



## Measuring the effects of serotonergic psychedelics on the structure of neural population activity

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Classical psychedelics primarily act via serotonin 2A receptors to cause changes in perception and cognition, and have shown promise in the treatment of various mental disorders [1]. Studies in humans often report that psychedelics increase the brain-wide spatiotemporal complexity of aggregate measures of neural activity [2], but such effects have not been examined at the level of populations of individual neurons [3]. We performed high-yield electrophysiological recordings from awake mice ( $n=16$ ) to record the spiking activity of  $>17,000$  neurons across forebrain structures including the prefrontal cortex, striatum, thalamus, amygdala, and hippocampus, while administering either LSD or saline via intragastric catheter. We found that the brain-wide spatiotemporal complexity of neural activity increased after LSD administration, but, surprisingly, this was also true after saline. While LSD doesn't drive broad increases in the complexity of neural population activity, it may be that specific structuring motifs that normally act to reduce the effective complexity of population activity – such as movement and inter-regional connectivity [4,5] – are specifically disrupted, and our ongoing analyses assess these relationships. Overall, we found that  $\sim 80\%$  of neurons significantly changed their firing rate under LSD, but observed a similar proportion of modulation in the control condition. However, the two conditions could be distinguished by the distinct anatomical profile of firing rate modulation, implicating the prefrontal cortex and hippocampus as important mediators for the effects of LSD. Our results raise critical questions about psychedelic-induced complexity increases measured in humans, and highlight that the effects of LSD may be driven by more subtle and anatomically specific changes in neural population activity than often suggested by contemporary results.

**psychedelics, LSD, neuropixels, neural population activity, entropy**

