

# Exploration of Psilocybin's Impact on the Pharmacological Effects of Nicotine

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## Abstract

Tobacco use and dependence is the leading cause of preventable death. Although most current tobacco users recognize these harmful effects, very few are able to successfully quit. Current smoking treatments all possess limited efficacy. A recent non-randomized open clinical study found that psilocybin, a psychedelic, was very effective in long-term smoking cessation after 2 to 3 doses. Recently, our lab found that administering a single dose of psilocybin 24 hours before spontaneous nicotine cessation significantly decreased the amount of somatic signs of withdrawal in nicotine-dependent mice. However, it is unknown if psilocybin affects other behavioral effects of nicotine. The objective of this research project is to investigate if psilocybin reduces and/or reverses nicotine withdrawal by altering the effects of nicotine, and this was tested by seeing how psilocybin post-actively impacts the pharmacological effects of nicotine in C57BL/6J male mice. Our study looked at the acute effects of nicotine (1.5 mg/kg, s.c.) on locomotor activity, body temperature, and thermal nociception using the tail-withdrawal test. 24 hours prior to nicotine administration, mice were given either psilocybin (1 mg/kg, i.p.) or saline. Our data showed that while nicotine significantly affected body temperature, nociception, and locomotor activity, there was no significant effect of psilocybin on these acute pharmacological effects. While psilocybin has been implicated in "resetting" the brain after substance use, our results suggest that psilocybin does not have a lasting effect on nicotinic receptors when given 24 hours prior to a single dose. In future directions, our study could be repeated with both a larger sample size and in female mice. It would also be important to investigate the time course of psilocybin on nicotine reward and intake in future studies. Further research on the brain mechanisms underlying psilocybin's effect on nicotine dependence will also be important.

## Introduction

Tobacco use and dependence is the **leading cause** of preventable death. Worldwide, **more than 7 million deaths per year** can be attributed to tobacco use. Although most current tobacco users recognize these harmful effects, very few are able to successfully quit.

The current three main treatments for nicotine dependence are nicotine replacement therapy, bupropion (a dopamine reuptake inhibitor), and varenicline (a partial nicotinic acetylcholine receptor agonist). Although these treatments have anywhere from doubled to tripled successful smoking cessation attempts when taken together, the success rate for these is still **less than 25%** for 12 month abstinence after target quit date. In addition, bupropion and varenicline both have **various serious side effects** such as gastrointestinal disturbance and neuropsychological issues. Given the low success rate and side effects of these treatments, it is clear an alternative is needed.

Recent research has investigated **psychedelics** as potential treatments for smoking cessation.

- Psychedelics are typically **serotonin (5-HT) 2A receptor agonists** that are hallucinogenic in nature and cause alterations in perception, cognition and sensory processing.
- Physical dependence and withdrawal from psychedelics **has not been documented** (Johnson, Griffiths, et al., 2018)
- In 2018, an open label study with 15 subjects investigated psilocybin for nicotine cessation and found that 6 months after the target quit date, **80%** of the subjects remained abstinent and 12 months later, **67% remained** (Johnson, Garcia-Romeau, 2018)
- More recently, it was also reported that lifetime psilocybin and mescaline usage is associated with **reduced odds** of current nicotine dependence (Jones, 2022).
- Recently, our lab also found that administering a **single dose of psilocybin** 24 hours before spontaneous nicotine cessation **significantly decreased** the amount of somatic signs of withdrawal in nicotine-dependent mice.

Given these recent findings on psilocybin and its effects on nicotine cessation and withdrawal, we thought it would be important to test if psilocybin is reducing nicotine withdrawal by altering the effects of acute dosing of nicotine. To test this hypothesis, we picked 3 known acute effects of nicotine (increased anti-nociception, reduced locomotion, and hypothermia) and tested the post-acute effect of psilocybin on these effects.

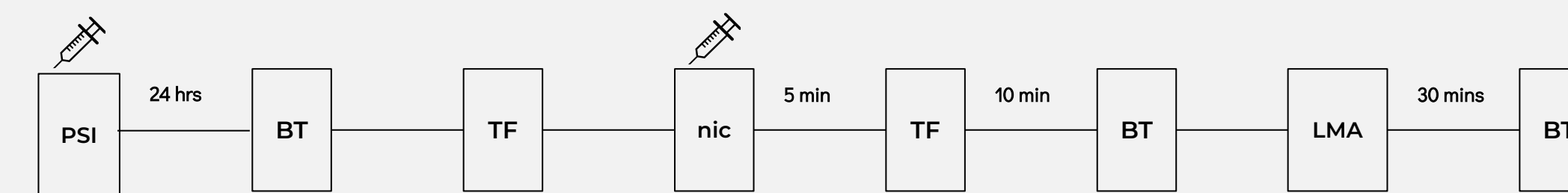
## Methods

In this study, 20 C57BL/6J adult male mice were used as test subjects. 5 mice were used for each test group: saline-saline, saline-nicotine, psilocybin-saline, and psilocybin-nicotine. Saline-saline was the negative control and saline-nicotine was the positive control.

The psilocybin (PSI) injection dose was 1 mg/kg, and injection was done intraperitoneally. This dose was used because our lab had previously seen almost complete reversal of nicotine withdrawal when this dose of psilocybin was injected 24 hours before spontaneous nicotine cessation. The nicotine (nic) injection dose was 1.5 mg/kg, and injection was done subcutaneously. This high dose was chosen so that any effect of psilocybin on the acute effect of nicotine could be seen clearly in the results.

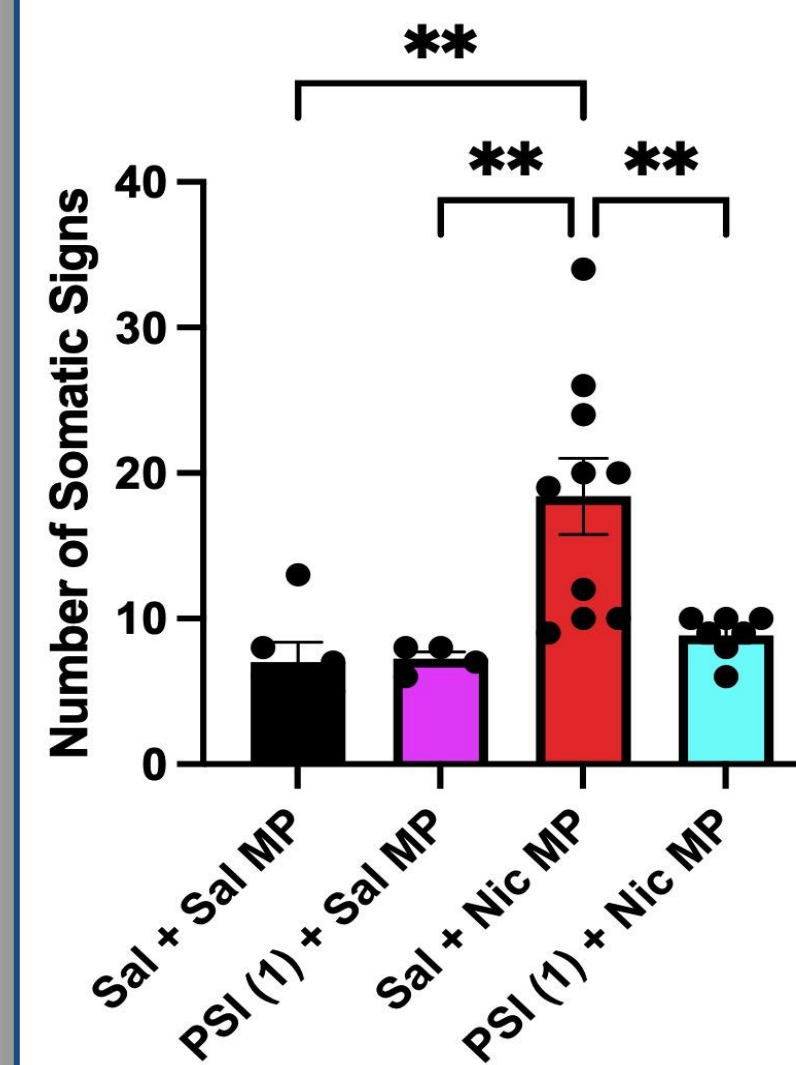
Body temperature (BT) was taken using a rectal thermometer. Thermal nociception was measured using the tail-flick test (TF), in which mice's tails are dipped in 50.2°C water and the time (in seconds) it takes for them to withdraw their tails from the water is taken. Locomotor activity (LMA) was measured by placing mice in locomotor activity boxes and counting the disruptions in infrared light beams.

Timeline:



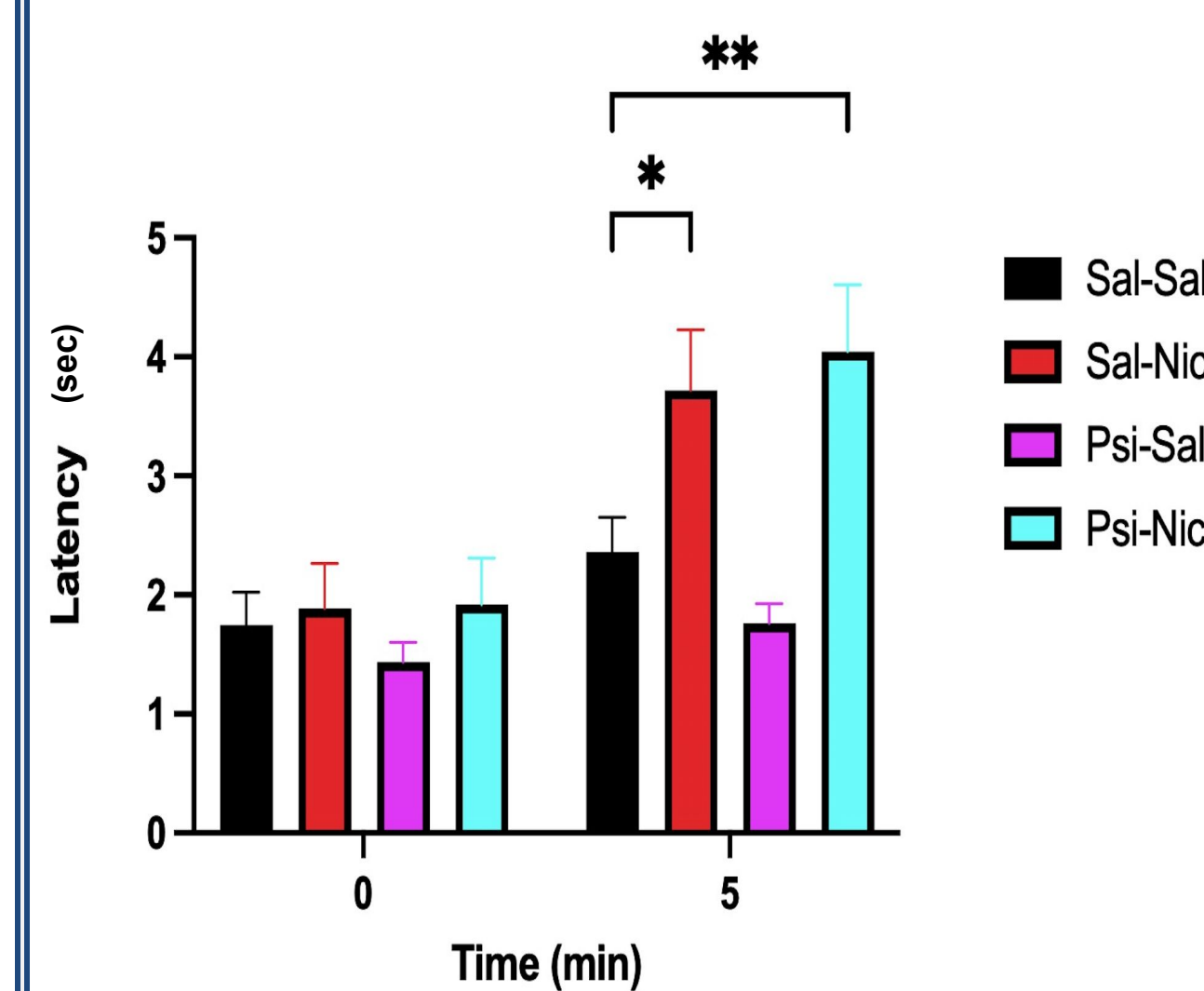
## Results

### Somatic Signs of Withdrawal



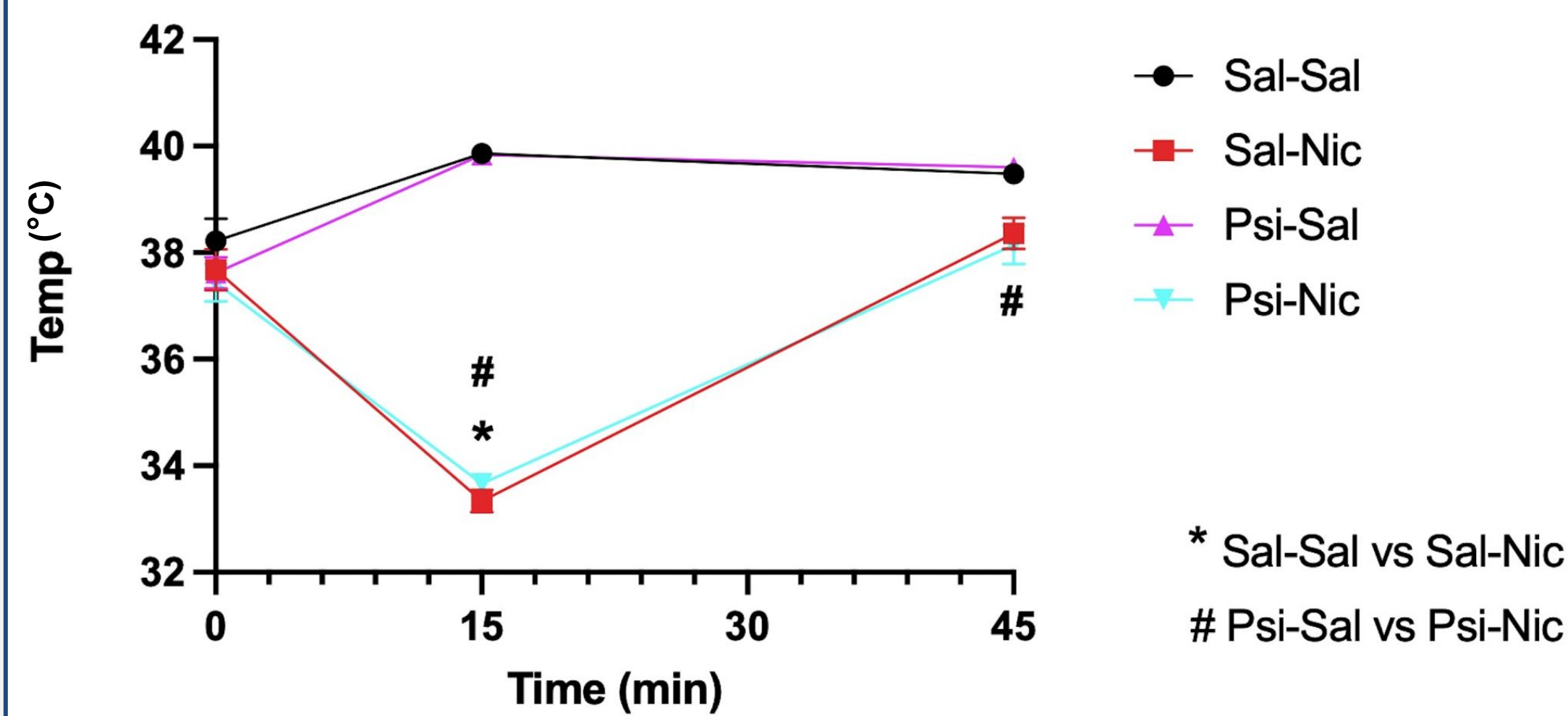
**Figure 1: Psilocybin decreases somatic signs of nicotine withdrawal** Somatic signs measured for 30 minutes 24 hours post MP removal. PSI at 1 mg/kg injected 22-24 hours prior to spontaneous nicotine cessation. \*\*p<0.01

### Tail-Flick

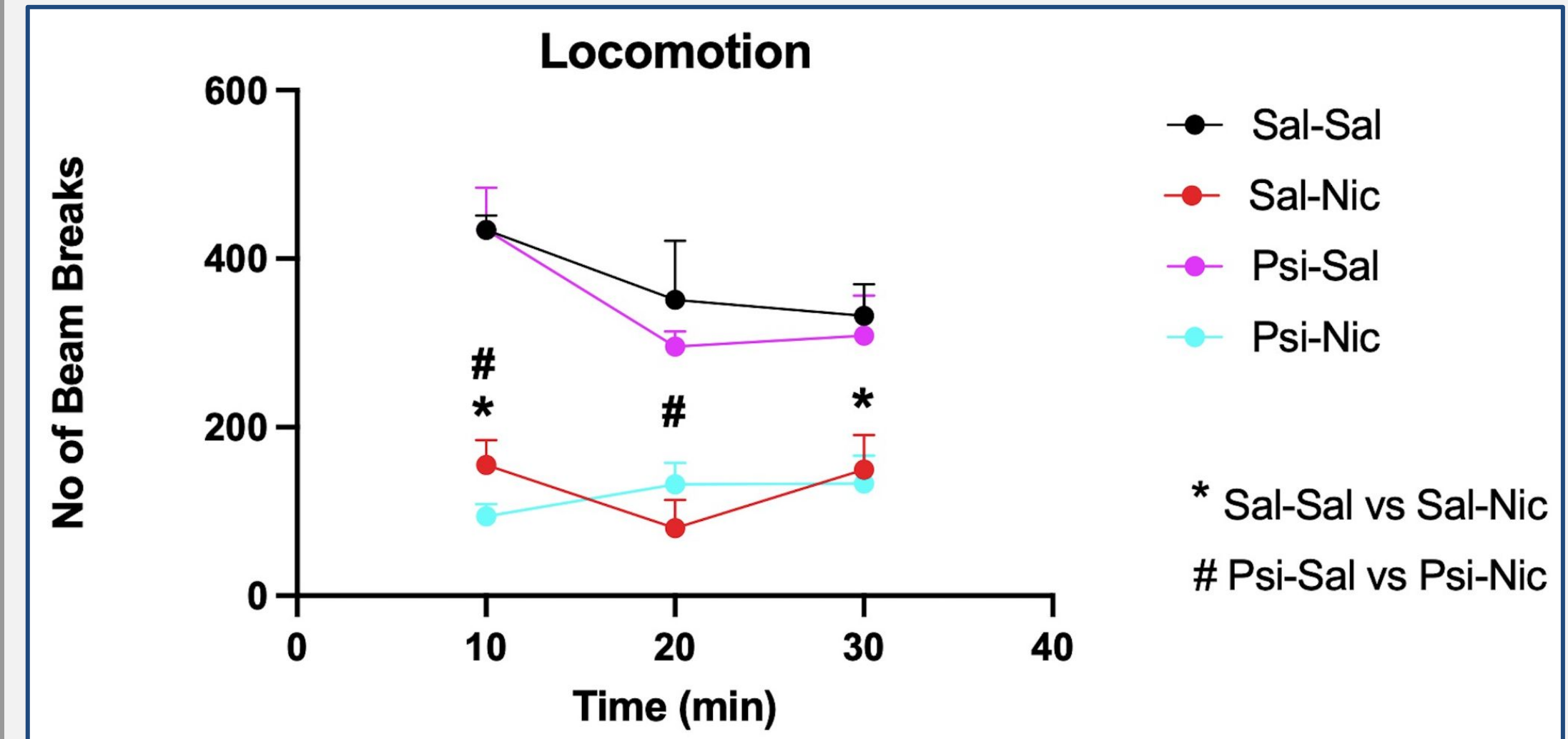


**Figure 2: Nicotine increases latency in tail-flick** Psilocybin pretreatment had no effect on nicotine's antinociceptive effects in the tail-flick test. \*p<0.05, \*\*p<0.01 vs Sal-Sal

### Body Temp



**Figure 3: Nicotine decreases body temperature** Psilocybin pretreatment had no effect on nicotine-induced hypothermia. \*p<0.05, #p<0.05



**Figure 4: Nicotine decreases locomotor activity** Psilocybin pretreatment had no effect on nicotine-induced hypomotility. \*p<0.05, #p<0.05

## Conclusion

Statistical analysis of our results suggests that psilocybin does not alter acute nicotinic responses in mice. This suggests that psilocybin does not have a lasting effect on nicotinic receptors when given 24 hours prior to a single dose. Our data does not support the hypothesis that PSI reduces withdrawal by altering activity of nicotinic receptors.

For future directions, it would be important to test on female mice to elucidate potential sex differences in the effect of psilocybin on nicotinic withdrawal. It would also be important to investigate the time course of psilocybin on nicotine reward and intake. Further research on the brain mechanisms underlying psilocybin's effect on nicotine dependence will be important. Particularly, due to recent studies showing that psilocybin "resets" brain networks and creates increased connectivity between alternative networks.

## References

- Higgins, G. A., & Sellers, E. M. (2021). 5-HT2A and 5-HT2C receptors as potential targets for the treatment of nicotine use and dependence. *Progress in brain research*, 259, 229–263. <https://doi.org/10.1016/bs.pbr.2021.01.007>
- Ho, Dien (2012). Antidepressants and the FDA's Black-Box Warning: Determining a Rational Public Policy in the Absence of Sufficient Evidence. *Virtual Mentor*, 14(6):483-488. doi: 10.1001/virtualmentor.2012.14.6.pfor2-1206.
- Isbell, H., Wolbach, A.B., Wikler, A. et al. Cross tolerance between LSD and psilocybin. *Psychopharmacologia* 2, 147–159 (1961). <https://doi.org/10.1007/BF00407974>
- Johnson, M. W., Garcia-Romeu, A., & Griffiths, R. R. (2017). Long-term follow-up of psilocybin-facilitated smoking cessation. *The American journal of drug and alcohol abuse*, 43(1), 55–60. <https://doi.org/10.3109/00952990.2016.1170135>
- Jones, G., Lipson, J. & Nock, M.K. Associations between classic psychedelics and nicotine dependence in a nationally representative sample. *Sci Rep* 12, 10578 (2022). <https://doi.org/10.1038/s41598-022-14809-3>
- Matthew W. Johnson, Roland R. Griffiths, Peter S. Hendricks, Jack E. Henningfield, The abuse potential of medical psilocybin according to the 8 factors of the Controlled Substances Act, *Neuropharmacology*, Volume 142, 2018, Pages 143-166, ISSN 0028-3908, <https://doi.org/10.1016/j.neuropharm.2018.05.012>.

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