictive of a higher likelihood of experiencing ego-dissolution under the psilocybin.

Within-Network Integrity

Analysis of mean clustering coefficient revealed that ego-dissolution was strongly associated with disintegration of the salience network (See Table IV and Fig. 3C). This finding was also supported when assessing differences between the placebo and postpsilocybin states.

Functional Connectivity: Whole-Brain Analysis

Analyzing functional connectivity in a whole-brain, hypothesis-free manner, we found that experiencing ego-dissolution was associated with reduced interhemispheric

TABLE III. Second principal component (relating to emotional valence of the experience) and diversity coefficients

Region (ROI #)	postPSI	prePSI - postPSI	prePSI	PCB	PCB-postPSI
RSC (58)	−0.7 (0.003)***	−0.2 (0.46)	−0.78 (<0.001)****	−0.72 (0.002)***	0.22 (0.43)
PCC (46)	−0.3 (0.29)	−0.18 (0.51)	−0.43 (0.11)	−0.61 (0.02)*	−0.45 (0.09)*

Pearson r (P-value)
*'–$P < 0.1$; *–$P < 0.05$; **–$P < 0.01$; ***$P < 0.005$; ****– $P < 0.001$
[†]RSC–Retrosplenial Cortex
[‡]PCC–Posterior Cingulate Cortex
[§]prePSI–prepsilocybin; postPSI–post-psilocybin; PCB–placebo

TABLE IV. Ego-dissolution phenomena and within-network integrity (mean clustering coefficients)

NWK	r (p_fdr)				
	postPSI	prePSI-postPSI	prePSI	PCB	PCB-postPSI
VIS:	−0.27 (ns)	−0.23 (ns)	− 0.45 (ns)	−0.23 (ns)	0.1 (ns)
SM:	−0.52 (0.09)*	0.11 (ns)	−0.33 (ns)	0.04 (ns)	0.56 (0.1)*
FP:	−0.54 (0.09)*	0.14 (ns)	−0.45 (ns)	−0.31 (ns)	0.4 (ns)
SAL:	−0.72 (<0.05)[a]	0.55 (0.23)*	−0.55 (0.16)	−0.21 (ns)	0.77 (<0.01)*
OFC:	−0.14 (ns)	0.12 (ns)	−0.07 (ns)	−0.39 (ns)	−0.17 (ns)
DLPFC:	−0.56 (0.09)*	0.3 (ns)	−0.52 (0.16)*	−0.5 (ns)	0.46 (ns)
DMN:	−0.45 (ns)	0.36 (ns)	−0.18 (ns)	−0.39 (ns)	0.28 (ns)

Pearson r (P-value)
VIS–Visual; SM–Sensorimotor; FP–Frontoparietal; SAL–Salience; OFC–Orbitofrontal;
DLPFC–Dorsolateral Prefrontal; DMN–Default Mode;
*– $P < 0.05$; **– $P < 0.01$ [FDR-corrected];
°– $P_{corr} > 0.05$ & $P_{uncorr} < 0.05$
ns–nonsignificant
prePSI–pre-psilocybin; postPSI–post-psilocybin; PCB–placebo

interplay and disconnection of the MTL areas from parietal lobes (See Fig. 3D). This analysis was repeated after excluding negative edges, and the resulting pattern was still the same.

DISCUSSION

The principal aim of the study was to identify changes in brain network properties related to psilocybin-induced ego-dissolution. As predicted, results revealed that this experience was associated with a disrupted interplay between the MTL and the neocortex. Analysis of within-network integrity revealed an association between decreased salience network integrity and ego-loss phenomena.

The brain network most often associated with self-consciousness is the DMN [Qin and Northoff, 2011], which is known to be engaged in a broad range of functions that fall under the construct of the ego/self (see introduction) [Buckner et al., 2008; Li et al., 2014; Ostby et al., 2012; Reniers et al., 2012]. The PHC is particularly thought to mediate cross-talk between the DMN and the hippocampus [Ward et al., 2014], and the disconnection between this region and the major brain networks seen in our study is broadly consistent with the previously hypothesized association between MTL-DMN decoupling and ego-dissolution [Carhart-Harris, 2007; Carhart-Harris and Friston, 2010; Carhart-Harris et al., 2014b].

However, we did not find disintegration of the DMN to be associated with ego-dissolution in the present analysis. Rather, the relationship between MTL-cortex decoupling and ego-dissolution was more generalized than predicted. In the present study, higher diversity of the posterior DMN nodes (both at baseline and under the drug) was

associated with increased likelihood of unpleasant, psychosis-like experiences like muddled thinking, unusual bodily sensations, and paranoid ideas. Reconciling the present results with previous ones, it is possible that the DMN is more related to the "narrative self" (ego-identity), whereas the dynamics of the salience network may promote other aspects of self-consciousness falling under construct of the "minimal" [Limanowski and Blankenburg, 2013] or "embodied self" [Seth, 2013] contributing to active inference and reality testing. Indeed, one of the most intriguing results of the present set of analyses was the finding that disintegration of the salience network related to ego-dissolution.

The salience network [Seeley et al., 2007] and its component regions (e.g. the anterior insula and dorsal anterior cingulate cortex) have previously been linked with reasoning under uncertainty [Donoso et al., 2014; Singer et al., 2009], mental effort [Engstrom et al., 2013], self-agency [Farrer and Frith, 2002], time perception [Craig, 2009], and salience evaluation [Menon and Uddin, 2010]. Atrophy in regions of the salience network such as is seen in fronto-temporal dementia, has been linked to reduced empathy, self-awareness, and self-control [Seeley, 2008; Seeley, 2010]. Electrical stimulation of the dorsal anterior cingulate region has recently been found to induce feelings of an impending challenge that must be overcome, described as a "will to persevere"[Parvizi et al., 2013]. Notably, the salience network and its components have also been put forward as potential neural correlates of self-consciousness and the "embodied self" in particular [Craig, 2009; Seth, 2013]. Compromised connectivity within this network has previously been linked with impaired self-awareness in patients with traumatic brain injury [Ham et al., 2014]. The salience network and its components receive a heavy dopaminergic innervations [Haber, 2011; Tian et al., 2013]

and are believed to play a role in modulating the switching between the default-mode and executive networks [Uddin, 2014]. In Parkinson's disease, patients on dopaminergic medication showed an enhanced action-effect binding (a measure of agency) relative to their own performance when off medication [Moore et al., 2010]. Furthermore, some pro-dopaminergic stimulants are known to counteract effort-induced depletion of regulatory control (also known as "ego depletion") [Sripada et al., 2014], which is generally consistent with the notion that stimulants provide an "ego-reinforcing" effect. The salience network has also been linked to perseverative behaviors including addiction [Goldstein and Volkow, 2011; Goldstein et al., 2010; Sutherland et al., 2012]. Damage to the insula has been associated with reduced craving [Naqvi et al., 2007] and fMRI studies have implicated impaired functioning of the salience network in addiction both at rest [Lerman et al., 2014] and during the performance of cognitively demanding tasks [Goldstein and Volkow, 2011; Goldstein et al., 2010]. Pro-dopaminergic medication has been found to normalize these abnormalities and to reduce impulsivity [Goldstein and Volkow, 2011]. Interestingly, there is historical and renascent support for the use of psychedelic drugs in the treatment of addiction [Krebs and Johansen, 2012] with high-dose sessions intended to promote ego-dissolution being the model of choice in early studies [Grof et al., 1977]. Future research may focus on the relationship between ego-dissolution and psychedelics' putative therapeutic action. Thus, it has already been suggested that ego-dissolution, as an important aspect of mystical experience [James, 1902; Maclean et al., 2012], is specifically relevant for positive therapeutic outcomes [Grof et al., 1977; Grof et al., 2008; MacLean et al., 2011].

Another intriguing aspect of the present results was the association between reduced interhemispheric connectivity and ego-dissolution. Coherent functioning between the hemispheres has previously been proposed to contribute to the maintenance of a sense of self, particularly highlighting its contribution to the sense of agency and awareness of the body parts [Uddin, 2011]. "Split-brain" patients show largely preserved self-awareness; however, "ownership" and agency are sometimes compromised in these individuals [Uddin, 2011]. An fMRI study of a patient who had undergone a complete commissurotomy found relatively well preserved interhemispheric connectivity postoperation, presumably due to preserved subcortical-cortical connections [Uddin et al., 2008]. It is noteworthy that many of the connections found to relate to ego-dissolution in the present analysis included a MTL region. We might infer from this that interhemispheric connections involving the MTLs are particularly important for the maintenance of a coherent sense of self.

The mind-altering effects of psychedelic drugs are known to vary considerably between individuals and efforts to determine predictors of drug-response have, to our knowledge, been limited to psychological measures [Carhart-Harris et al., 2014a; Studerus et al., 2012]. The present analyses are novel therefore, since they examined potential neurobiological predictors of response by looking at network metrics in the baseline data (placebo and pre-psilocybin states). In a previous behavioral study, sensitivity to the suggestibility-enhancing effects of LSD was best predicted by baseline "conscientiousness" [Carhart-Harris et al., 2014a], that is, higher baseline conscientiousness predicted higher suggestibility under the drug. This finding was interpreted as implying that those who are normally most resistant to suggestion (i.e. highly conscientious individuals) are more sensitive to the (suggestibility-enhancing) effects of psychedelics. The present results may be interpreted in a similar way, since individuals who displayed a low diversity of connections in executive regions (consistent with efficient network segregation–which is known to be reversed by psilocybin [Carhart-Harris et al., 2013; Roseman et al., 2014], were the most likely to report ego-dissolution under the drug. These results are broadly supportive of the idea that efficient network segregation is related to firm ego-boundaries and that those who possess especially firm boundaries at baseline are more sensitive to the (ego-dissolving) effects of psychedelics.

The present results can be interpreted from a Bayesian [Doya et al., 2011] and free-energy minimization [Carhart-Harris and Friston, 2010; Friston, 2010] perspectives. According to this view, the brain is seen as an inference machine making predictions about the world [von Helmholtz, 1866] and updating them based on experience and more specifically "surprise" [Friston, 2010; Friston et al., 2013]. From this perspective, any mental act, including perception, is analogous to a scientific experiment: an inference is made based on prior knowledge and then modified or updated based on what is experienced [Fletcher and Frith, 2009]. According to our observations, psychedelics alter these core functions of the brain with the effect of diminishing confidence or "certainty" about perceived phenomena. It is intriguing to speculate about the mechanics underlying this phenomenon and the present results implicate a role for decreased PHC-neocortex communication and/or decreased salience network integrity. Since the Bayesian model of brain function rests on hierarchical processing, further work is required to understand the relationships between the networks implicated in the present results, particularly focusing on the hierarchical relations between the default mode, salience and control networks and their roles in higher cognition [Buckner, 2013; Seth, 2013].

IMPLICATIONS FOR PSYCHOSIS RESEARCH

Similarities between early acute psychotic and psychedelic states have been highlighted by many authors [Bercel et al., 1956; Carhart-Harris et al., 2013; Grof et al., 2008; Spitzer et al., 1996; Vollenweider and Geyer, 2001; Vollenweider et al., 1998] and psychedelics offer a useful means of studying brain mechanisms underlying various

psychotic phenomena including ego-disturbances. Broadly speaking, many phenomena occurring during psychedelic states can be considered "psychotic" in some sense and it is logical to infer that the changes in brain dynamics observed here with psilocybin may also arise spontaneously in nondrug-induced psychoses, especially in those states where "ego-disturbances" are a core feature [Bleuler, 1911; Bleuler, 1934; Jaspers, 1913].

In the present study, the first principal component yielded from the subjective measures of psychedelic experience was strongly associated with ego-dissolution phenomena. This component also favored "productive" features of the psychedelic experience and was relatively independent from the emotional valence of the experience. This structure of psilocybin-induced psychedelic experience observed in our study replicates results from previous exploratory factor analysis of two independent samples [Maclean et al., 2012]. Similarly, in a meta-analysis conducted by Studerus et al. [Studerus et al., 2010], items related to ego-dissolution (such as "feeling of unity," "burring of boundaries between the self and surroundings," "disappearance of time") were strongly correlated with each other and, at the same time, were relatively independent from negative affect and psychosis-like features of the experience (like catatonic symptoms, paranoia, ideas of "alien control," etc.). The authors particularly conclude that under certain assumptions, altered states of consciousness can be conventionally differentiated based on whether they describe pleasant or unpleasant phenomena related to ego-disturbances.

Remarkably, a similar structure of psychotic experience in schizophrenia has been reported previously with a "loss-of-boundary" component being related to the majority of productive phenomena, and persecutory ("paranoid") negatively charged delusions being relatively independent from other symptoms [Bakhshaie et al., 2011; Minas et al., 1994]. As noted by Studerus et al., the appropriate factor structure describing altered states of consciousness particularly depends on its specific use [Studerus et al., 2010]. It is argued here that a two-factor model may be of interest for psychiatric research, particularly when drawing parallels between drug-induced and endogenously occurring ego-disturbances.

It is important to highlight that higher scores on the first component were not explicitly associated with the presence of frightening aspects of the experience (more often, but not always, seen in acute endogenous psychotic states). Rather, it was negative loadings on the second component that were associated with negative aspects of the psychedelic experience: specifically, this component was associated with low scores on "muddled thinking", "suspiciousness", "strangeness" and "unusual bodily sensations", and high scores on items pertaining to positive "spiritual" aspects of the experience (see Table I and Fig. 2). This suggests that ego-dissolution per se is not an intrinsically unpleasant and/or pathological experience,

and may in fact even be therapeutically useful [MacLean et al., 2011]. This, however, does not prevent us from drawing parallels with endogenous psychotic states, which may also manifest with positively charged and even mystical/spiritual content of the experiences [Buckley, 1981; Copolov et al., 2004]. This matter touches on a contentious and long-running debate (whether or not spiritual experiences should be pathologised) that is beyond the remit of the present paper. Of note, unlike psychedelic states, acute endogenous psychosis has been demonstrated to manifest with increased activity and connectivity of the key DMN nodes, which, in turn, is associated with positive symptoms of schizophrenia [Buckner, 2013]. One of the principal distinguishing features between drug-induced ego-dissolution and endogenously occurring ego-disturbances may be that the former is anticipated and even welcomed, whereas the latter is not. When ego-dissolution is expected it is less likely to be met with distress and resistance. Related to this, since all of the participants in the present study had previous experience with psychedelics, further research directly comparing phenomenology of psychedelic states in experienced and inexperienced subjects is needed.

In the present study, we did not find effects of ego-loss on the diversity of the posteriomedial cortex. Instead, it was the second component ("emotional valence" of the experience) that demonstrated strong associations, so that unpleasant "content" of the experience was associated with higher functional diversity of the posterior DMN node, RSC. Our results therefore support the idea that ego-disturbances might be the sine qua non of a broad range of drug-induced and endogenously occurring psychotic states arising from disintegration of the salience network and decoupling of the hippocampal formation from the major neocortical communities. Taking a Bayesian perspective, disturbance of ego-functions (like reality-testing) results in impaired inference about the world. This may result from a breakdown in the brain's normal hierarchical organization, perhaps forcing perception to rely more heavily on priors, which, in turn, may have "negative" or "positive" affective valence. This idea is also nicely in line with the so-called "set and setting" concept [Zinberg, 1984], according to which previous experiences and personality of a patient taking psychedelic drug, together with the environment of the session, are two critical factors influencing the content of the psychedelic experience. Further work is required to determine mechanisms underlying these effects; however, based on the present results, it is reasonable to speculate that interplay between the DMN (incl., MTL regions) and the salience network may be involved.

LIMITATIONS

Several methodological aspects of the present work have to be addressed. One important limitation is the relatively small sample size. Therefore, caution is advised when

generalizing our findings to broader populations, especially to people without previous psychedelic experience and psychosis-prone individuals.

Unlike most of the previous studies analyzing direct effects of psychedelics on brain dynamics, the present analyses were specifically focused on those aspects of the drug experience that were the most variable among subjects. To do this, we extracted a composite score based on PCA of the 22 VAS items. PCA is a useful data-reduction technique that identifies main components (within a multivariate dataset) that account for the largest proportion of the variance within the data. The first principal component typically identifies a subset of variables that are correlated with each other but also contain high between-subject variance. Items related to ego-dissolution fitted these criteria better than any of the others. It should be made clear that the results of the PCA did not imply that ego-dissolution is the most marked or reliable effect of the drug; rather, it told us that it is the most variable among subjects and is closely related to many "productive" features of the experience. One interpretation of an item or variable that shows high between-subject variance is that it is "noisy," and when the variable is subjective, this might be because different individuals interpret it differently. This interpretation of the present PCA result is contradicted however by the high correlations between three items pertaining to ego-dissolution. This suggests that the ego-dissolution construct has convergent validity and so is measuring a meaningful aspect of the subjective experience.

It must be conceded however, that the construct of ego-dissolution requires much more work to develop its validity. Moreover, characterizing various aspects of Ich-störungen was not possible with the measures employed in the present study and the extracted composite score may describe several phenomenologically and physiologically related processes (e.g. disturbances of both the "narrative" and the "embodied" self). The use of multiple measures (e.g. subjective and behavioral), evaluating different domains and aspects of ego-disturbances in the same studies is therefore advised. Thus, efforts should be made to demonstrate the convergent and divergent validity of the ego-dissolution construct in various endogenously occurring and drug-induced altered states of consciousness. Assessments tools like the Ego Pathology Inventory assessing different aspects of ego-consciousness could be useful in this respect [Scharfetter, 1981].

CONCLUSIONS

The present results implicate MTL-cortical decoupling, decreased salience network integrity, and reduced inter-hemispheric communication in psilocybin-induced ego disturbance and suggest that the maintenance of "self" or "ego," as a perceptual phenomenon, may rest on the normal functioning of these systems. Future work is required to standardize evaluation of ego dissolution and ego-disturbances more generally in order to investigate their similarities and

differences among different altered states of consciousness. In this way, we also hope to develop our understanding of the "self" or "ego", its neural correlates, and how it can be compromised in different conditions.

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