Adolescent Exposure to Psilocybin Alters the Perception of Rewarding and Fearful Stimuli in Adulthood: An Awake MRI Study in Male and Female Mice

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Introduction

Psilocybin, a psychedelic 5-HT2A agonist, is currently in clinical and preclinical trials for treatment of psychiatric disorders. Single or multiple small doses can have rapid, long-lasting effects by enhancing neuroplasticity, such as increased synaptic connectivity, which may alter one's perception of affective cues. Healthy volunteers in clinical settings show decreased emotional reactivity to fearful stimuli, and growing research suggests hallucinogens impact environmental perception. However, the effects of psilocybin exposure on the developing adolescent brain remain understudied.

In this experiment, adolescent mice received oral doses of 3.0 mg/kg of psilocybin every other day for 10 days (5 total treatments). Three months later, awake mice were imaged for brain activity and connectivity changes in response to rewarding and threatening scents. Data registered to a 3D MRI mouse atlas showed site-specific BOLD signal changes across 140 brain regions.

Experimental Design

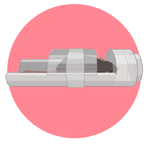
Adolescent male and female mice (18-22 g) were divided into groups receiving either vehicle (*n*=14) or psilocybin (*n*=14) treatment. Awake functional magnetic resonance imaging (fMRI) was conducted 3-4 months later in adulthood. Animals were housed on a reverse light-dark cycle with all procedures carried out under dim red-light illumination for ecological validity of circadian rhythms.

Postnatal Day 51

Treatment via Oral Gavage

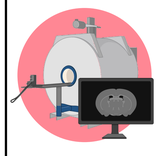
- 3.0 mg/kg psilocybin via 100 µl oral gavage *or* equivalent saline dose via 100 µl oral gavage
- 5 doses over 10 days

Postnatal Day 150



Acclimation for fully awake fMRI

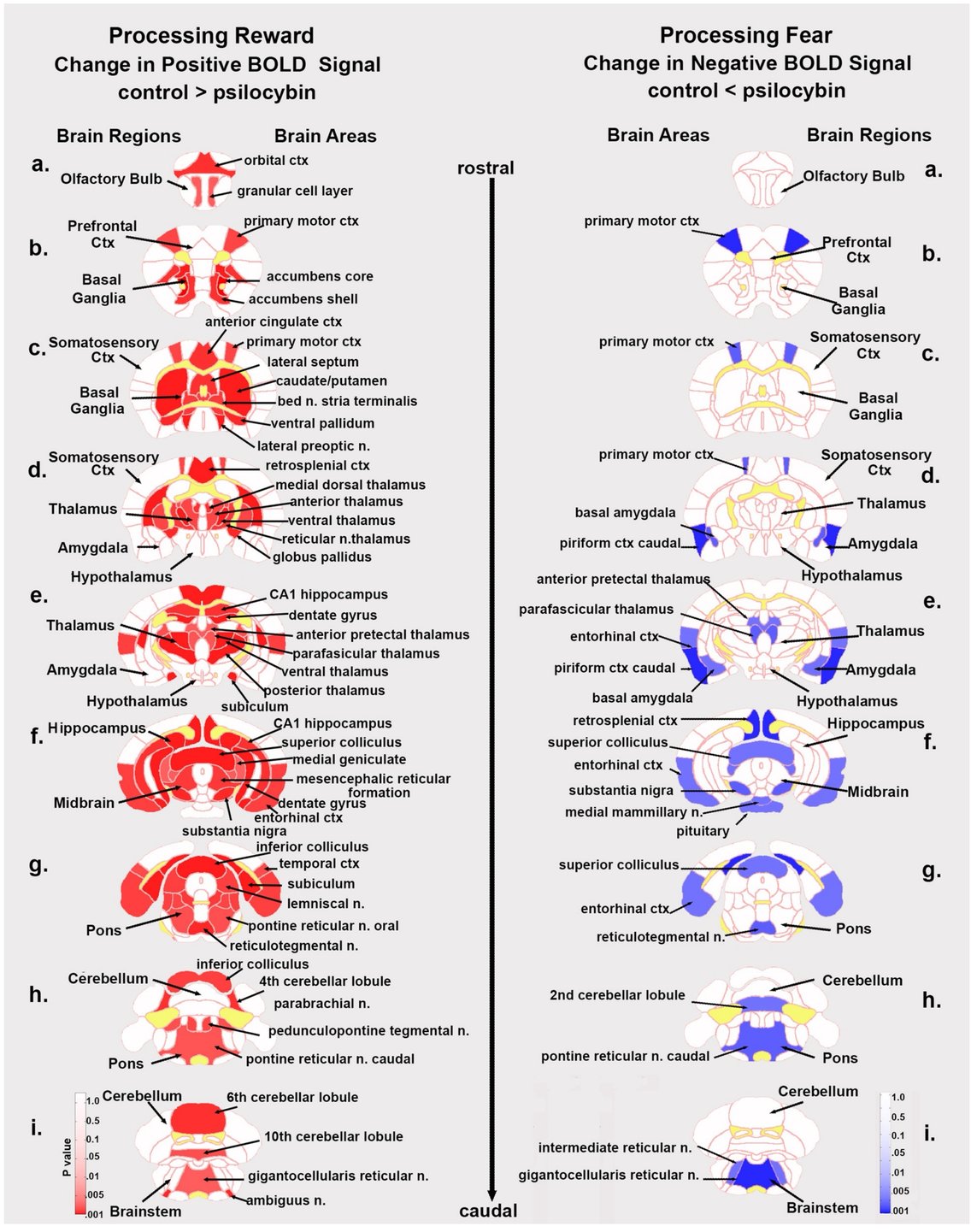
- Progressive habituation to MRI restraint and scanner noise to reduce stress and motion during scanning



7T Functional Magnetic Resonance Imaging (fMRI)

- Measuring blood-oxygen-level-dependent (BOLD) signal responsivity changes to rewarding, threatening, and neutral cues in three separate sessions
- **Rewarding Cue: Benzaldehyde (almond scent)**
- **Threatening Cue: Fox urine scent**
- **Neutral Cue: Air**

Psilocybin Exposure in Adolescence Results in Lasting Changes to BOLD Response to Rewarding Environmental Cues



Outcomes & Discussion

Reward Response

Decreased positive BOLD signal in the psilocybin-treated group relative to control animals indicates **decreased activation in reward-related regions** (e.g., ventral striatum, nucleus accumbens) after adolescent psilocybin exposure. This suggests that psilocybin may attenuate the neural response to rewarding stimuli, reflecting altered hedonic processing or a reduced motivational salience for rewards, leading to a blunted reward response in adulthood.

Fear Response

Increased negative BOLD signal in the psilocybin-treated group relative to control animals indicates decreased activation in response to threatening stimuli. Further behavioral work will be needed to determine whether psilocybin exposure may be used to reduce the salience of fear-related cues and facilitate fear extinction or re-contextualization, or whether this is a maladaptive response.

Neutral Response

Analysis of BOLD signal in response to the neutral cue is ongoing. This finding will elucidate whether adolescent psilocybin exposure influences sensory processing or contextual awareness in adulthood, altering attention and perceptual salience to neutral stimuli beyond rewarding or threatening cues.

Summary

Taken together, **this study demonstrates that adolescent psilocybin exposure results in lasting alterations to one's perception of environmental cues**. Specifically, responsivity to rewarding and, to a lesser extent, threatening stimuli may be dampened later in life. Future studies are needed to explore the mechanisms shaping these behaviors.

Concurrent & Future Studies

Effect on Brain Microstructure, Connectivity, and Behavior

- Structural and Functional MRI
  - Diffusion Weighted Imaging
  - Voxel-Based Morphometry
  - Resting-state Functional Connectivity
- Cognitive Behavioral Assays
  - Open Field Test
  - Light-Dark Box Test

Therapeutic Applications

- Treatment of repetitive mild traumatic brain injury
- Determination of optimal dosages and sex-specific effects

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Stay connected! ✉ **masadi.s@northeastern.edu**

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