Imaging the Neural Pathways Activated by Oral Ecstasy (MDMA) In Conscious Marmoset Monkeys.

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Introduction:

MDMA, or "ecstasy", is increasingly popular among young adults, it is estimated that 1.2 million teenagers used MDMA in the past month. Studies have been conducted to investigate the long term neurological effects of MDMA, but the immediate effects of MDMA on brain function remain unknown. Functional MRI is a non-invasive tool for looking at neurological function with high temporal and spatial resolution. Non-human primates offer an addition advantage as they provide a relevant model to the MDMA effects on cognitive abilities and social relationships. Using fMRI we followed changes in brain activity in response to oral ingestion of MDMA in fully conscious marmoset monkeys. Changes in the visual cortical response to photic stimulation were also investigated before and after MDMA.

Methods:

Common marmosets (n=5, Callithrix jacchus) were anesthetized with medetomidine (0.1mg/Kg, Pfizer) and ketamine (3mg/Kg) IM. The animal was placed in an animal restrainer with built in RF electronics (Insight Neuroimaging Sys.). This system was placed in the scanner and anesthesia was reversed with atipamizole (Pfizer). Animals were set up with pulse oximetry and capnography for recording physiologic responses.

Imaging was conducted in a 4.7T/40cm imager (Bruker) with a 12 cm, 22 G/cm gradient. Anatomical images were acquired; TR= 3000 ms, TE= 48 ms, 8 echos , 10 NEX, 256x256 matrix, 3.5 cm FOV, 14 slices, 1.5 mm slice thickness. BOLD fMRI images were acquired with a spin-echo EPI; TR= 2-4s, TE= 55 ms, 64x64 matrix, and same geometry as the anatomical set. A block visual stimulus experiment was conducted consisting of 4-6 epochs of 60s off, 60s with a blinking LED array on. Following this, 45 min of fMRI were conducted with 5 min of baseline, a 0.15ml oral dose of vehicle (water), followed 5 min later by a 1 mg/kg oral dose of MDMA. The subsequent 35 min of activity was collected, followed by more visual stimulation experiments. Behavioral alterations were noted, and blood was collected.

Brain activation was mapped for the vehicle and the MDMA periods using Stimulate (Strupp, 1996). ROIs were defined for the active areas and BOLD intensity was plotted. Data from the visual experiments were similarly analyzed.

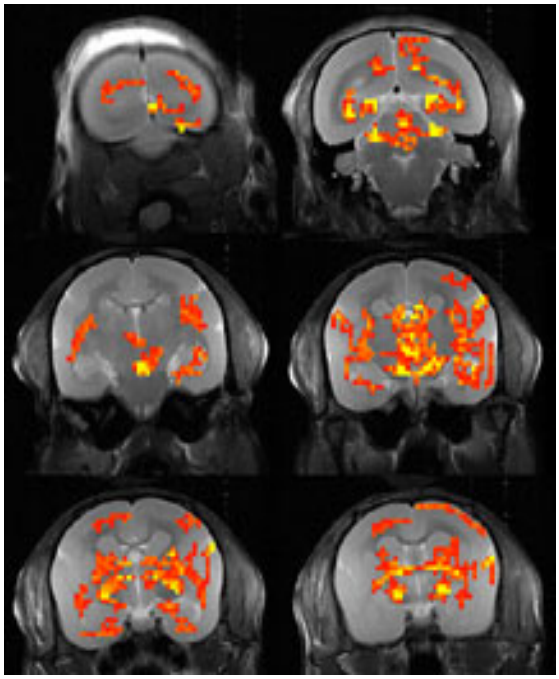

Figure 1: Typical activation in a representative marmoset.

Results:

No significant activation resulted from the administration of the vehicle. Robust activations were seen in all animals after MDMA administration in the visual cortex, subiculum, hippocampus, somatosenory cortex, caudate, putamen, globus pallidus, hypothalamus, amygdala, and frontal cortex. Time courses of these data indicate that the frontal cortex is the first area to activate, and the dorsal striatum returns toward baseline after 25-30 minutes while all other structures remain active. The hypothalamus activated the most robustly at the end of the period. Physiological data show no significant change over the 40 min period of drug uptake for heart rate, respiration rate, $EtCO_2$, or SpO_2. Activation in the visual cortex in response to stimuli was greater after exposure to MDMA (Fig 2). Behavioral changes noted after the experiment included a reduced startle response and enhanced approach behavior.

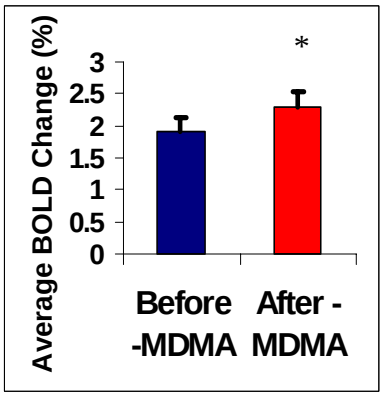

Figure 2: Activation of the visual cortex increases significantly after MDMA administration. * p= .0037

Conclusions:

These data show that it is technically feasible to conduct acute drug studies with conscious non-human primates. Most robust activation occurred in the subiculum/hippocampus, posterior hypothalamus, dorsal striatum, and medial prefrontal/cingulate cortex. Also, visual cortex activation in response to stimulation is increased by MDMA. This increased excitability has been seen in human users with EEG measurements. MDMA's action to increase serotonin levels in the brain may be responsible for this activation/sensitivity. Future studies will investigate acute perfusion changes as well as chronic studies or brain metabolites, perfusion, activational changes, and cognitive and social deficits.