Psilocybin and Ketamine Alter Neurites in a Stressed Rat

Paloma C. Frautschi[1], Ajay P. Singh[1,2] & John-Paul J. Yu[1,2,3,4]

[1] Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI 53705, USA
[2] Graduate Program in Cellular and Molecular Biology, University of Wisconsin-Madison, Madison, WI 53706, USA.
[3] Neuroscience Training Program, Wisconsin Institutes for Medical Research, University of Wisconsin-Madison, Madison, WI 53705, USA
[4] Department of Psychiatry, University of Wisconsin School of Medicine and Public Health, Madison, WI 53705, USA

Department of Radiology
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

INTRODUCTION

Over the past two decades, there has been increased interest in psychedelic compounds as an alternative treatment for neuropsychiatric illness. Recently, psilocybin, a 5-HT2A agonist, and ketamine, an NMDA antagonist have shown promise in clinical trials for alleviating symptoms associated with treatment-resistant major depressive disorder (MDD).

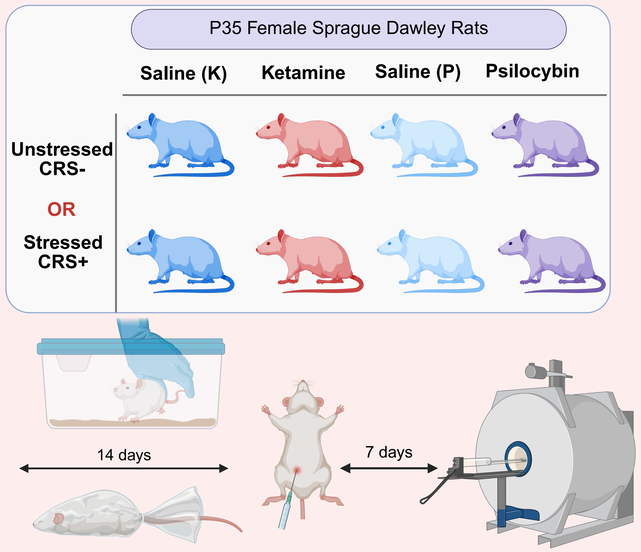
Diffusion-weighted MR techniques like neurite orientation dispersion and density imaging (NODDI) offer insight into structural changes taking place in the brain. This study uses a preliminary diffusion MR analysis to look at changes that occur after a single injection of psilocybin or ketamine.

IMAGING PARAMETERS

Brains were *ex vivo* imaged on a 4.7T Agilent magnetic resonance imaging system with a 3.5-cm-diameter quadrature volume RF coil (Agilent Technologies, Santa Clara, CA). Multislice, diffusion-weighted spin echo images were used to acquire 10 non-diffusion-weighted images (b=0 s/mm^2) and 75 diffusion-weighted images (25 images: b=800 s/mm^2; 50 images: b=2000 s/mm^2) using noncollinear, diffusion-weighting directions. Nifti files were masked and segmented using a standard DTI-based rat brain atlas.

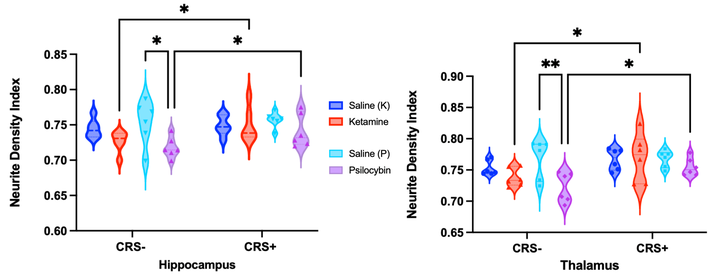
METHODS

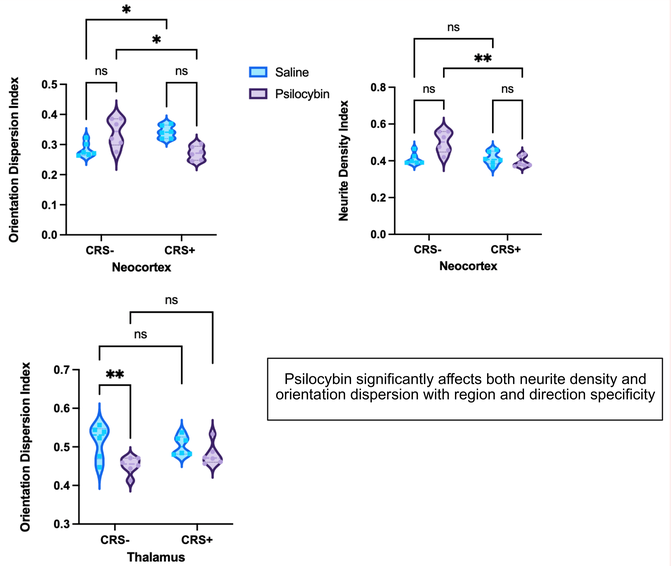
1. P35-37 Sprague-Dawley (Charles River) female rats were divided into a chronic restraint (CRS+) or non- chronic restraint (CRS-) group. The CRS+ groups were immobilized in a plastic bag with a breathing hole for 3h daily, for two weeks. The CRS- group was handled daily for two weeks.
2. On day 14, (N=6) were injected with 2mg/kg psilocybin, 5ml of saline (psilocybin group), 10mg/kg ketamine or 5ml saline (ketamine group).
3. One week after the injection, the brains were perfused, extracted, and ex-vivo imaged (n=6 per treatment x behavior group). The four treatment groups were compared with 2-way ANOVA (Tukey posthoc) for diffusion metric means of NODDI (NDI, ODI) in the hippocampus, neocortex, amygdala, thalamus, and basal ganglia.



RESULTS

Psilocybin and Ketamine significantly affect neurite density index in unstressed rats vs stressed rats





Psilocybin significantly affects both neurite density and orientation dispersion with region and direction specificity

- In the CRS+ hippocampus and thalamus, both psilocybin (p=0.0425, 0.0166) and ketamine (p=0.0495, 0.0177) had a significant effect on measures of neurite density.
- In the neocortex, only psilocybin had a significant effect. Notably, the stress paradigm induced a significant increase in ODI in the saline group (p=0.0428). However, psilocybin caused an decrease (p=0.0207), suggesting a potential "reversal" effect.
- Despite ketamine decreasing in therapeutic efficacy after a week, our results suggest that certain regions demonstrate lasting structural effects.
- The alterations in neurite density may point to possible remodeling that could be consistent with neuroplastic alterations.
- The observed diffusion patterns suggest distinct mechanisms of action for both psilocybin and ketamine.
- The lack of significance in the amygdala and basal ganglia could indicate a different temporal remodeling.

CRS- vs CRS-	Hippocampus	Thalamus	Neocortex
Psilocybin (v. Saline)	NDI ↓	NDI ↓ ODI ↓	

CRS+ vs CRS-	Hippocampus	Thalamus	Neocortex
Saline (v. Saline)			ODI ↑
Psilocybin (v. Psilocybin)	NDI ↑	NDI ↑	NDI ↓ ODI ↓
Ketamine (v. Ketamine)	NDI ↑	NDI ↑	

CONCLUSION

- Psilocybin and ketamine both uniquely alter brain microstructure in a rat model of stress-induced depression in the hippocampus, thalamus and neocortex.
- Diffusion-weighted imaging techniques can characterize such changes.

Future directions:

- Confirmatory histology to quantify adaptive neuronal changes
- Inclusion of a male group, and tests of stress and depressive behavior

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