Archival Report

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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

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ABSTRACT

BACKGROUND: The compound 3,4-methylenedioxymethamphetamine (MDMA) is a potent monoamine releaser that produces an acute euphoria in most individuals.

METHODS: In a double-blind, placebo-controlled, balanced-order study, MDMA was orally administered to 25 physically and mentally healthy individuals. Arterial spin labeling and seed-based resting state functional connectivity (RSFC) were used to produce spatial maps displaying changes in cerebral blood flow (CBF) and RSFC after MDMA administration. Participants underwent two arterial spin labeling and two blood oxygen level–dependent scans in a 90-minute scan session; MDMA and placebo study days were separated by 1 week.

RESULTS: Marked increases in positive mood were produced by MDMA. Decreased CBF only was observed after MDMA, and this was localized to the right medial temporal lobe (MTL), thalamus, inferior visual cortex, and the somatosensory cortex. Decreased CBF in the right amygdala and hippocampus correlated with ratings of the intensity of global subjective effects of MDMA. The RSFC results complemented the CBF results, with decreases in RSFC between midline cortical regions, the medial prefrontal cortex, and MTL regions, and increases between the amygdala and hippocampus. There were trend-level correlations between these effects and ratings of intense and positive subjective effects.

CONCLUSIONS: The MTLs appear to be specifically implicated in the mechanism of action of MDMA, but further work is required to elucidate how the drug's characteristic subjective effects arise from its modulation of spontaneous brain activity.

Keywords: Amygdala, 5-HT, fMRI, Hippocampus, MDMA, PTSD, Serotonin

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The compound 3,4-methylenedioxymethamphetamine (MDMA) releases serotonin (5-hydroxytryptamine [5-HT]), dopamine, and norepinephrine (1). It is also a popular recreational drug that is valued by users because of its acute prosocial and euphoretic properties (2). Although MDMA has been administered in human research on numerous occasions (3–5), few studies have investigated its acute effects on brain function using functional magnetic resonance imaging (fMRI) (6–8) or other neuroimaging modalities (9–11).

The compound MDMA has a relatively unique profile of subjective effects, described as a hybrid between a stimulant and psychedelic (12). It acts at dopamine, norepinephrine, and 5-HT transporters to inhibit reuptake and stimulate release; however, the greater action of MDMA at the serotonin transporter differentiates it from most other stimulants (13) and accounts for much, but not all, of its euphoretic effects (14,15). Although the pharmacology of MDMA is reasonably well understood, little is known about its effects on global brain function. More recently, MDMA has been investigated as a potential adjunct to psychotherapy in the treatment of posttraumatic stress disorder (PTSD), with positive, albeit preliminary, outcomes (16,17).

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Despite significant developments in resting state fMRI in recent years (18), there have been no resting state fMRI studies on the acute effects of MDMA. In the present study, we combined arterial spin labeling (ASL) and resting state functional connectivity (RSFC) to address this knowledge gap. The magnetic resonance imaging technique ASL provides a quantitative measure of cerebral blood flow (CBF) or perfusion (19), and RSFC measures functional coupling between spatially distributed brain regions via spontaneous fluctuations in the blood oxygen level–dependent (BOLD) signal (20). Combining these complementary techniques can yield important new information on how a drug alters brain activity to produce its characteristic subjective effects (21). Given the recognized acute prosocial and positive mood effects of MDMA (6,22), we predicted changes in CBF and RSFC in brain systems implicated in social and affective processing—limbic structures and the medial prefrontal cortex (mPFC) (23,24). On this basis, three regions (i.e., ventromedial prefrontal cortex [vmPFC], bilateral hippocampi, and amygdalae) were selected for seed-based RSFC analyses (20).

Supporting the importance of this research is: 1) the relative dearth of human functional neuroimaging data on what is one of the most popular drugs of potential misuse (25); 2) the ability of MDMA to produce an acute state of euphoria and the poor understanding of the neural underpinnings of such states (26); 3) the ability of MDMA to produce marked 5-HT release (13), supporting its utility in serotonergic challenge (27); and 4) preliminary evidence for the potential of MDMA as a therapeutic agent (17).

METHODS AND MATERIALS

Supplement 1 contains the complete Methods and Materials section.

Design

This was a within-subjects, double-blind, randomized, placebo-controlled study. Participants were scanned twice, 7 days apart—once after MDMA and once after placebo. A schematic of the scanning protocol is shown in Figure 1. The study was approved by the National Research Ethics Service West London Research Ethics Committee, Joint Compliance and Research Office of Imperial College London, Research Ethics Committee of Imperial College London, Head of the Department of Medicine of Imperial College London, Imanova Centre for Imaging Science, and Faculty of Medicine of Imperial College London. The study was conducted in accordance with Good Clinical Practice guidelines. A Home Office Licence was obtained for the storage and handling of a Schedule 1 drug. Imperial College London sponsored the research.

Participants

The study included 25 healthy participants (mean age, 34 ± 11 years; 7 females) with at least one previous experience with MDMA. None of the participants had used MDMA for at least 7 days or other drugs for at least 48 hours, which was confirmed by a urine screen. An alcohol breathalyzer test confirmed that none of the participants had recently consumed alcohol. Participants had used MDMA an average of 35 ± 51 times before (range, 1–200 times), and the mean time since last use was 1400 ± 2351 days (range, 7–7300 days). Participants were screened for good physical and mental health, and magnetic resonance imaging compatibility. Screening involved routine blood tests, electrocardiogram, heart rate, blood pressure, and a brief neurologic examination. The Mini International Neuropsychiatric Interview version 5 (MINI-5) was performed by an experienced psychiatrist to assess mental health. All subjects were deemed physically and mentally healthy, and none had any history of drug or alcohol dependence or diagnosed psychiatric disorder. Participants had mean Beck Depression Inventory scores of 3.9 ± 4.8 (range, 0–18) and Spielberger State-Trait Anxiety Inventory scores of 31.7 ± 5.9 (range, 20–46).

RESULTS

Basic Subjective and Physiologic Effects

The intensity of the subjective effects of MDMA was variable across subjects. Five subjects failed to notice any subjective effects during the scanning period, whereas three gave maximal ratings, indicating "extremely intense" effects. Peak drug effects were reported 100 min after ingestion of MDMA (the intensity was rated at 52 ± 32%; range, 0%–100%; 0% = no effects and 100% = extremely intense effects) coinciding with the beginning of the second ASL scan (103 min after capsule ingestion). However, the average intensity remained relatively consistent throughout the scanning period (i.e., intensity was rated at 44 ± 35% at the end of the first ASL scan and 43 ± 32% at the end of the second BOLD scan). Most volunteers reported positive mood effects after MDMA, and items referring to aspects of positive mood were among the highest scored (e.g., the item "I felt amazing" was the highest rated item after MDMA administration) (Figure 2).

Mean Plasma Concentration of MDMA

Biochip Array Technology (Randox Laboratories Ltd., Co., Antrim, United Kingdom) was used to detect MDMA from plasma samples obtained shortly after each participant's MDMA scanning session (i.e., 2 hours after capsule ingestion). The mean concentration of MDMA was 214 ± 66 ng/mL.

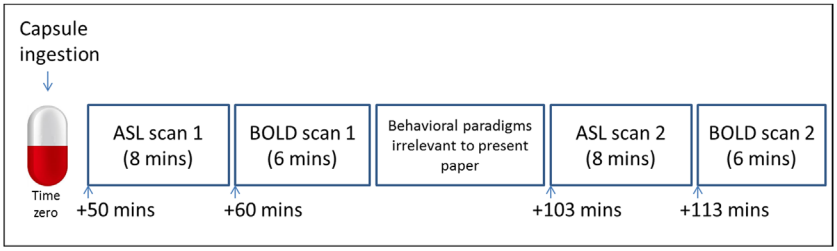

Figure 1. Schematic showing scanning protocol. Placebo (vitamin C) or 3,4-methylenedioxymethamphetamine (MDMA) hydrochloride (100 mg) was ingested at time zero, and the first arterial spin labeling scan performed 50 min later. This was a repeated measures design; the two scans (placebo and MDMA) were performed 1 week apart, and the scan order was counterbalanced so that half of the volunteers received MDMA for the first scan, and half received MDMA for the second scan. ASL, arterial spin labeling; BOLD, blood oxygen level–dependent.