Acute Behavioral Effects of Psilocybin in Nonhuman Primates

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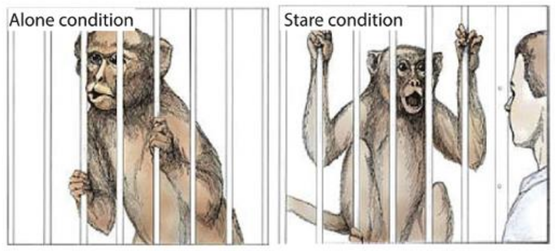
Background

Recognized for its rapid-acting antidepressant effects in humans[1], psilocybin has become a center of research interest for its potential therapeutic utility in other psychiatric conditions, namely anxiety disorders[2,3,4]. Psilocybin acts as a $5HT_{2A}$ receptor agonist, however the mechanisms underlying its therapeutic effects remain unknown. While most of the mechanistic investigations of psilocybin have been done in rodent models[5] relatively little work has been done to understand psilocybin's effects on anxiety and depression-related behaviors in nonhuman primates (NHPs). Nonhuman primate research is particularly valuable owing to the similarity between NHPs and humans in their behaviors, social organization, and brain structures; this makes them a powerful model organism to translate findings to humans. The Kalin Lab has a well-established NHP model of pathological anxiety[6], which is ideally suited to investigate psilocybin's effects on threat-related behaviors in NHPs.

Study Design

Using a within-subjects, counterbalanced, crossover design, 5 rhesus macaques (2M, 3F) randomly received 0, 0.3, and 1 mg/kg intramuscularly with 12-15 days between treatments. Directly following treatment, nonhuman primates were subjected to a modified Human Intruder Paradigm where they are observed alone in the test cage, with Stare conditions occurring at 15, 30, 60, 90, 120, and 180 minutes after injection. Each Stare condition lasted three minutes in which the human intruder maintained direct eye contact with the nonhuman primate. Outside of those times, the primate was alone in the test cage. Behavioral observations were scored by two trained observers, utilizing data from the Stare contexts and the five minutes before each Stare in statistical analyses.



Statistical Analysis

Statistical analyses were conducted using R with the lme4 package. Transformations were applied to most behaviors prior to analysis to normalize residual distributions. Those highlighted in the focus of this poster were all log transformed. The only exception to this is freezing which was analyzed untransformed. In all cases, behavioral data was segmented into bins for the Stare and Alone conditions (3 and 5 minute bins, respectively). To obtain duration or frequency per minute values, duration or frequency of the behaviors was divided by the length of the bin. For behaviors expressed across contexts (Drowsiness, Locomotion, Stereolocomotion, Hypervigilance, Freezing, Environmental Exploration, and Cooing), we used a linear mixed effects model to observe the fixed effects of treatment, context, and the treatment by context interactions. For those behaviors expressed only during Stare (Teeth Grinding, Experimenter Hostility, and Barking), we analyzed the main effect of treatment from the Stare observations. Both models included a random intercept for each subject and coded dose and context as factors. Bonferroni correction was applied to adjust for multiple comparisons.

Behaviors Expressed Across Contexts

Behavior	Treatment	Treatment x Time
Drowsiness	**0.00084****	**0.78**
Locomotion	**6.5e-8****	**0.17**
Stereolocomotion	0.0040**	0.097
Hypervigilance	0.93	1.9e-5**
Freezing	**0.085**	**0.0018****
Environmental Exploration	0.00059**	0.54
Cooing	0.71	0.17

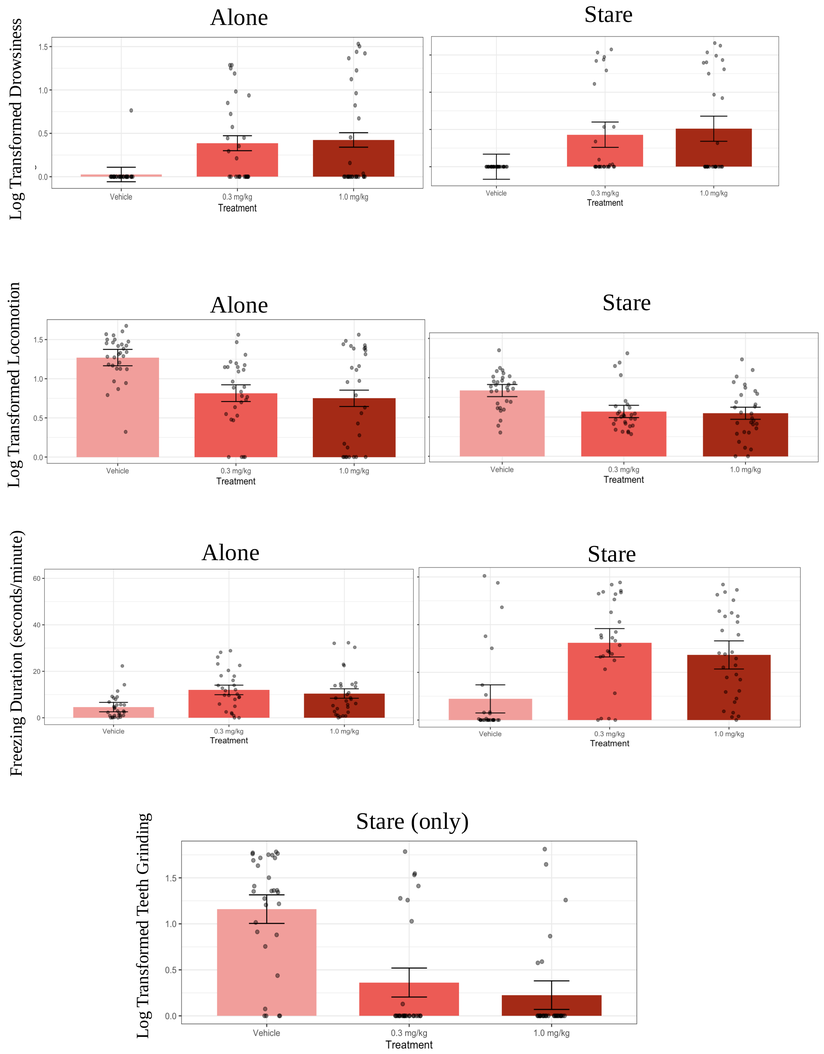
** indicates p < 0.0071 and survives multiple comparisons correction

Behaviors Expressed Only During Stare

Behavior	Treatment	Treatment x Context
Teeth Grind	**2.9e-11****	**0.00025****
Experimenter Hostility	5.3e-6**	0.014**
Barking	0.00014**	0.092

** indicates p < 0.0071 and survives multiple comparisons correction

Results



Psilocybin treatment significantly decreased locomotion across contexts (Stare and Alone), ($F(2,165.08) = 18.33$; $p = 6.5e\text{-}8$). Psilocybin also induced drowsiness across contexts ($F(2,165.06) = 7.39$; $p = 0.00084$). During the Stare condition, psilocybin reduced teeth grinding ($F(2,78.02) = 33.66$; $p = 2.9e\text{-}11$) and increased freezing. Importantly, this increase in freezing behavior was observed only during the Stare condition, resulting in a significant treatment by context interaction ($F(2,165.00) = 6.57$; $p = 0.0018$).

Conclusion

Psilocybin decreased the expression of typical, adaptive behaviors such as locomotion and teeth grinding while simultaneously increasing the expression of atypical behaviors like drowsiness as well as maladaptive behaviors like freezing. These specific behavioral changes, especially those during the Stare condition, suggest an acute increase in anxiety during threatening conditions, which reveals important context-specific effects of psilocybin. In humans, it has been well established that set and setting influence the quality of the psychedelic experience, and this observation is supported by the context-dependent increase in anxiety observed in NHPs during the aversive Stare condition. These findings also support what has already been reported in both humans and rodents demonstrating acute, psilocybin-induced anxiety with therapeutic effects only observed much later after administration. In future studies, we plan to investigate the potential therapeutic effects of psilocybin on anxiety-related behaviors 24 hours after injection.

References

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