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RESEARCH REPORT

Single-dose psilocybin alters resting state functional networks in patients with body dysmorphic disorder

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Body dysmorphic disorder (BDD) is a severe psychiatric condition characterized by preoccupation with perceived flaws in one's appearance, which the individual views as defective or ugly. Psilocybin, a serotonin 2A receptor agonist with psychedelic properties, has emerged as a potential therapeutic agent for depression and other psychiatric disorders. This study aimed to identify subacute neural changes predicting symptomatic response to psilocybin treatment in adults with BDD. Eight adults with moderate-to-severe nondelusional BDD were administered a single oral 25 mg dose of psilocybin, accompanied by psychological support, and underwent resting state functional magnetic resonance imaging assessments 1 day before and 1 day after the dosing. Both a region of interest (ROI)-to-ROI analysis and multivariate pattern analysis (MVPA) were used to identify changes in resting state functional connectivity (rsFC) at day 1 after dosing that predicted treatment response at week 1, measured by change in Yale-Brown Obsessive Compulsive Disorder Scale Modified for BDD (BDD-YBOCS) score. All participants completed the dosing and follow-up assessments over 12 weeks. BDD-YBOCS scores decreased at week 1 and week 12 after dosing ($p<0.001$ for both). MVPA revealed a significant increase in rsFC within the Executive Control Network (ECN) at day 1. Increased rsFC within the ECN (dlPFC – Superior Parietal Lobule [FPL]), between the ECN and Default Mode Network (dlPFC – Precuneus), and between the ECN and the Salience Network (dlPFC – insula) were predictive of improvement in BDD symptoms at week 1. These findings are the first report of subacute brain effects of psilocybin in patients with BDD. Given the small sample size and uncontrolled design of the study, larger controlled studies are necessary to validate these observations.
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Keywords: Body dysmorphic disorder, psilocybin, resting state fMRI, functional connectivity, treatment response.

Introduction

Body dysmorphic disorder (BDD) is a chronic psychiatric disorder characterized by an obsessive fixation on perceived flaws or defects in physical appearance, which appear slight or nonexistent to others (1). The population point prevalence of BDD is estimated to be from 0.7% to 2.4% (2, 3). BDD is a debilitating and persistent disorder, and is often comorbid with eating disorders, obsessive-compulsive disorder (OCD), depression, and anxiety disorders (4), complicating diagnosis and treatment. Studies using resting state functional magnetic resonance image (rs-fMRI) have revealed that patients with BDD exhibit altered brain resting state functional connectivity (rsFC) within and between brain regions involved in visual processing (5), emotional regulation, and attention (6–8). These alterations may underlie the distorted perception of bodily appearance within the BDD population.

Both cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) have appeared efficacious for treating BDD; however, many individuals either cannot tolerate or do not benefit from these treatments, suggesting a great need for novel treatments (9). Psilocybin, a serotonin 2A receptor (5-HT2A) agonist with psychedelic properties, has recently shown promise in randomized controlled trials for treating depression (10, 11) and OCD (12). Psilocybin has demonstrated promising results in alleviating symptoms such as thought rumination (13–15), which may also be a prominent symptom in BDD (16, 17). The neural mechanisms through which psilocybin achieves therapeutic effects remain poorly understood. Imaging studies have examined psilocybin effects acutely (during the psychedelic experience that occurs for up to 8 hours after dosing), subacutely (at 1 day to 1 week post-dosing), or long-term (at greater than 1 week post-dosing) in healthy controls (HC) and depressed individuals.

This study focused on the subacute effects of psilocybin on rsFC at 1 day post-dosing, less than 24 hours after the psychedelic experience had ended. Previous rs-fMRI studies have found rsFC to be altered subacutely within the Executive Control Network (ECN) and between the ECN and other networks and brain regions following psilocybin administration in HC and individuals with depression. Specifically, in HC, reduction of rsFC in the ECN was observed 1 week after psilocybin administration. Greater reduction in ECN rsFC predicted increased mindfulness 3 months later (18). Another study of subacute effects, however, found that psilocybin increased whole-brain rsFC connectivity at 1 week and 1 month post-psilocybin (19). In individuals with depression, at 1 day post-administration of psilocybin, rsFC was increased in ventromedial prefrontal cortex and bilateral inferior lateral parietal cortex (10). This change in rsFC was predictive of the treatment response in depressed patients after 5 weeks (10). Another study in depression reported rsFC 1 day after psilocybin to be significantly increased between the ECN and the Default Mode Network (DMN), and between the DMN and the Salience Network (SN), but reduced within the DMN (20). Furthermore, increased dynamic rsFC in the cingulate cortex was observed 1 week after psilocybin treatment in individuals with depression (21).

There have been no previous reports of the effects of psilocybin on brain rsFC in individuals of BDD. In the first study of psilocybin for BDD, we recently reported significantly decreased BDD symptoms after a single open-label 25 mg dose of psilocybin (22). This study reports on the subset of those participants who also completed rs-fMRI, aiming to investigate subacute effects on rsFC and their correlation with symptom change in adults with BDD. We hypothesized that in BDD, similarly to what was observed in individuals with depression 1 day post-treatment, psilocybin would increase functional connectivity of the following networks: ECN, DMN, and SN, and that these changes would predict treatment outcomes.

Methods

Participants

Twelve adults with moderate-to-severe nondelusional BDD received a single oral dose of psilocybin 25 mg with psychological support (demographic information found in Table 1). Eight participants completed both pre- and post-dosing (day 1) MRI assessments, and these

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Table 1. Demographic and clinical characteristics of the sample

Gender, *n*	
Male	3
Female	5
Race/Ethnicity, *n*	
White, non-Hispanic	6
White, Hispanic	0
Black, non-Hispanic	0
Black, Hispanic	0
Asian/Pacific Islander	2
Other	0
Education, *n*	
College graduate	4
Graduate or professional school	4
Age, mean (SD) years	36.75 (8.82)
Duration of BDD, mean (SD) years	23.91 (11.83)
Comorbidity, *n*	
Major depressive disorder	3
Attention deficit hyperactivity disorder	1
Generalized anxiety disorder	1
Posttraumatic stress disorder	0
Number of SSRI/SNRI trials, mean (SD, range)	2.75 (3.37, 1–11)
Time from last dose of SSRI/SNRI to study treatment, mean (SD, range), weeks	320 (219.53, 6–572)
Total number of psychotherapy trials, mean (SD, range)	1.38 (1.77, 0–5)
Exposure based therapy trials, mean (SD, range)	0.63 (1.41, 0–5)

comprise the sample analyzed for this report. Four participants did not complete MRI assessments due to having a contraindication to MRI or due to scheduling difficulties. The study design was reviewed and approved by the New York State Psychiatric Institute Institutional Review Board, and participants' informed consent was obtained after study procedures had been fully explained.

Inclusion criteria were: 1) age 18–55 years; 2) principal diagnosis of nondelusional DSM-5 BDD for >6 months; 3) at least moderate severity [total score ≥24 on the Yale Brown Obsessive Compulsive Scale Modified for BDD (BDD-YBOCS) (23) and score ≥4 on the Clinical Global Impression Severity Scale) (24)], and 4) history of nonresponse to (or intolerance of) a prior trial of an SSRI, serotonin-norepinephrine reuptake inhibitor, or clomipramine, at dose equivalent to ≥20 mg/day fluoxetine for ≥2 months. Absence of delusionality was operationalized by a 6-item total score of ≤18 on the Brown Assessment of Beliefs Scale (25).

Exclusion criteria included current major depressive disorder of greater than moderate severity (17-item Hamilton Rating Scale for Depression score >20) (26); current significant suicidality or attempt in the past year; current or past bipolar disorder, psychotic disorder, borderline personality disorder, or dissociative disorder; alcohol or substance use disorder in the past 3 months, or positive urine drug screen for illicit substances of abuse; significant cognitive impairment; use of investigational medication within 3 months, depot antipsychotic within 6 months, or serotonergic medication within 2 weeks (6 weeks for fluoxetine); presence of significant medical illness; history of seizure disorder; and females who were pregnant, breastfeeding, or sexually active and not using adequate contraception. Current CBT for BDD was exclusionary, but participants were required to be seeing a psychotherapist with whom they could continue non-CBT psychotherapy after dosing, to further support integration of their psilocybin experience (beyond the psychological support provided within the study).

Treatment Procedures

These are detailed in Schneier *et al.* (22). Briefly, study drug was administered orally at 9 AM as five 5 mg capsules of COMP360 psilocybin, COMPASS Pathways' proprietary synthetic formulation, in conjunction with psychological support. The 25 mg dose was selected based upon prior findings of efficacy and tolerability for depression (27).

Assessments

Clinical assessments were carried out at baseline (1 day before dosing), the end of the dosing day (day 0), day 1, and weeks 1, 2, 3, 6, 9, and 12 post-dosing. MRI scans were collected at baseline and day 1. The primary efficacy measure was BDD symptom severity in the prior week, as measured by the BDD-YBOCS, a clinician-rated scale (total score range: 0–48, with higher scores indicating greater severity).

Neuroimaging Procedures

Neuroimaging Data Acquisition. MRI data were acquired 1 day prior to the first treatment session, and again 1 day after treatment using a 3T General Electric PREMIER (GE Medical Systems, Waukesha, WI, USA) with a 32-channel receive-only head coil. A high-resolution T1-weighted three-dimensional BRAVO sequence was acquired using the following parameters: T1 = 1060 ms, Flip angle = 8°, field of view = 25.6 cm, 256 × 256 matrix, slice thickness = 1 mm. Ten-minute eyes-open resting state scans were acquired with TR = 900 ms, TE = 26 ms, FA = 52°, FOV = 21.6 cm, slice thickness = 2.4 mm, number of slices = 60, number of volumes = 300.

Imaging Preprocessing. rs-fMRI images were preprocessed using MATLAB version R2020b (The MathWorks, Inc., Natick, Massachusetts) and statistical parametric mapping software (SPM12; Welcome Trust Centre for Neuroimaging, UCL, London, United Kingdom). Preprocessing steps included slice-time correction and motion correction using a six-parameter rigid body transformation, then co-registration to each participant's T1-weighted structural image. Co-registered images were normalized to the Montreal Neurological Institute (MNI) canonical template, and smoothed with an 8 mm full-width-at-half-maximum Gaussian kernel. Functional connectivity analyses were performed on the smoothed images.

Functional Connectivity Analysis

Denoising. Resting-state functional connectivity analyses were carried out using CONN-fMRI Functional Connectivity toolbox v13 (28). Before correlation analysis, band-pass filtering with a frequency window of 0.01 to 0.09 Hz was performed. Outlier detection was carried out with artifact detection tools (ART) implemented in CONN. Outlier volumes in each participant were identified as having large spiking artifacts (i.e., volumes >3 standard deviations from the mean image intensity), or large motion (i.e., 0.5 mm for scan-to-scan head-motion composite changes in the *x*, *y*, or *z* direction). Anatomical images were segmented into grey matter, white matter, and cerebrospinal fluid (CSF) regions. Covariates corresponding to head motion (six realignment parameters and their derivatives), outliers (one covariate per outlier consisting of an 1 s for the outlier timepoint and 0 s for all other timepoints), and the BOLD time series from the subject-specific white matter and CSF masks were used in the connectivity analysis as covariates of noninterest, and were removed from the BOLD functional time series using linear regression.

We carried out three analyses: The first analysis was to identify brain regions where change in rsFC from pre- to post-dosing (day 1) was predictive of treatment outcomes measured by reduction of BDD-YBOCS score from baseline to week 1. The change in BDD-YBOCS score at week 1 was used as the primary clinical outcome in this study because it was the earliest timepoint at which symptom severity could be assessed over a week, the usual time frame for assessment with this instrument. The second analysis was to explore brain regions where change in rsFC from pre- to post-dosing (day 1) was predictive of treatment outcomes measured by reduction of BDD-YBOCS from baseline to week 12. The third analysis was to identify change in rsFC from pre- to post-dosing (day 1).

rsFC analyses were carried out in two ways, using 1) region of interest (ROI)-to-ROI correlation analysis based on prior networks of interest, and 2) whole brain multi-variate pattern analysis (MVPA).

1) ROI-to-ROI connectivity analysis was performed using 19 network ROIs selected from classical networks defined from default CONN toolbox network atlas: DMN (4 ROIs), SN (3 ROIs), ECN (4 ROIs), dorsal attention network (DAN) (4 ROIs), and language network (4 ROIs) (29). All ROIs were defined based on CONN's independent component analysis (ICAs) of the

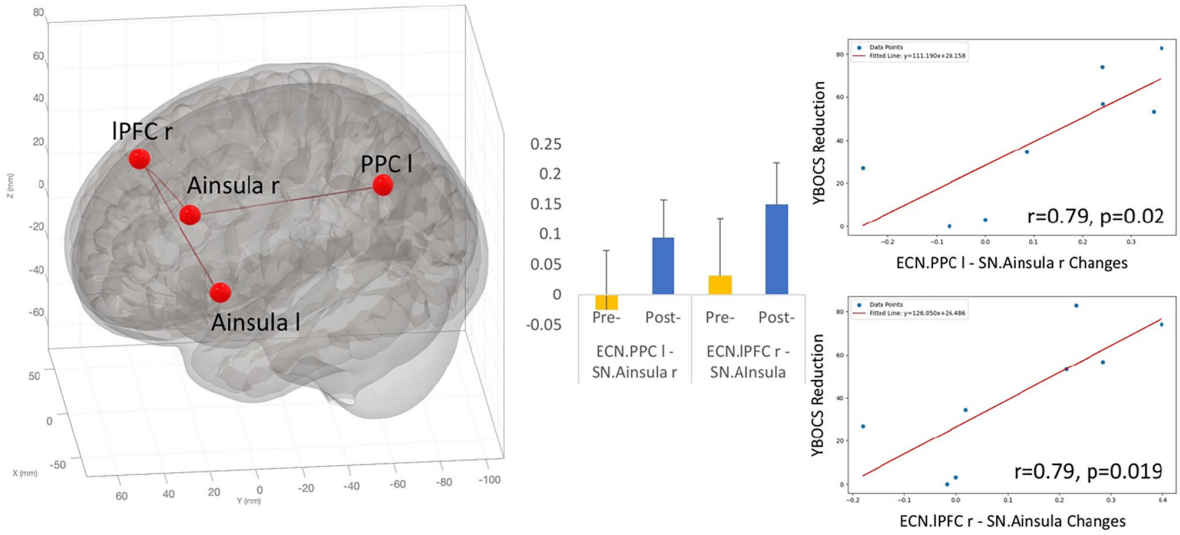

Figure 1. ROI-to-ROI analysis showed that the increased FPN – SN rsFC (lateral PFC right [lPFCr] – anterior insula left and right, and posterior parietal cortex left [PPCl] – anterior insula left and right) predicted reduction of clinical symptoms (BDD-YBOCS) from baseline to week 1, $p < 0.05$ cluster-level p-FDR corrected. LPFCr – left anterior insula, and LPFCr – right anterior insula have been averaged and generated lPFCr – anterior insula (AInsula). A total of 19 ROIs from 5 networks were included in the analysis: default mode (DMN), salience (SN), dorsal attention (DAN), executive control (ECN), and language network (LAN).

Human Connectome Project (HCP) dataset of 497 participants (28). We included 171 ROI-to-ROI connectivity pathways from the 19 ROIs [19 × 19-19)/2]. The mean BOLD time series was computed across all voxels within each ROI. Bivariate regression analyses were used to determine the linear association of the BOLD time series between each pair of regions for each subject. Both positive and negative correlations were examined. Each connectivity is tested independently against a null hypothesis and considered as significant if it meets the prespecified *p*-value threshold. The significant ROIs are subsequently grouped into clusters; these clusters suggest the observed effects are consistently significant as it is above the threshold. The resultant correlation coefficients were transformed into z-scores using Fisher's transformation to satisfy normality assumptions. Surviving the height threshold of $p<.05$, these ROI-to-ROI pathways are adjusted for multiple comparison using the FDR method, and FDR cluster-level threshold of $p < .05$ were considered significant. Age and sex were regressed out as covariates of no interest in all subjects.

2) We also applied MVPA for model-free voxel-wise rsFC analysis using the CONN toolbox. The first step of this approach is to identify regions/seeds where change in rsFC was associated with change in the main clinical outcome in all three analyses. This step allows narrowing down of seed brain ROIs from the vast number of possible regions. For each subject and MRI session, we computed pair-wise correlations between each voxel and all other voxels, which represents how similar the voxels respond throughout the rsfMRI data acquisition. To manage the large amount of data, principal components analysis was performed to reduce data dimensionality (default number of 64 components) by projecting the data from high dimensional space to lower dimensional subspace (principal subspace) such that the variance of the projected data was maximized; this captures the variances of the data using reduced amount of data. The four strongest spatial principal components were selected (30). In other words, each voxel had a four-dimensional representation of the spatial pattern of its connectivity to all other voxels for each subject. Then, to assess the association of changes in rsFC from baseline to day 1 with changes in BDD symptoms from baseline to week 1 (analysis 1) and to week 12 (analysis 2), and to assess changes in rsFC from pre- to post-dosing (analysis 3), an omnibus *F* test was carried out comparing the between-subject variance across all voxels' connectivity patterns in four-dimensional space. This test yielded seeds that displayed a similar between-subject variance of their spatial connectivity. Thus, these clusters define areas of similar change in the rsFC patterns associated with changes in clinical outcome. These seeds were extracted as ROI masks and were applied for seed-to-voxel whole-brain analysis to determine whole-brain connectivity patterns that were associated with the clinical outcome (change in BDD-YBOCS). Clusters surviving a height threshold of $p < .05$ and FDR cluster-level threshold of $p < .05$ were considered significant.

Results

All eight participants completed dosing and follow-up clinical assessments over 12 weeks. BDD-YBOCS scores decreased significantly from pretreatment to week 1 and to week 12 ($p < 0.001$ for each), as previously reported for the full sample (22).

1. **Changes in functional connectivity predicting symptom improvement at week 1 with psylocibin**

ROI-to-ROI analysis revealed that changes in rsFC of each of two regions of the ECN (right lateral PFC [lPFCr] and left posterior parietal cortex [PPCl]) with the SN (insula) predicted symptomatic improvement. Greater increases in these rsFCs were predictive of greater response to treatment measured by reduction of YBOCS score from baseline to week 1 ($p < 0.05$ cluster-level *p*-FDR corrected) (Figure 1).

The MVPA replicated findings of the ROI-to-ROI analysis that increased ECN rsFC predicted clinical outcome, and identified one seed region in the ECN, specifically in the dlPFC [48 38 22] (Figure 2). Using this cluster, a seed-based whole-brain correlation analysis of rs-fMRI data, corrected for multiple comparisons at cluster level (peak level: $p < 0.05$, uncorrected; cluster level: $p < 0.05$, FDR-corrected), indicated that greater rsFC within ECN (dlPFC-superior parietal lobe [SPL]), between ECN and SN (dlPFC-anterior cingulate cortex [ACC]), and between ECN and DMN (dlPFC-precuneus) predicted greater response to treatment at week 1 (Figure 2).

2. **Changes in functional connectivity predicting symptom improvement at week 12 with psylocibin**

ROI-to-ROI analysis did not reveal any significant changes in rsFC that predicted symptomatic improvement at week 12. However, a trend-level result suggested that change in ECN-SN (lPFCr-Insula) was predictive of a greater response to treatment measured by reduction of YBOCS score from baseline to week 12 ($p < 0.008$ uncorrected).

The MVPA of change in rsFC predicting change in symptoms from baseline to week 12 revealed significant clusters including the thalamus [8 –6 8], the insula [–42 8 –6], the inferior parietal lobe (IPL) [–54 –38

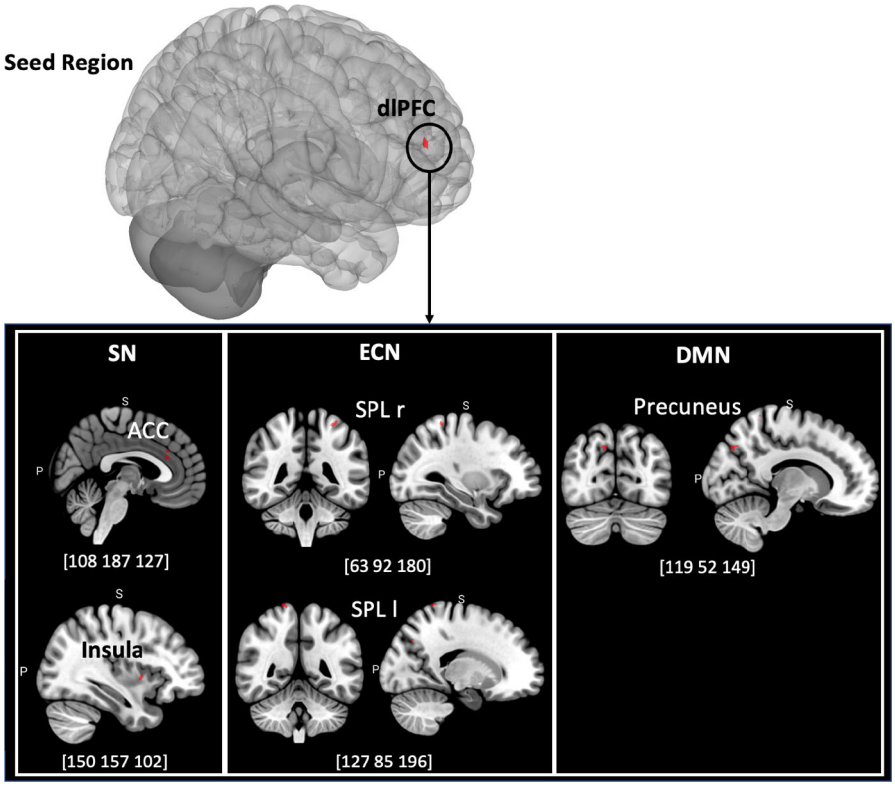

Figure 2. Whole brain MVPA revealed that one seed region dlPFC lPFC [48 38 22] predicted symptomatic improvement at week 1. Using this cluster as a seed region, a seed-based whole-brain correlation analysis revealed that increased within-ECN, ECN-SN, and ECN-DMN connectivity predicted symptomatic improvement (BDDYBOCS) at day 1, peak level: $p < 0.05$, uncorrected; cluster level: $p < 0.05$, FDR-corrected.

38], and the ACC [16 34 24]. Using these clusters as seeds, separate seed-based whole-brain correlation analyses were conducted for each seed region, and these did not reveal any other regions associated with symptomatic improvement at week 12 (Figure 3).

3. **Changes in functional connectivity from baseline to day 1**

ROI-to-ROI analysis did not reveal any significant changes in rsFC from baseline to day 1.

The MVPA of change in rsFC from baseline to day 1 revealed one significant cluster in the dlPFC [–36 46 02]. Using this cluster, a seed-based whole-brain correlation analysis of rs-fMRI data, corrected for multiple comparisons at cluster level (peak level: $p < 0.05$, uncorrected; cluster level: $p < 0.05$, FDR-corrected), showed significant increase within the ECN connectivity (dlPFC- SPL) (Figure 4).

Discussion

These findings are the first report of brain changes after psilocybin administration in patients with BDD. Findings indicate that within-ECN connectivity increased. Moreover, increased within-ECN, ECN-DMN, and ECN-SN connectivities at day 1 predicted greater reduction in symptoms at week 1, as measured by the decrease in BDD-YBOCS scores.

To assess the clinical relevance of these early changes in rsFC, beyond any broad, nonspecific effects of psilocybin on brain networks, we conducted regression analyses to identify any specific changes in connectivity that were predictive of positive treatment outcomes. These analyses suggest that the therapeutic effects of psilocybin are predicted by changes in more-specific connectivity patterns, including those within the ECN, between the ECN and the SN, and between the ECN and the DMN. These findings suggest that psilocybin's clinical benefits may derive from its capacity to foster more functionally integrated brain network activity, particularly involving these key networks.

Within-ECN

The ECN, characterized by its extensive connectivity with other brain networks, plays a role in adapting and responding to the external environment through communication between neural networks (31, 32). The ECN is particularly involved in set-shifting, the cognitive ability to switch attention between different tasks. This function is crucial for

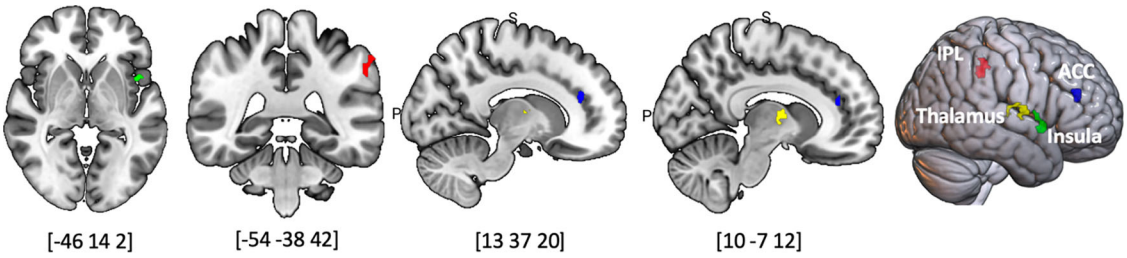

Figure 3. Whole-brain MVPA revealed that seed regions including the thalamus [8 –6 8] (yellow), insula [–42 8 –6] (green), IPL [–54 –38 38] (red), and ACC [16 34 24] (blue) predicted symptomatic improvement at week 1. Using these clusters as seed regions, no further regions were identified.

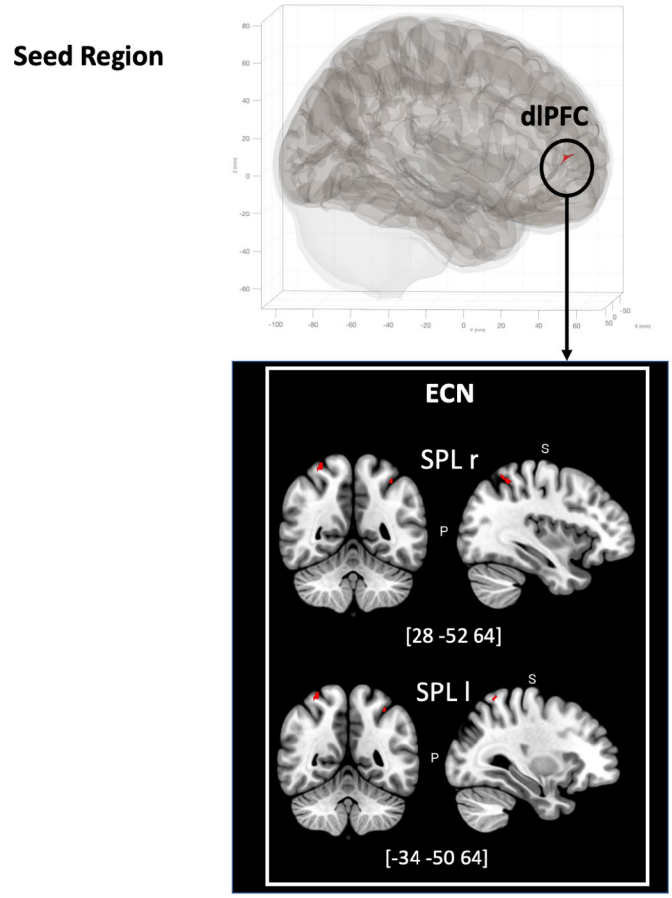

Figure 4. Using MVPA, rsFC was significantly increased within the ECN (dorsolateral prefrontal cortex [dlPFC]) from baseline to day 1. Using dlPFC as a seed, seed-to-whole brain analysis revealed increased dlPFC-SPLr [28 –52 64] and SPLl [–34 –50 52] from baseline to day 1. Peak level: $p < 0.05$, uncorrected; cluster level: $p < 0.05$, FDR-corrected.

mental flexibility and is often disrupted in neuropsychiatric disorders. Impaired set-shifting is a characteristic feature of BDD (33, 34), and may manifest clinically as difficulty moving thoughts or attention away from appearance-focused obsessional thinking. Emerging evidence suggests that psilocybin may enhance cognitive flexibility and set-shifting. One study reported neurochemical changes in ACC 1 week after acute psilocybin administration, and increased cognitive flexibility assessed by set-shifting task 4 weeks post-psilocybin (21, 35). Our findings of increased subacute within-ECN connectivity, specifically between dlPFC and SPL, and of greater rsFC within the ECN (dlPFC-SPL) predicting greater response to treatment at week 1, align with observations in HC immediately after psilocybin administration (36). In contrast, McCulloch *et al.* (18) reported decreased rsFC within-ECN in HC 1 week after psilocybin administration. Inconsistency in the direction of connectivity change may be related to differences in the time of scanning in relationship to psilocybin administration, or baseline differences between samples. In summary, subacute rs-fMRI studies suggest that psilocybin leads to changes in connectivity within the ECN. Moreover, our finding that increased within-ECN connectivity after psilocybin administration predicts clinical improvement in patients with BDD is consistent with the previous report of ECN (right SPL) involvement in the psychopathology underlying BDD (18) and suggests that this increase may promote clinically-relevant enhanced mental flexibility and decreased rigidity of thought patterns (21, 37).

ECN-SN

Connectivity between the ECN and the SN is important for the detection of salient cues, leading to efficient allocation of cognitive resources. Differential activation within the SN and the ECN in response to the stop-signal task suggests that while the SN identifies salient events, the ECN is involved in inhibitory control and set-shifting (38). The SN may be a potential a biomarker in BDD participants, as suggested by structural and task-based fMRI findings of SN regions (8, 36, 39, 40). In HC, one study revealed increased rsFC connectivity between the ECN and SN acutely, at 70 minutes following psilocybin administration (36). Our study assessed ECN-SN rsFC subacutely, 1 day post-psilocybin. Specifically, we noted that greater rsFC between the ECN and insula predicted clinical improvement at week 1 (41). Enhanced ECN-insula rsFC might facilitate executive control over emotional and salient stimuli, by shifting attention away from emotionally salient cues and supporting emotional regulation (38, 42, 43). Consequently, this may represent a mechanism through which psilocybin contributes to a reduction in the obsessive, negative emotionally-valenced preoccupation with perceived flaws characteristic of BDD.

ECN-DMN

The DMN is involved in self-referential thoughts, mind-wandering, and internally focused tasks. rsFC between the ECN and the DMN plays an important role in switching between task-focused states and introspective or self-referential states. Decreased ECN-DMN connectivity has been identified as a biomarker underlying depression, implying executive dysfunction in regulating the DMN through inhibitory control and emotional regulation (44). Increased ECN-DMN rsFC has been observed subacutely after psilocybin in a depressed sample (20). A longer-term follow-up MRI study also observed increased ECN-DMN 3 weeks after psilocybin administration (21). Lastly, increased ECN-DMN 1 day after psilocybin treatment has been found to predict alleviation of depressive symptoms (10). Our findings of increased ECN-DMN rsFC predicting symptom reduction at week 1 in patients with BDD is consistent with this literature. Reduced rsFC between the ECN (SPL) and the DMN (posterior cingulate cortex) has been associated with severity of self-focused attention in BDD (16, 45). The observed post-psilocybin increase in rsFC between the ECN (LPFC) and the DMN (precuneus) is consistent with a functional enhancement of emotion regulation capacity in BDD through facilitating the switch away from self-focused attention (46, 47).

We used both ROI-to-ROI and MVPAs in this study. The MVPA not only replicated the findings from ROI-to-ROI analysis, but also extended them by identifying additional significant target clusters. MVPA is capable of finding patterns of neural imaging data at voxel-level. Unlike traditional univariate approaches (e.g., ROI-to-ROI) that evaluate each region or connection in isolation, MVPA considers the full spatiotemporal pattern of brain activity. This allows capture of subtle interactions between regions, which might be missed when looking at each region separately, as is common in ROI-to-ROI analyses. Our results suggest that MVPA here detected nuanced patterns of rsFC involving the DMN that were not prespecified in the ROI-to-ROI analysis. Furthermore, MVPA identified specific increased connectivities of dlPFC with the SPL, ACC, and precuneus, which indicate a broader integrative role of the dlPFC across multiple networks (ECN, SN, and DMN) predictive of treatment response at week 1.

Week 12: Consistent with the findings predicting week 1 outcome, the ROI-to-ROI analysis revealed a trend result suggesting that increased connectivity between ECN-SN (lPFCr-Insula r) was predictive of a greater response to treatment at week 12. However, this result did not survive correction for multiple comparisons. In contrast, the MVPA found no significant rsFC of these identified seed regions to be predictive of clinical outcome at week 12. The loss of significance suggests, perhaps unsurprisingly, that long-term outcomes may be less directly tied to the early changes in network connectivity that could diminish over time. McCulloch *et al.* (16) reported impermanence of neuroplasticity in HCs, noting a significant reduction in within-ECN rs-FC at week 1 that was no longer evident at the 3-month timepoint. The long-term maintenance of the early clinical response observed following psilocybin administration could be affected by many factors, including preexisting psychopathology, brain

function, and interaction with environmental influences, such as the ongoing psychotherapy received by most participants in this study.

Limitations of this study include its small sample with limited diversity, which included six Caucasians and two of Asian/Pacific descent, all with a college degree and higher. The small sample size and the absence of a control group suggests that the observations must be considered tentative, but nonetheless provide the foundation of psilocybin's therapeutic potential in BDD warranting future investigations. Future studies of more diverse and larger samples are needed to verify these observations and evaluate their generalizability. Second, the absence of a control group raises concerns about nonspecific confounds contributing to the observed neurobiological changes. These confounds could include expectancy effects and the effects of psychological support and psychotherapy received by all participants. Future studies should include a control group to clearly differentiate the specific effects of psilocybin from potential placebo effects and to establish a causal relationship between psilocybin administration and observed changes in neural connectivity and symptomatology. Third, the study's single-dose design, with MRI repeated 1 day after dosing, was chosen to minimize participant burden and to focus on the subacute clinical and neural effects of psilocybin. Obtaining a more comprehensive understanding of psilocybin's mechanisms and durability of treatment effects will require study of multiple-dosing regimens with longer follow-up periods, and with imaging repeated at acute, subacute, and longer-term timepoints.

The current study protocol also examined rsFC changes only at 1 day after administration of psilocybin. Future studies should incorporate scanning across acute, subacute, and long-term timepoints to facilitate a more comprehensive understanding of the longitudinal impact of psilocybin. Imaging at the acute timepoint may reflect neural correlates of the psychedelic experience, at the subacute timepoint early changes in clinical symptoms, and at longer-term timepoints persistent changes in clinical symptoms. Future studies should also explore whether acute subjective effects of psilocybin are associated with neural connectivity changes at these timepoints. Lastly, previous task-based research in BDD participants has identified abnormalities within visual, perceptual, and attention-related networks (7, 45), altered connectivity between fusiform facial area and hubs within DMN and SN while viewing images of other faces (39, 40). The ECN alteration that was observed in this preliminary study may be related to cognitive control over SN and DMN hubs, thus achieving altered connectivity between SN and/or DMN and other visual, perceptual, and attention-related networks. Future studies should explore the ECN's role in interventional use of psilocybin in BDD.

In summary, our study provides a preliminary exploration of neurobiological mechanisms underlying psilocybin treatment for BDD. We found increased within-ECN connectivity, and found that the increased within-ECN, ECN-SN, and ECN-DMN connectivity predicted clinical improvement from baseline to week 1. Our findings are consistent with viewing the ECN as a central hub of the neurobiological underpinnings of BDD and suggest that psilocybin may exert its therapeutic effect through modulation of these networks. This indicates potential neural targets for enhancing the effectiveness of treatments for BDD and may guide future therapeutic strategies.

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