FUNCTIONAL MRI OF CONSCIOUS MARMOSETS FOLLOWING ORAL MDMA.

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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 an 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 cortex's response to stimulate 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., Fig 1). This system was placed in the scanner and anesthesia was reversed with atipamizole (Pfizer).

Imaging was conducted in a 4.7T/40cm imager (Bruker). 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 above. 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 minutes of fMRI were conducted with 5 minutes of baseline, a 0.15ml oral dose of vehicle (water), followed 5 minutes later by a 2 mg/kg oral dose of MDMA. The subsequent 35 min of activity was collected, followed by more visual experiments.

Brain activation was mapped for the vehicle and the MDMA periods. ROIs were defined for the active areas and BOLD intensity was plotted. Data from the visual experiments was similarly analyzed.

Figure 1. Commercially available restraint apparatus for high resolution fMRI of conscious animals.

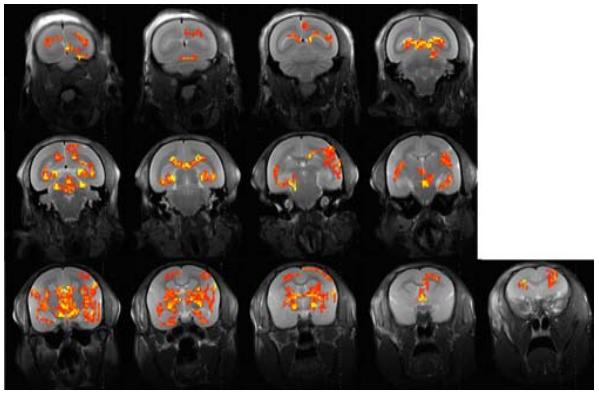

Figure 2: Functional activation following MDMA administration is overlaid on anatomical data from one example animal.

Results

No significant activation resulted from the administration of the vehicle (Fig 4). Strong 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 (Fig 2). Time courses of these data indicate that the frontal cortex is the first area to activate, and the dorsal striatum return toward baseline after 25-30 minutes while all other structures remain active (Fig 3). Physiological data shows no change over the period of drug administration (Fig 5). Activation in the visual cortex (Fig 6a) was greater after exposure to MDMA (Fig 6b,c). Behavioral changes noted after the experiment included a reduced startle response and enhanced approach behavior.

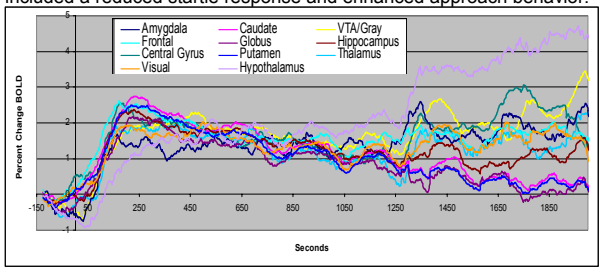

Figure 3: Time course of data averaged from 3 animals. MDMA administration is at time=0. The frontal cortex is the first area to activate. The caudate/ putamen/ globus pallidus begin to return to baseline after 30 minutes. The hypothalamus activated the most robustly at the end of the experiment.

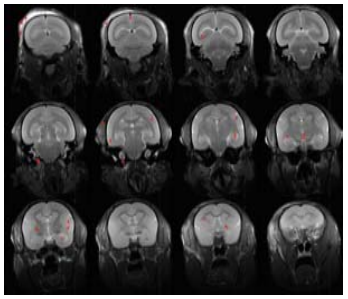

Figure 4: Vehicle (water) caused no significant activation. All analysis parameters were identical to MDMA analysis.

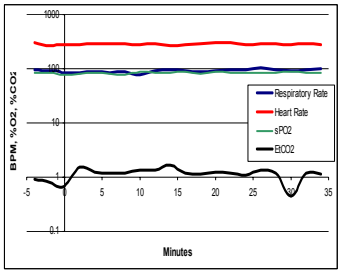

Figure 5: Physiological data from the MDMA administration (arrow) shows no substantial effects. Note Logarithmic Scale.

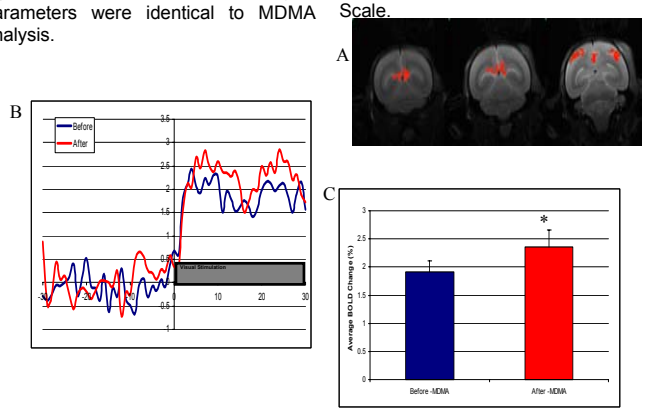

Figure 6: Visual stimulation before and after MDMA. A) Typical activation overlay B) Averaged BOLD signal time courses of off/on for 5 animals, 2 trials each before and after C) Bar graph of average activation before and after MDMA. * P=.000037

Conclusions

1. These data show it is technically feasible to conduct acute drug studies with conscious non-human primates.
2. Most robust activation occurred in the sibiculum/hippocampus, posterior hypothalamus, dorsal striatum, and medial prefrontal/cingulate cortex
3. Visual cortex activation is increased by MDMA.

Future Directions

Long term studies with regular MDMA administration to adolescent monkeys will be conducted looking for changes in: cognitive performance, psychosocial behavior, neuro-anatomy, neuro-function, neurochemistry, and cerebral perfusion

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