Syllabus: MRI and MRS of Ecstasy Users

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Overview

MDMA (Ecstasy) is a popular recreational drug that is neurotoxic to brain serotonin axons when studied in animal models of MDMA administration. Human MDMA users have a broad range of chronic psychiatric and cognitive symptoms linked to the drug. At the same time, MDMA may have promise as a psychotherapeutic medication for psychiatric conditions. Given the popularity of Ecstasy and its potential use as a pharmacotherapeutic, understanding whether MDMA produces serotonin or other neurotoxicity in humans remains a critical public health issue.

Ecstasy Use

MDMA is sold under the street name of Ecstasy. While illicitly-marketed Ecstasy is not necessarily pure MDMA, pill purity has been increasing in recent years. Users tend to select Ecstasy that produces the desired effects of MDMA. MDMA is used for its combination of psychostimulant, pro-social, and mild hallucinogenic properties.

Animal models of Ecstasy toxicity

Animal models of MDMA administration have shown that MDMA produces long-lasting loss of serotonin axons. However, controversy remains regarding the relationship of animal dosing regimens to human use. Lower dose or lower frequency animal dosing regimens do not appear to produce frank axon loss. MDMA also produces other brain changes, including scattered loss of brain neurons and changes in cellular morphology, such as altered spine number or morphology.

A framework for interpreting human imaging studies of Ecstasy

Human neuroimaging studies can be interpreted in the context of a cortical model that accounts for the predicted consequences of loss of brain serotonin axons or reductions in brain serotonin signaling. Nuclear imaging studies have provided indirect data that is consistent with MDMA-induced reductions in serotonin signaling, either due to axon loss or reduced serotonin release in intact axons. Multiple studies have demonstrated that MDMA use is associated with lower levels of axon terminal serotonin transporters, a result that could be secondary to loss of axons and their associated serotonin transporters or due to MDMA-induced chronic down-regulation of serotonin transporter number. Evidence suggests also that the post-synaptic serotonin 2A receptor, which predominates in the cerebral cortex, is up-regulated following chronic MDMA use. This finding is consistent with reduced pre-synaptic serotonin release and associated compensatory up-regulation of the receptor. Predicted consequences of reduced
serotonin signaling include reductions brain volume loss, altered brain metabolites, and altered cortical neurophysiology. As discussed below, these findings have been largely confirmed in human MDMA users.

**Structural MRI in Ecstasy Users**

Amphetamines have been associated with reduced brain gray matter in human recreational drug users. Reduced serotonin signaling associated with MDMA use may lead to brain gray matter changes through loss of serotonin coupling to brain neurotrophic factors. MDMA also produces scattered neuron loss in animal models, suggesting an additional mechanism through which MDMA may be associated with reduced brain gray matter. Other mechanisms may also contribute to gray matter loss in association with MDMA use. Thus far, the data on brain gray matter changes in MDMA users is equivocal, with a study from our group finding multiple regions of gray matter loss and others finding no effects of MDMA on gray matter. Polydrug use by MDMA users may complicate efforts to isolate MDMA effects, as might recency of MDMA use.

**Magnetic Resonance Spectroscopy in Ecstasy Users**

MRS studies in MDMA have investigated N-acetylaspartate (NAA) as a specific neuronal marker and myoinositol (mI) as a potential marker of increased glial activity following MDMA-induced cellular injury. Earlier studies suggested that NAA was reduced in some brain regions while mI was increased in MDMA users. Later studies have not found evidence for an association of MDMA use with altered NAA or mI. This may be related to the complexity of MDMA effects on brain constituents.

**Functional MRI in Ecstasy Users**

Numerous functional MRI studies have found altered regional brain activation in MDMA users across multiple tasks. FMRI studies employing complex cognitive tasks have found a range of findings from no effect of MDMA to increased or decreased task-associated activation. Our lab has used simple sensory and motor tasks to potentially isolate consistent effects of MDMA exposure on cortical neurophysiology at the earliest stages of sensory or motor processing. These studies, when interpreted in the context of other animal and human studies, suggest that MDMA exposure may lead to increased cortical excitability, possibly via reduced serotonin inhibitory effects in cortex.

**Summary**

Human recreational MDMA/Ecstasy use is associated with long-lasting changes in serotonin markers that are consistent with serotonin axon loss or with chronic reductions in serotonin signaling. Some evidence suggests that MDMA use is associated with structural brain consequences (reduced brain gray matter) consistent with reduced serotonin signaling. MRS measures do not suggest that MDMA exposure is consistently associated with changes in NAA.
or ml. Most concerning is fMRI evidence suggesting that MDMA use is associated with chronic shifts in cortical excitability. Given the popularity of MDMA as a recreational drug, its emerging potential for psychotherapeutic use, and clear evidence of chronic neurotoxic effects in humans, recreational MDMA use remains a problem of critical public health significance.

General References/Further Reading


