Commentary

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The Ups and Downs of 3,4-Methylenedioxymethamphetamine: Linking Subjective Effects to Spontaneous Brain Function

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Psychoactive drugs, especially drugs with so-called psychedelic properties, exert profound effects on sensory perception, cognition, and emotion by modulating target neurotransmitter systems. The compound 3,4-methylenedioxymethamphetamine (MDMA) exerts stimulant and psychedelic effects through its actions on dopamine, norepinephrine, and serotonin (5-hydroxytryptamine, [5-HT]) transporters, by inhibiting their reuptake and stimulating their release. In addition to producing euphoria and positive mood, MDMA appears to produce unique "prosocial" or "empathogenic" feelings. These effects distinguish MDMA from other stimulant and hallucinogenic drugs and are believed to be driven by its greater action at the 5-HT transporter. In humans, our understanding of these subjective and interoceptive effects has relied mainly on reports from users and a few controlled laboratory studies. A fundamental question—where and how MDMA and other psychedelic drugs exert their effects in the human brain—remains largely unanswered.

In this issue of *Biological Psychiatry*, Carhart-Harris *et al*. (1) address this knowledge gap by employing two modes of functional magnetic resonance imaging (fMRI), arterial spin labeling to measure cerebral blood flow (CBF) and resting-state functional connectivity (RSFC) to measure region-to-region coupling of spontaneous activity after a single dose of MDMA or placebo in a double-blind, balanced-order design in healthy experienced users. Behaviorally, MDMA induced "intense" and positive mood effects. For RSFC analyses, the authors used a seed-based approach to examine brain connectivity with the ventromedial prefrontal cortex (PFC), hippocampus, and amygdala as representative paralimbic/limbic nodes of socioemotional functioning. The CBF in the medial temporal lobe, thalamus, inferior visual cortex, and somatosensory cortex was decreased by MDMA. It also increased RSFC between amygdala and hippocampus and decreased RSFC between midline cortical regions, medial PFC, and medial temporal lobe. It decreased RSFC between ventromedial PFC and posterior cingulate cortex and between medial PFC and hippocampus. These neural effects of MDMA were related to self-reports: subjective intensity of drug effects was correlated with a reduction in hippocampus and amygdala CBF, and drug intensity and positive mood were correlated at trend level with RSFC within the ventromedial PFC, hippocampus, and amygdala network.

By examining MDMA effects on brain function in relation to its behavioral effects, this study takes an important step, adding valuable mechanistic insight into where in the brain MDMA exerts its potent psychoactive effects. This study critically begins to provide a brain-based framework (perfusion and connectivity) to help explain the unique prosocial or empathogenic effects of MDMA. The findings may help us to understand its appeal in nonmedical contexts as well as its potential use as an adjunct to psychotherapy. The study highlights some scientific challenges for pharmacoimaging studies more generally and points to important and much needed avenues for future research. We note some key issues in methods and interpretation and future directions raised by Carhart-Harris *et al.* First, how can we relate the mood and neural (fMRI) effects of drugs to their underlying neurochemical mechanisms of action? Second, can we advance our understanding of the neural targets of drug action by comparing MDMA with the psychedelic, prosocial, and mood-elevating effects of other psychoactive drugs? Third, how do the acute effects of drugs on mood and brain function relate to their effects on sensory, cognitive, emotional, and social function?

Task-dependent and task-independent (i.e., resting state) fMRI scans provide important data about regional and circuit-wide CBF and functional activation and connectivity. However, fMRI provides no direct information about the neurochemical mechanisms that underlie these changes. Carhart-Harris *et al.* use existing knowledge of the predominant pharmacologic mechanism of action of MDMA on 5-HT transporters, regional distribution of 5-HT receptor systems in the brain, and prior evidence of serotoninergic effects on brain function and subjective effects to attribute the CBF and RSFC brain changes by MDMA to 5-HT actions. However, MDMA also directly and indirectly acts on other monoamines, which could contribute to the observed effects. Novel approaches are needed to link brain function changes to modulation of specific neurotransmitters to identify the receptor and molecular mechanisms that underlie the effects of a drug. This issue applies broadly to pharmacologic challenge studies that use fMRI techniques to investigate brain and behavior. Studies incorporating in vivo and dynamic measures of endogenous levels or release of neurotransmitters at the synapse (e.g., positron emission tomography with arterial spin labeling or RSFC fMRI (2)) will address these knowledge gaps as technological and conceptual advances in this emerging area tie the magnetic resonance imaging–based measures to specific neurotransmitter function.

On a related note, advances in neuroimaging analyses permit the study of drug effects on brain function at the network, rather than regional, level (3). These new approaches

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are data-driven and complement seed-based analytic approaches such as the approach taken by Carhart-Harris *et al.*, which are hypothesis-driven but constrained to the region-based patterns selected a priori. Because the brain is organized into complex interconnected and distributed neural networks needed to synchronize to implement cognition, affect, and social interactions, psychoactive drugs such as MDMA most likely act through widely systems-level neural mechanisms. With the reported analytic methods of CBF and RSFC between brain regions, it is difficult to ascertain the direction (e.g., region A exerts positive effect on region B but not vice versa) or if changes in neuronal activity are driven by excitatory or inhibitory processes. Effective connectivity approaches (e.g., dynamic causal modeling) and whole-brain analyses such as independent components analysis and brain connectome (e.g., pattern classification, graph theory) may help in understanding the complex, distributed, dynamic, and propagating nature of psychoactive drugs. Carhart-Harris *et al.* refer to a separate report on effects of MDMA in an analysis of intrinsic RSFC based on independent components analysis (4). Taken together, this is an area rich with potential for expanding our understanding of how drugs affect brain function and behavior.

Because of its distinctive prosocial subjective effects, MDMA is considered unique. However, MDMA acts on several neurotransmitter systems, and it is important to compare its neural (e.g., perfusion, activation, connectivity) and behavioral effects with other, different psychoactive or psychedelic drugs with overlapping mechanisms of action. One class of drug that shares many actions and effects with MDMA is the stimulants. Schrantee *et al.* (5) reported that acute d-amphetamine, similar to MDMA, reduced functional connectivity in the cortico-striatal-thalamic network and that this was positively associated with amphetamine-induced dopamine release. Modafinil, which has stimulant-like mood effects but with questionable actions on dopamine, did not affect resting-state connectivity (6). The mood effects of MDMA have also been attributed to its ability to release oxytocin, a neuropeptide involved in social bonding. Oxytocin increases amygdala and medial PFC functional connectivity at rest but decreases amygdala-to-insula connectivity in response to social signals of threat (7). Finally, MDMA also has some properties common to hallucinogenic drugs. Carhart-Harris *et al.* reported that psilocybin, a prototypic hallucinogenic that also has effects on social function, decreased orthogonality between the default-mode and task-positive networks and had much more extensive RSFC changes relative to MDMA (4). By comparing the behavioral and neural actions of these other drugs, related but distinct from MDMA, we will begin to identify the mechanisms underlying the unique social effects of MDMA.

Although human psychopharmacology studies demonstrate convincingly that humans can accurately report on the experience of subjective drug effects, there is also a need to develop more refined and sensitive measures of internal states related to psychoactive drugs. This is especially true for measures that relate to social and interpersonal function. Carhart-Harris *et al.* asked their participants to rate their state using relatively nonspecific measures of positive affect and altered consciousness. Changes in brain perfusion and connectivity were induced by MDMA even while subjects were lying in a magnetic resonance imaging scanner "at rest"—arguably a nonsocial state. These effects were associated with self-reports of drug "intensity" and positive mood, but may not be specific to social effects, which may be difficult to ascertain using existing behavioral measures, especially in the scanning environment. This limitation may be addressed in future studies that combine fMRI with behavioral social paradigms that probe dynamic real-world interpersonal interactions (economic exchange games [trust game, ultimatum game, prisoners' dilemma], social rejection/reward, and theory of mind/mentalizing). Ideally, these paradigms would parallel the paradigms used in animal models (8) to facilitate mechanistic conclusions regarding the "social" effects. Several recent studies used targeted tasks or measures to assess the effects of MDMA on social rejection (9) or effects of psilocybin on ego dissolution (10). Sensitive measures of drug-induced changes in mood and behavior offer enormous potential to elucidate the brain mechanisms by which drugs alter social, cognitive, and affective function.

In conclusion, Carhart-Harris *et al.* show that MDMA produces intense positive mood states as well as robust neural effects including decreases in sensory, limbic, and prefrontal perfusion and changes in paralimbic-limbic intrinsic coupling. Future studies are expected to build on this important finding, perhaps with the addition of neurochemical imaging and refined measures of behavior change in awake, functioning humans and advance our understanding of how MDMA produces its unique behavioral effects. This type of research will open exciting new and translational avenues for studying why people use drugs and how to design and test interventions that target social dysfunction.

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References

1. Carhart-Harris RL, Murphy K, Leech R, Erritzoe D, Wall MB, Ferguson B, *et al.* (2015): The effects of acutely administered 3,4-methylenedioxymethamphetamine on spontaneous brain function in healthy volunteers measured with arterial spin labeling and blood oxygen level-dependent resting state functional connectivity. Biol Psychiatry 78: 554–562.
2. Fisher PM, Hariri AR (2012): Linking variability in brain chemistry and circuit function through multimodal human neuroimaging. Genes Brain Behav 11:633–642.

3. Lu H, Stein EA (2014): Resting state functional connectivity: Its physiological basis and application in neuropharmacology. Neuropharmacology 84:79–89.
4. Roseman L, Leech R, Feilding A, Nutt DJ, Carhart-Harris RL (2014): The effects of psilocybin and MDMA on between-network resting state functional connectivity in healthy volunteers. Front Hum Neurosci 8:204.
5. Schrantee A, Ferguson B, Stoffers D, Booij J, Rombouts S, Reneman L (2015): Effects of dexamphetamine-induced dopamine release on resting-state network connectivity in recreational amphetamine users and healthy controls [published online ahead of print Jul 7]. Brain Imaging Behav.
6. Esposito R, Cilli F, Pieramico V, Ferretti A, Macchia A, Tommasi M, *et al*. (2013): Acute effects of modafinil on brain resting state networks in young healthy subjects. PLoS One 8:e69224.
7. Gorka SM, Fitzgerald DA, Labuschagne I, Hosanagar A, Wood AG, Nathan PJ, *et al*. (2015): Oxytocin modulation of amygdala functional connectivity to fearful faces in generalized social anxiety disorder. Neuropsychopharmacology 40:278–286.
8. Blanco-Gandia MC, Mateos-Garcia A, Garcia-Pardo MP, Montagud-Romero S, Rodriguez-Arias M, Minarro J, *et al*. (2015): Effect of drugs of abuse on social behaviour: A review of animal models. Behav Pharmacol 26:541–570.
9. Frye CG, Wardle MC, Norman GJ, de Wit H (2014): MDMA decreases the effects of simulated social rejection. Pharmacol Biochem Behav 117:1–6.
10. Lebedev AV, Lovden M, Rosenthal G, Feilding A, Nutt DJ, Carhart-Harris RL (2015): Finding the self by losing the self: Neural correlates of ego-dissolution under psilocybin. Hum Brain Mapp 36: 3137–3153.