The Impact of Hallucinogens on Active Sampling and the Olfactory Bulb

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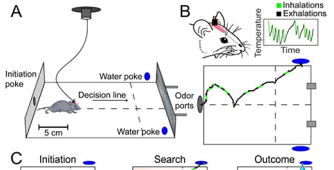
Abstract

Olfactory hallucinations occur in many disorders, including Parkinson's disease, epilepsy, schizophrenia, and migraines, but the neural mechanisms underlying these hallucinations are unknown. Mechanistic studies of hallucination in animal models are fundamentally limited, since animals do not verbalize what they perceive. However, in lieu of a verbal report, internal states can be inferred from an animal's externally observable behavior. Using computational tools, our lab has shown that a mouse's perceptual states can be inferred from close analysis of strategic sniffing behavior. Further, we have found that behaviorally-inferred states can predict the population structure of spontaneous activity in the olfactory bulb. We now leverage these advances to infer hallucinatory states from mouse behavior. Importantly, many hallucinogens act on serotonin pathways, which feed heavily into the mouse olfactory system. Further, we have found that injection of the hallucinogen DOI alters the rhythmic structure of sniffing behavior. In ongoing work, we are investigating how DOI impacts population dynamics in the olfactory bulb. This work will provide fresh insights into the link between active sampling, olfaction, and hallucinogens.

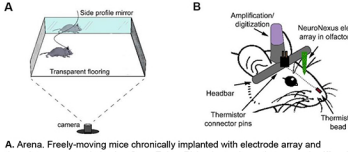
Methods

Freely Moving Olfactory Search Task



A. Arena. Mice poke the initiation poke to initiate a trial. Odor is delivered from one of two odor ports and mice must navigate to the corresponding water poke to receive a water reward. Decision is determined as the side the mouse's head is on at the decision line, enforced by real-time video tracking. Sniffing is recorded through overhead commutator. **B.** Sampling. Sniffing is recorded and monitored via thermistor implant. Movement is tracked by red paint on top of the head. Movement within one trial is shown in synch with inhalation and exhalation. **C.** Trial design. Mice poke an initiation poke on the left side of the arena to initiate a trial. Odor is emitted from one of two ports on the opposite end of the arena. Mice navigate the odor gradient to receive a water reward.

Spontaneous behavior ("Seinfeld condition")

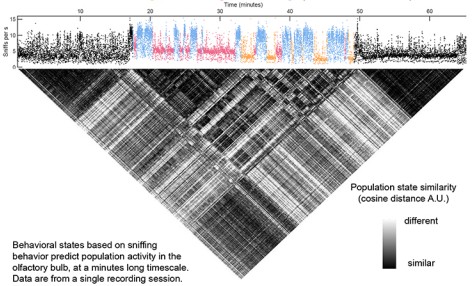


A. Arena. Freely-moving mice chronically implanted with electrode array and thermistor are recorded using Open Ephys **B)** Implant schematic to record sniff and neural activity in freely moving mice. Thermistor is placed above the nasal epithelium in the nasal cavity. Electrode is placed into the OB on a microdrive to lower probe

How does a hallucinogen affect breathing rhythms?

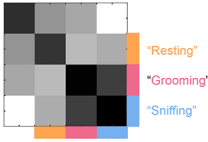
Olfactory bulb population activity maps the rhythmic states of breathing

HMM states: "Resting", "Grooming", & "Sniffing" (head-fixed in black)

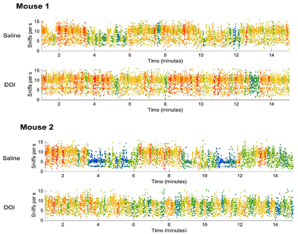


Behavioral states based on sniffing behavior predict population activity in the olfactory bulb, at a minutes long timescale. Data are from a single recording session. *Top.* Individual dots indicate individual sniffs. Sniffs from the head fixed period are colored black. For sniffs during freely-moving, the colors indicate behavioral states assigned by a Hidden Markov Model, which was trained with sniff frequency and movement speed data. Orange indicates "resting", Pink indicates "Grooming", Blue indicates "Sniffing" *Middle.* Cosine distance matrix for OB population activity over time ((n= 1 mouse; 42 simultaneously recorded units; 10 s bins). The distance matrix is rotated 45 degrees, so the diagonal aligns with the time axis above. *Bottom.* Average cosine distance for all time bins in a given state, color-coded as above

Behaviorally-defined states capture population activity states



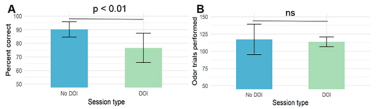
Hallucinogen changes the structure of breathing behavior



Mice were injected with 3 mg/kg DOI IP then placed into an arena for uninstructed behavior and sniff recordings. The x-axis is time in the recording session, and the y-axis is the instantaneous frequency of each sniff. Individual dots indicate individual sniffs. The colorscale indicates the movement speed of the nose (tracked with DeepLabCut), with warmer colors representing faster movement. Both mice demonstrated increased movement speed and increased sniffing throughout the DOI session. Sniffing remained increased in times of decreased activity. Saline sessions showed expected sniff synchronization with movement, where low activity aligned with decreased sniff.

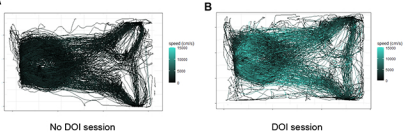
How does a hallucinogen impact olfactory perception?

Hallucinogen impairs olfactory performance without compromising task adherence



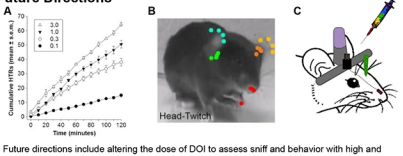
Mice were administered 3 mg/kg DOI IP and placed into the olfactory navigation assay task 5 min later.
A. Mice perform worse on the odor navigation task when on DOI compared to previous sessions. **B.** Despite the decreased accuracy, mice perform an equivalent number of trials when administered DOI compared to sessions without DOI. No DOI sessions are calculated from the 10 sessions prior to DOI administration.

Path Tortuosity Less Direct with Faster Movements



Within subject comparison of movement in the arena from a DOI and No DOI session. Tracking was done in DeepLabCut. Mice were administered 3 mg/kg DOI IP and placed into the olfactory navigation assay task 5 min later. **A.** The No DOI session tracking revealed a less tortuous path with more direct paths. **B.** The DOI session tracking revealed faster nose movement speed and a more tortuous, exploratory path within the arena.

Future Directions



Future directions include altering the dose of DOI to assess sniff and behavior with high and low doses. We also plan on assessing the head-twitch response (HTR) in correlation with sniff. Lastly, we intend to administer DOI to mice chronically implanted with electrodes. **A.** As the dosage of DOI increases, the frequency of the HTR increases[1]. **B.** DLC Pro tracking of the HTR by the Hines Lab[2]. **C.** Depiction of mouse receiving DOI with a chronic electrode implant.

References

1. Canal & Morgan, 2012
2. Contreras et al., 2021