Commentary

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Bridging Psilocybin-Induced Changes in the Brain's Dynamic Functional Connectome With an Individual's Subjective Experience

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Psilocybin, the psychedelic compound found in "magic mushrooms," holds promise as a treatment for a variety of mental health disorders including depression, anxiety, eating disorders, and substance use disorders. In a typical course of treatment, psilocybin is co-administered alongside psychological and therapeutic support from trained practitioners. Individuals undergoing psychedelic sessions can have altered experiences of the world, including ego dissolution, i.e., the reduction in the boundary between one's self and surroundings; increasing feelings of unity with others and spiritual, blissful, or insightful states (oceanic boundlessness); unconstrained and hyperassociative cognition; profound alterations in the perception of time and space; synesthesia; visual hallucinations/distortions; and amplification/volatility of emotional states. In addition to the acute effects that an individual experiences during a psychedelic session, there is some evidence of longer-term changes in personality and mood, including increases in openness and extraversion, decreases in neuroticism, and increases in mindful awareness. Experiential components of these drug-assisted therapy sessions, in particular oceanic boundlessness, mediate therapeutic outcomes; however, not all patients respond in the same way to psilocybin or other psychedelics (1). Therefore, understanding psilocybin's effects on the brain, why they impact individuals differently, and how these mechanisms relate to subjective experiences is crucial for the development of personalized and effective therapy.

In the current issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Mortaheb *et al.* (2) reanalyzed resting-state functional magnetic resonance imaging (fMRI) data from 49 healthy individuals who received either psilocybin (0.17 mg/kg, $n = 22$, 12 males, age [mean ± SD] 23 ± 2.9 years) or placebo (bitter lemon, $n = 27$, 15 males, age 23.1 ± 3.8 years) (3). fMRI scans were acquired approximately 102 minutes postadministration, during the drug's peak subjective effects. This parallel group design differs somewhat from other within-subject psychedelic studies in which the same individuals are scanned both under placebo and under psychedelics. The result is additional intersubject variability in the analysis of the fMRI data due to the lack of placebo from the same individual for comparison. fMRI allows for high spatial resolution imaging of the brain's blood oxygen level–dependent (BOLD) signal, which is a proxy for neuronal activation. Static functional connectivity, assessed by correlating regional BOLD time series over the entire length of the fMRI scan, was calculated for both psilocybin and placebo fMRI scans. In addition, Mortaheb *et al.* calculated sliding-window dynamic functional connectivity, which allows for assessment of the temporal evolution of discrete functional connectivity states over the fMRI scan. The authors observed widespread increases in static functional connectivity under psilocybin that, using dynamic functional connectivity methods, was accompanied by a heightened occurrence of a recurrent hyperconnected pattern. Further analysis revealed a correlation between entering the hyperconnected state and experiences of oceanic boundlessness and visionary restructuralization, e.g., complex/elementary imagery, audiovisual synesthesia, and changed meaning of percepts. These findings broadly align with previous studies on psychedelics, although using slightly different methods of dynamic brain connectivity (4).

Interestingly, the hyperconnected pattern was characterized by low BOLD signal amplitude. Decreased BOLD signal amplitude has been related to heightened cortical arousal (5), suggesting that the hyperconnected pattern may be mediated by increased vigilance. Global BOLD signal is a topic of debate in the neuroimaging literature on psychedelics, as the decision on how to treat it (i.e., preserve it or remove its influence using global signal regression) has been shown to influence results. Indeed, when Mortaheb *et al.* (2) reproduced their analysis using global signal regression, the hyperconnected pattern was no longer present. Because of this, the authors advocate for preserving the global signal in dynamic analyses and propose that the global signal is a complementary metric to extracted dynamic functional connectivity patterns. This argument resonates with the author's previous work on mind blanking, which also exhibited a hyperconnected state—one that was accompanied by increased signal amplitude. In our own work, we have shown that psychedelics also decrease the transition energy between fMRI brain states, a metric that is influenced by BOLD signal amplitude; however, this result so far seems largely uninfluenced by global signal regression (6). Another component that influences the BOLD-based global signal and should be considered is changes to neurovascular coupling, which psilocybin may induce (7). Changes in neurovascular coupling mean that the fMRI signal may not be as reflective of neuronal activity. One way to overcome this limitation when imaging brain activation during psychedelics is the use of more direct measurements of neuronal activation, e.g., electroencephalography (EEG), that do not depend on vasculature. To this end, one recent study investigating the effects of *N*,*N*-dimethyltryptamine (DMT) on brain activity patterns collected simultaneous fMRI and EEG after administration of the drug and placebo (8). In our recent preprint (9), we analyzed the data from this study and

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showed that transition energy calculated using fMRI data was tightly coupled with EEG-based measures of brain activity entropy (lower transition energy tracked with increased brain activity entropy). It is worth noting that our DMT study also showed that transition energy significantly correlates with concurrent, continuous measures of subject-reported intensity of the DMT experience. However, our analysis of the lysergic acid diethylamide (LSD) and psilocybin data did not reveal a relationship between retrospective questionnaire assessments of subjective effects (e.g., oceanic boundlessness) and psychedelic-related transition energy decreases. More work needs to be done using simultaneous BOLD-based fMRI and EEG in individuals undergoing psychedelic sessions, perhaps with concurrent measures of subjective effects, to disentangle the neural and neurovascular effects of these compounds on individuals' experiences.

While Mortaheb *et al.* (2) make a compelling case for the utility of the global signal for elucidating dynamic brain effects with the methods, there are still components of the global signal that may arise from spurious effects such as head motion, respiration, and hardware artifacts (10). In-scanner head motion is a known confound in psychedelic neuroimaging, and the authors show here with reasonable confidence that their findings are not merely motion artifacts. First, they show that there was no between-condition difference in mean framewise displacement. Second, there was no difference in mean framewise displacement among the 4 dynamic functional connectivity patterns they identified. Lastly, neither averaged static functional connectivity nor BOLD signal amplitude was correlated with framewise displacement. The field has more work to do to fully elucidate the influence of motion and other physiological and nonphysiological artifacts on resting-state fMRI data when testing psychedelics.

Overall, this work presents a statistically rigorous and robust analysis of how psilocybin-induced changes in the brain's functional connectivity network (specifically, global hyperconnectedness) relate to various elements of individuals' subjective psychedelic experiences (specifically, oceanic boundlessness and visionary restructuralization). In the past several years, psychedelics have gained increasing attention for their potential in treating various mental health disorders. The subjective experience of an individual during the psychedelic session has been linked to therapeutic efficacy; however, it varies widely across individuals. A better understanding of the neural effects of psychedelics and how these effects relate to an individual's subjective experience and longer-term personality or behavior changes will allow for more targeted and personalized application of psychedelic-assisted therapy.

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Article Information

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